# NUMBER REPRESENTATION IN THE PARIETAL LOBES

**Silke M. Göbel**

**A dissertation submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Oxford**

**St. Hugh's College** **Michaelmas Term 2002**



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## ABSTRACT

This thesis considers the importance of the inferior parietal lobe for calculation and Arabic number comparison. The first experiment demonstrates that repetitive Transcranial Magnetic Stimulation (rTMS) can be used on normal subjects to replicate findings from studies of patients whose ability to calculate after brain injury was impaired. While subjects were solving addition tasks, rTMS was applied over anterior and posterior areas of the inferior parietal lobule and the adjoining intraparietal sulcus (aIPL+S, pIPL+S). In line with results from patient studies, magnetic stimulation showed a disruptive effect only over left IPL+S. It had no disruptive effect when delivered over right inferior parietal lobule and the adjoining intraparietal sulcus.

To investigate the representation of number magnitude in the human brain rTMS was subsequently applied to the same inferior parietal regions while subjects performed a number comparison task. With numbers between 31 and 99, repetitive TMS over the pIPL+S disrupted organisation of the putative "number line". rTMS had no disruptive effect when delivered over aIPL+S, in either the left or right hemisphere. With numbers between 1 and 9, however, TMS over the pIPL+S did not impair task performance. Here, TMS had a disruptive effect when delivered over aIPL+S, in either the left or right hemisphere, thus suggesting that areas in the inferior parietal lobes might be specialised for certain number sizes.

The idea of a spatial mental number line was further investigated in a detailed single-case description of a person with an automatic mental number line. In the last experiment, functional Magnetic Resonance Imaging (fMRI) was used to investigate number comparison. The fMRI study gave some indication that small numbers might be represented in the aIPL+S region. In general, the fMRI results suggest that parietal cortical contribution to number magnitude representation is intimately related to its role in basic sensorimotor processes.

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**DIE HEXE:** *Du mußt verstehn!*
*Aus Eins mach Zehn,*
*Und Zwei laß gehn,*
*Und Drei mach gleich,*
*So bist du reich.*
*Verlier die Vier!*
*Aus Fünf und Sechs,*
*So sagt die Hex,*
*Mach Sieben und Acht,*
*So ist's vollbracht:*
*Und Neun ist Eins,*
*Und Zehn ist keins.*
*Das ist das Hexen-Einmaleins!*

**FAUST:** *Mich dünkt, die Alte spricht im Fieber.*

**MEPHISTOPHELES:** *Das ist noch lange nicht vorüber.*

taken from Faust I (Goethe)

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## LONG ABSTRACT

This thesis examines the role of the human inferior parietal lobule (IPL), including the intraparietal sulcus (IPS), in number representation. Two different experimental methods, Transcranial Magnetic Stimulation (TMS) and Functional Magnetic Resonance Imaging (fMRI) were used. Transcranial Magnetic Stimulation was employed to disrupt neuronal activity selectively in discrete areas of left or right anterior and posterior IPL. Subjects were stimulated while they carried out either a simple addition task or number comparison tasks. The effect of magnetic stimulation on response time was analysed. Functional Magnetic Resonance Imaging was used to associate activity in several areas of the brain with numerical and non-numerical task events.

Chapter 1 is an introductory chapter and reviews the literature that is relevant to the experiments. The anatomy of the parietal lobes, and more specifically of the inferior parietal lobe, is outlined briefly. Damage to the parietal lobes is often associated with acalculia, an impairment of the ability to solve arithmetic problems. The literature on acalculia is reviewed in chapter 1. Findings from acalculic patients led to the development of cognitive models of numerical processing and calculation. Several of these models are presented. For some of these models, for example Dehaene's (1992) triple code model, there are suggestions of neural implementations. These neural implementations attribute an important role in number magnitude representation to the inferior parietal lobules.

This thesis uses the wealth of research on acalculic patients and the parietal lobes as a starting point. From there it investigates the neural foundations of the representation of numbers in normal subjects by using two neuroimaging techniques: repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI). The principles of TMS and fMRI are presented in

chapter 2. TMS is an interference technique based on magnetic stimulation. A magnetic pulse is generated that leads to an electric current in the underlying brain tissue. This induced electrical activity can be thought of as an increase in neural noise that obscures the processing of task-relevant neural signals. The spatial and temporal extent of cortical effects produced by TMS is discussed along with safety guidelines and experimental design issues. Functional magnetic resonance imaging uses nuclear magnetic resonance to image brain activation indirectly by detecting changes in the ratio of deoxygenated to oxygenated haemoglobin. Brain areas with higher Blood Oxygen Level Dependent (BOLD) signal changes are thought to use more energy and therefore to be more active. Research on the relation between the BOLD signal and neuronal activity is reviewed. The spatial resolution of this technique is better than its temporal resolution. This has effects on the experimental design of fMRI experiments. The chapter concludes with a brief introduction to image analysis.

In chapter 3 the first TMS experiment is described. The objective of this experiment was to investigate whether TMS can be used to replicate basic findings on patients and to tackle discrepancies between patient data and results from neuroimaging studies in an addition task with normal subjects. Along with evidence from patient studies it was hypothesised that left hemispheric parietal TMS stimulation should result in an increase in reaction times in an addition task. However, there should be no effect of right hemisphere stimulation. For trials without magnetic stimulation it was expected that the larger the size of the sum of the two operands the longer would be the reaction times.

Fourteen subjects were asked to calculate sums from 21+22 to 47+49. In seven subjects rTMS was applied in two separate sessions over left posterior IPS/

angular gyrus (pIPL+S) or left anterior IPS/supramarginal gyrus (aIPL+S). In the second group of seven subjects rTMS was applied, again in two separate sessions, over right pIPL+S or right aIPL+S. For each site subjects performed 4 blocks of 50 trials. On 10 trials in each block rTMS was applied for 500ms at 10Hz. The pIPL+S site at which the rTMS was delivered was identified by subjects' performance in a visual search task. For the aIPL+S site the hand area in the subjects' motor cortex was first identified. The calculation task was carried out while rTMS was delivered 3cm posterior and 1cm lateral from the hand area.

On trials with and without rTMS the problem-size effect was observed wherein calculation times were longer for larger than for smaller sums. With rTMS there was a significant increase in reaction times for stimulation over left pIPL+S independently of problem-size. This increase was specific to stimulation over the left hemisphere. There was no increase in reaction times when stimulation was applied over right pIPL+S or right aIPL+S. These results are in line with lesion studies and show that rTMS over left inferior posterior parietal regions, but not over right inferior parietal regions, leads to impaired and slower performance on addition tasks. This confirms the importance of the left inferior parietal lobe in simple calculation. TMS was thus used successfully in this experimental situation to obtain results in a normal sample that show parallels with the pattern of deficits observed in patients. This might be the first study in which deficits seen in acalculic patients could be reproduced in normal adults by rTMS stimulation. These results strongly justify the use of TMS as a neuroimaging tool for investigating the neural basis of number processing. In chapters 4 and 5 TMS was used to interrupt a more basic numerical process that is seldom disrupted in patients: number magnitude representation.

In chapter 4 repetitive transcranial magnetic stimulation was used in three experiments to investigate the importance of the inferior parietal cortices for number magnitude representation and whether numerical representation takes a spatial form. Subjects were presented with numbers between 31 and 99. The number 65 was never presented and subjects were required to indicate with one of two possible key presses whether the number on the screen was greater or less than 65. In experiment 1 (n = 9) and 2 (n = 6), the index fingers of the right and left hands were used to indicate the 'greater than' and 'less than' responses respectively. Stimuli remained on the screen until subjects made a response. The intertrial interval was one second. Subjects performed 4 blocks of 78 trials, preceded by an initial training block of 10 non-TMS trials. On 10 trials in each experimental block rTMS was applied over cortex for 500 ms at 10 Hz. In experiment 1, TMS was applied over left and right pIPL+S. The parietal site at which the rTMS was delivered was identified by first asking subjects to perform a visual search task. The number classification task was then carried out while rTMS was delivered at the same site. In experiment 2, TMS was applied over left and right aIPL+S. To localise this area the hand area in the subjects' motor cortex was identified and the number comparison task was carried out while rTMS was delivered 3 cm posterior and 1 cm lateral from this site. On trials without rTMS the classical distance effect was observed wherein classification times were longer for numbers closer to 65 than for numbers further away. In experiment 1 two effects were observed with rTMS over left or right pIPL+S. First there was a generalised increase in reaction times across the number line, thus replicating the effects seen in patients with left parietal cortex damage. Second, the effects of rTMS were greater for numbers larger than 65 than for numbers smaller than 65. These effects were specific to stimulating over pIPL+S. In contrast

magnetic stimulation over left or right aIPL+S in experiment 2 had no effect on task performance. The behavioural data provide a replication of the distance effect. Classification reaction times for numbers close to the reference number take longer than classification reaction times for numbers much smaller or greater than the reference number. rTMS over posterior, but not anterior IPL regions lead to impaired and slower performance on the number classification task confirming the importance of this region in number representation. Experiment 3 was carried out to ensure that the effect of rTMS over pIPL+S was driven by the spatial characteristics of the number stimuli and their mental representation in space rather than just the response required in the task. Experiment 3 followed the same procedure as experiment 1, but subjects (n = 7) were now required to use a reversed-response version, i.e. to press the left button with their left index finger for numbers larger than the reference number and the right button with their right index finger for number that were smaller. rTMS over the left pIPL+S still slowed down subjects' classification of numbers larger than the reference even though a reversed-response version of the number comparison task was used. Thus a simple response account cannot explain the rTMS-induced reaction time deficits obtained in both experiments 1 and 3. These results confirm the importance of both left and right pIPL+S in number representation. There is evidence that, on the number line, numbers smaller than the reference are represented on the left side of space while numbers that are larger than the reference are represented on the right side of space. Left posterior parietal TMS particularly affects numbers represented on the contralateral side of space. The preeminent role of the pIPL+S region as opposed to the aIPL+S region might partly be a function of the type of number stimuli used.

The stimuli used in chapter 4 were double-digit numbers and there is some evidence that the precise region of the parietal cortex that is critical in a number task varies. In chapter 5 rTMS was therefore used to investigate the neural basis of number comparison with smaller single-digit numbers. Eight subjects were presented with numbers between 1 and 9. The number 5 was never presented. Subjects had to indicate with one of two possible key presses whether the number on the screen was greater or smaller than 5. In four separate sessions rTMS was applied over left pIPL+S, right pIPL+S, left aIPL+S and right aIPL+S. For each site subjects performed 4 blocks of 72 trials, preceded by a training block of 10 non-TMS trials. On 8 trials in each block rTMS was applied for 500ms at 10Hz. The rTMS trials occurred pseudo-randomly.

On trials without rTMS the classical distance effect was observed wherein classification times were longer for numbers closer to 5 than for numbers further away. With rTMS two effects were observed. First, in contrast to results in chapter 4, there was a significant increase in reaction times across the number line for stimulation over left or right anterior IPL+S, but no change in reaction times for stimulation over left or right posterior IPL+S. Second, the effects of rTMS over left aIPL+S were greater for numbers higher than 5 than for numbers lower than 5. These results together with experiments of chapter 4 suggest that tasks involving larger numbers involve the more posterior IPL+S region while tasks involving small numbers involve more the anterior IPL+S region. It may be the case that smaller numbers, which are often learned early in life, depend on a distinct code that may emphasise verbal memory for rote counting or hand-based counting strategies. The anterior IPL+S region has been implicated in both motor attention and verbal memory. It seems plausible that a spatial representation of magnitude would be of

particular importance when such verbal and manual overlearned coding strategies are not available; the posterior IPL+S region might be most essential on such occasions.

In chapter 6 an overview of the literature on explicit visual-spatial representation of numbers, called number forms, is given and the number form of one subject (HS) is described in detail. HS's number form is subdivided into several parts. He described it like a motorway going up a long hill and in some parts it looked to him like the route his family drove to his grandmother's house when he was young. HS said that his number form was activated automatically each time he was confronted with a number and that he used his number form in every aspect in life. Explicit number forms like the number form of HS may only be special cases of a more general association between space and numbers that might be present in most subjects. Behavioural evidence suggests that one spatial representation of numbers in normal subjects is as a 'number line'.

In chapter 7 an fMRI study of number comparison is presented. This study was carried out to see whether the regional specialisation on number size found with TMS in chapters 4 and 5 can be replicated by using a different brain imaging method: fMRI. Additionally, it has been suggested that activations in the IPS vary with the distance between the numbers to be compared. In number comparison the smaller the distance between a number and the reference the longer the reaction times. Activation in the IPS, however, has also been related to attentional and intentional selection and it is possible that activity in this region is a reflection of reaction time. The fMRI experiment therefore investigated the effect of numerical distance independently from reaction time. During number comparison blocks, subjects (n = 12) had to indicate whether digits were greater or smaller than a

reference (5 or 65). In control blocks they were asked to perform a perceptual task (vertical line present/absent) either on numerical or non-numerical stimuli. Number comparison versus rest yielded a large bilateral parietal-motor patchwork. However, no areas showed more activation during number comparison than during the control tasks. Furthermore, no areas were more active during number comparison of stimuli with distance close than those with distance far or vice versa. A left-lateralised parietal-motor patchwork, however, varied significantly with reaction times. Our findings suggest that previous distance-related IPS activations might have been mainly due to basic sensorimotor selection processes, which underlie changes in reaction time. The IPS's contribution to magnitude discrimination tasks may, therefore, be related to basic sensorimotor selection processes and not just to the representation of number magnitude. A region of interest analysis, focussing on the parietal cortex, suggested similar conclusions. However, during number comparison judgement there was a higher percentage of mean signal change for smaller than larger numbers in the anterior IPL+S region thus indicating that small numbers might be represented differently.

In chapter 9 the main findings of the thesis are summarised and discussed. TMS was established as a neuroimaging tool to investigate numerical cognition. Furthermore, it could be shown that the contribution of the inferior parietal lobe is essential during calculation and number comparison. Evidence for a visuospatial number representation in normal subjects was presented and results from TMS and fMRI studies seem to indicate that small numbers are represented differently.

Whether these findings are specific to visual representation, the precise nature of visuo-spatial number representation and the relation between visuospatial and motoric number representation has to be investigated by further research.

# 1. General introduction

Numbers are an inherent part of our every day life. Often it is unnoticed how important it is to be able to understand numbers, but it becomes evident when this understanding suddenly breaks down. In a world without numbers it would not be possible to measure distance or tell the exact time. People would not be able to judge their own height or that of a building; nor would they be able to buy something in a store or to calculate the speed or positions of boats and airplanes.

The most impressive example in the literature of an almost complete breakdown of numerical ability is patient CG (Cipolotti, Butterworth, & Denes, 1991). After a cerebral vascular accident in the region of the left middle cerebral artery she lost her understanding of numbers above four completely. She was no longer able to tell the time, dial a telephone number, recognise money or check change. In addition, she could not tell her own age, clothes size, telephone number, the number of her house nor the ages of her husband and children. Numbers matter.

## 1.1 History of numbers

Although today numbers seem to be such an integral part of our world, the history of numbers and arithmetic only began some 10 000 years ago. Historians believe that prehistoric people began to use numbers when they started farming (Ifrah, 1994). They needed to know such things as how many sheep they owned or how many rows of grain they planted or how long it would be before harvest season arrived. Probably, prehistoric farmers mainly used one-to-one correspondence. A shepherd for example could keep track of his flock by dropping a pebble into a pile or by cutting a notch in a twig for every sheep that went to pasture in the morning. Interestingly, two words that people use today to describe doing arithmetic,

calculating and tallying, come from the Latin words for pebble (calculus) and notch (taleus).

Later, Egyptians developed the art of counting further, but their system of numeration was cumbersome. For example the number 1000 was symbolised by a lotus flower and the number 2000 was symbolised by a picture of two lotus flowers growing out of a bush (Ifrah, 1994). The numeration system in hieroglyphics was clumsy and awkward to work with. Number 999 for instance required 27 individual marks. Nevertheless, they used this number system extensively. For example, it is said more than 5000 years ago an Egyptian ruler recorded on a macehead the capture of 120 000 prisoners, 400 000 oxen and 1 422 000 goats (Millett, 1990). The event is inscribed on a ceremonial mace which is now in the Ashmolean museum in Oxford (see figure 1-1).




**Figure 1-1:** An ancient ceremonial macehead from Egypt with hieroglyphic number symbols (lower left corner in the schematic representation, red circle) can be found in the Ashmolean museum, Oxford.

The first to exhibit an interest in the foundations of mathematics were the ancient Greeks. Early Greek philosophy was dominated by a dispute as to whether

arithmetic or geometry is more basic. Underlying this dispute was a perceived dichotomy. While Democritus believed that the universe is made up of discrete atoms which can be counted, Thales of Miletus defended the view that it consisted of one or more continuous substances. It is likely that this debate was inspired by a linguistic distinction between countable and uncountable nouns analogous to English words such as apple and water. But as Aristotle pointed out water can be measured by counting cups of water (Annas, 1976).

### *1.2 Philosophy of mathematics and numbers*

The definition of mathematics or even a number is by no means an easy one. As Russell (1919) stated, very few people are prepared with a definition of what is meant by "number" or "0" or "1", and the discovery that 1 is a number must have been difficult. Although the Dictionary of Contemporary English (Gadsby, 1995) clearly defines a number "as a word or sign which represents an amount or a quantity", there is no agreement between mathematicians, philosophers and logicians upon the precise definition of number and how numbers relate to the world (Shapiro, 2000).

Today, there are at least three classes of opinion as to the subject matter of mathematics: realism, idealism and logicism (Curry, 1954). Plato's and Pythagoras' approaches are seen as realist accounts. Plato believed that mathematical entities are not just human inventions but have a real existence. Pythagoras was certain that not only mathematics but everything else could be deduced from numbers. Realists believe like Plato and Pythagoras that mathematical propositions express the most general properties of our physical environment. However, Curry (1954) stated that although this is a very common view of mathematics, it is untenable today on account of the essential role played by infinity in mathematics.

Philosophers belonging to the idealistic approach define mathematics as dealing with properties of mental objects. Natorp (1910) for example sees numbers as the purest and simplest product of thought. He claims that the first precondition for the logical understanding of number is the insight that number has nothing to do with existing things but that number is only concerned with pure regularity of thought.

Many modern philosophers of mathematics belong to a school of thought founded by Frege, logicism (Benacerraf & Putnam, 1983). They basically see mathematics as a branch of logic. The traditional logicist programme consists of systematic translations of mathematical statements into a language of pure logic. For Frege, statements about natural numbers are statements about the extensions of certain concepts. The number three, for example, is the extension of the concept that applies to all and only those concepts that apply to exactly three objects. A further development of these thoughts, which was nevertheless harshly attacked by Frege (1903), is found in formalism. In this school of thought the central concept in mathematics is that of a formal system and their research is concerned with rules and foundations of this formal system (Shapiro, 2000). Nevertheless, even if the system of numbers and mathematics turns out to be a vast and ingenious conceptual structure without empirical content, it has been an indispensable and powerful theoretical instrument for the scientific understanding and mastery of the world of our experience.

There is still no consensus about the foundations of numbers and mathematics, they form the subject of a lively debate among a small group of interested mathematicians, logicians and philosophers (see Jaquette, 2001). The philosophical debate surrounding the foundations of mathematics is mirrored by a controversy on the origins of mathematical knowledge. According to empiricists like

Mill and Kitcher (Shapiro, 2000) our understanding of number comes from observations of the world. In contrast nativists such as Kant (1900) and Chomsky (1993) imply that our understanding of number is inherent in the structure of our minds.

### *1.3 Neural basis of number representation*

Although these are fascinating topics, this thesis is not concerned with the relation of numbers to the real existing world, nor will it debate empiricist versus nativist accounts of our understanding of numbers. Rather, its aim is to investigate the question of how we represent numbers in our brain.

What happens in the brain when people engage in numerical tasks such as simple mental arithmetic? Which are the important brain areas for number representation and manipulation? In the process of dealing with numbers various brain structures must be involved. When we read digits or number words the visual cortex is required for us to perceive the stimuli. In order to understand spoken numbers the auditory cortex has to be active and the motor cortex is needed when uttering number words and writing digits. So it seems that all the major cortical brain regions including the occipital (visual), temporal (auditory) and frontal (motoric) lobes are somehow engaged in our daily encounter with numbers. But is there also a specific brain area that is essential to the representation of numbers? As early as 1918 an answer to that question was suggested by Peritz. He described a patient who was impaired in dealing with numbers after a brain injury, and concluded that only the parietal lobes seem to be essential for the representation of numbers. His conclusion was later to be supported by many studies. This thesis follows that tradition and will therefore focus on the parietal basis of number representation.

## *1.4 Parietal Lobes*

In this section, an overview of the general function of the parietal lobes will be given. Information about the role the parietal lobe plays in human perception and behaviour can be derived from anatomical studies, animal experiments, patients with parietal lobe lesions and neuroimaging of the intact parietal lobe.

### *1.4.1 Anatomy*

In both humans and monkeys, the parietal lobe is situated caudal to the central sulcus and superior to the Sylvian fissure. It is divided into an anterior and a posterior part. The anterior part consists of the post-central sulcus and caudal bank of central sulcus. It includes Brodman areas (BA) 1, 2, 3 and 43 (the parietal operculum) and contains primary somatosensory areas. The posterior part is divided by the intra-parietal sulcus (IPS) into a superior parietal lobule (SPL) and an inferior parietal lobule (IPL). The main focus of this thesis will be the posterior parietal lobe; for details on the anterior parietal lobe see Burton & Sinclair (2000), Iggo (1973) and Johansen-Berg & Lloyd (2000).

The posterior parietal cortex is composed of multiple areas that differ on cytoarchitecture and connectivity. Brodman (1909) first described two areas in the human inferior parietal lobule (IPL) below the intraparietal sulcus (IPS): area 39 (angular gyrus) and area 40 (supramarginal gyrus). He named the two areas above this sulcus in the superior parietal lobule (SPL) area 5 and area 7 (see figure 1-2).

Most of what is known about connexions in the posterior parietal lobe stems from research on monkeys. Brodman's taxonomy for the posterior parietal lobe in monkeys differs from that just described for humans (see figure 1-3). As in humans Brodman area 5 lies superior to the IPS, but Brodman's area 7 in monkeys lies below the IPS, except for a small part of area 7 at the caudal end of the SPL. Later,

Vogt (1911) subdivided monkey area 7 below the IPS into posterior area 7a and anterior area 7b.

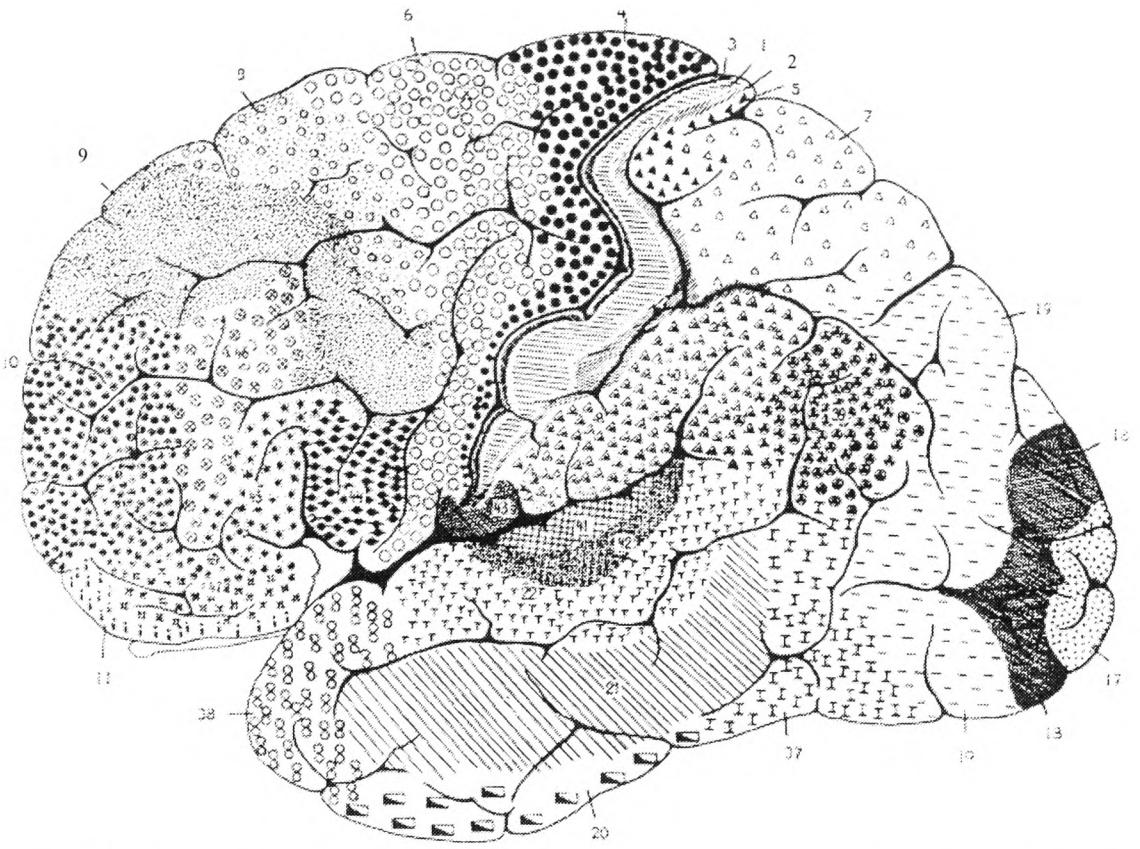


**Figure 1-2:** The cytoarchitectural areas of the lateral side of the human brain taken from Brodman (1909)

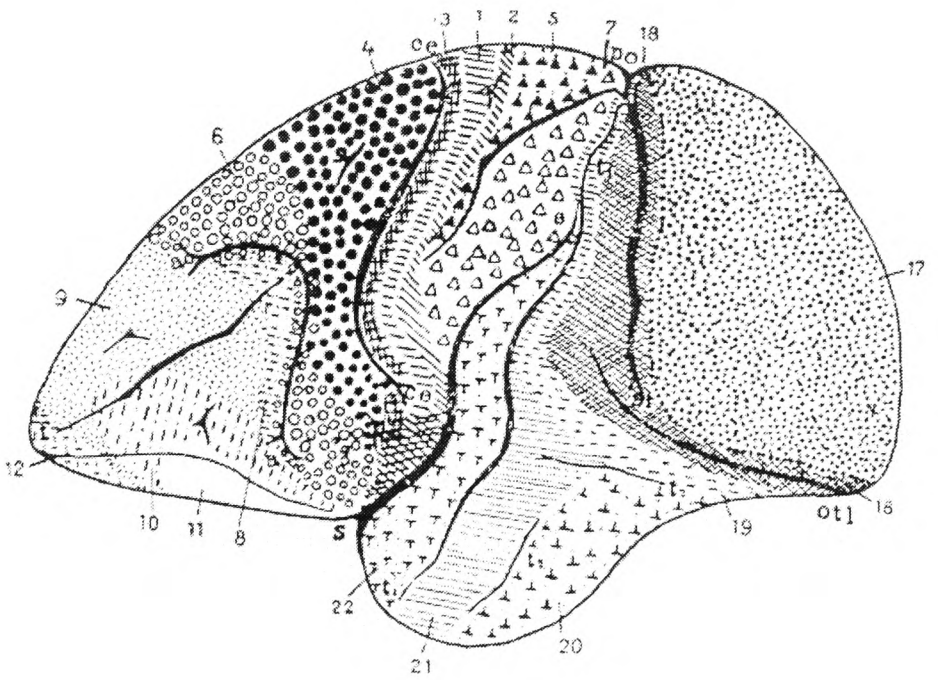


**Figure 1-3:** The cytoarchitectural areas of the lateral side of the monkey brain (Cercopithecus) taken from Brodman (1909)

So far over 70 inputs to and outputs from area 5 and 7 have been identified in the monkey. It is far beyond the scope of this thesis to cover all connexions, for details see Hyvärinen (1982), Cavada (2001), Cavada & Goldman-Rakic (1989a, 1989b),

Andersen, Asanuma, Essick, & Siegel (1990). Table 1-1 summarises the main connexions of the posterior parietal cortex in macaque monkeys.

**Table 1-1:** Main connexions of posterior parietal cortex in macaque monkeys

| **Brodman area (BA)** | *connexion with* |
|---|---|
| BA 5 | primary somatosensory cortex (BA 1, 2, 3), primary motor cortex (BA 4), dorsal premotor areas (BA 6) supplementary motor areas, vestibular cortex, area 7b<br>*subcortical:* lateral posterior thalamic nuclei, putamen and pontine nuclei |
| BA 7a/LIP | extrastriate visual areas, frontal and supplementary eye field, dorsal prefrontal cortex (area 46), superior temporal sulcus (STS), caudal portions of the cingulate gyrus (BA 23a)<br>*subcortical:* hippocampal formation, pulvinar-thalamic nuclei, caudate, pontine nuclei |
| BA 7b/AIP | BA 5, primary somatosensory cortex (BA 1, 2, 3), ventral premotor cortex (BA 6), prefrontal cortex, superior temporal sulcus (STS)<br>*subcortical:* dentate nucleus of cerebellum, pulvinar and lateral posterior thalamus, putamen |

As displayed in table 1-1 area 5 mainly connects somaesthetic structures with limb and motor structures. This table also shows clearly that the connexions of area 7b are quite distinct from those of area 7a. While area 7a is interconnected with structures important for the selection of visual or oculomotor goals, area 5 and 7b are interconnected to structures concerned with the selection of limb movements.

The highest level of convergence seems to be located in the IPS. Recently, several separate areas in the IPS [posterior, medial, lateral, ventral and anterior intraparietal (PIP, MIP, LIP, VIP, AIP)] have been described on the basis of differential neuronal activity (Colby & Duhamel, 1996) (see figure 1-4a). Galletti et al. (1999) also described three areas on the medial parietal surface: areas V6, V6a and area 7m (see figure 1-4b). Cavada et al. (2000) consider V6 as a typical pre-striate visual area whereas she argues that the complexity of recorded units in V6a speaks for its inclusion among parietal visual areas.

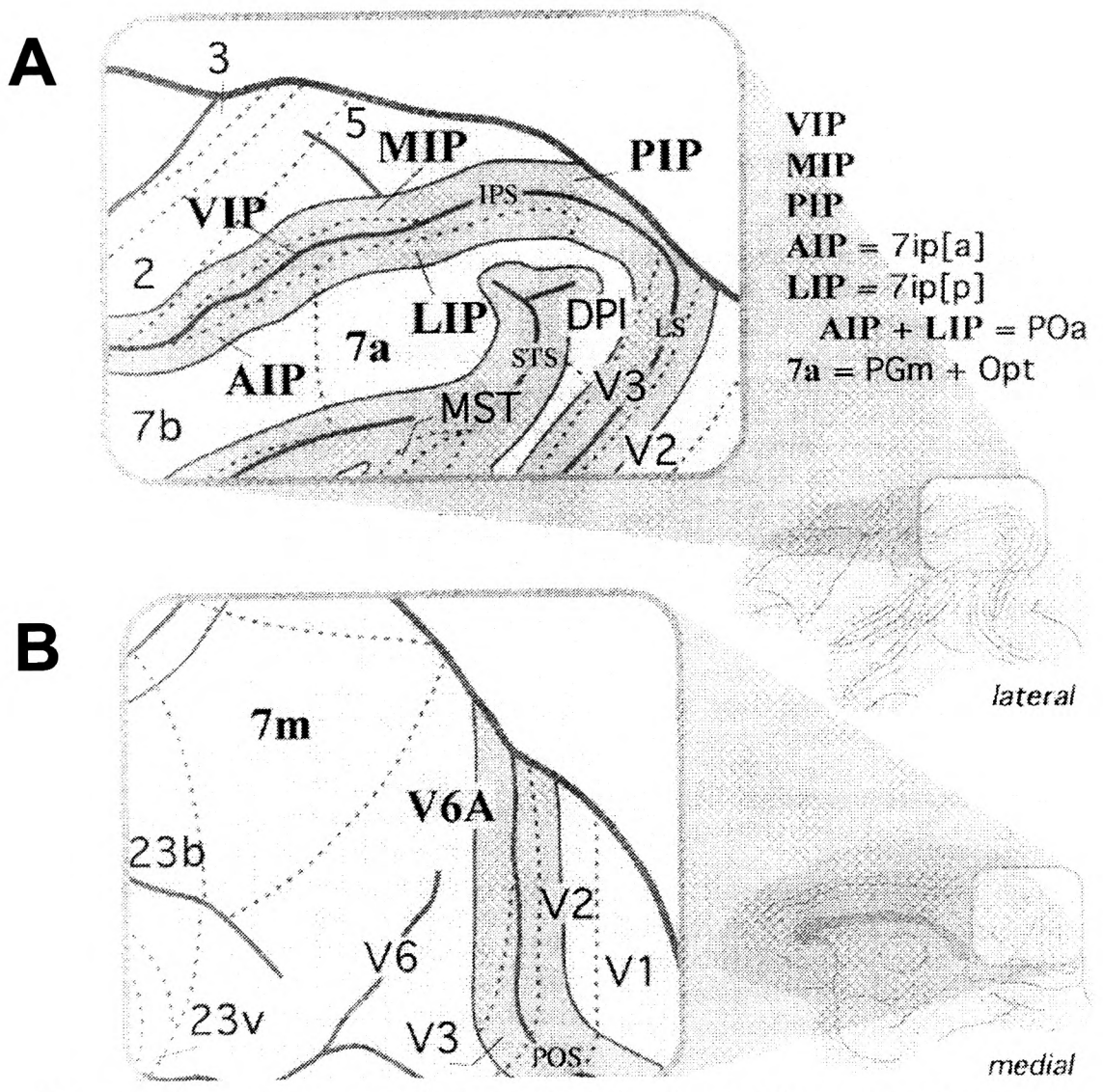



**Figure 1-4:** A current parcellation of the visual parietal cortex in the macaque monkey taken from Cavada (2000)
(IPS: intraparietal sulcus, LS: lunate sulcus, POS: parieto-occipital sulcus, STS: superior temporal sulcus)

### *1.4.2 Single-unit responses*

Neurones in different parietal areas represent the locations of stimuli in terms of different spatial reference frames (Cohen & Andersen, 2002). Many recent studies

have explicitly explored these different reference frames. This literature will not be reviewed here. For a detailed overview see Colby (1999) and Andersen & Buneo (2002).

Neurons in the posterior parietal cortex (PPC) share many characteristics: most receive combinations of sensory, motivational, and related motor inputs and their discharge is often much enhanced when the animal is interested in a target, attends to the target or makes a movement in relation to it (Stein, 1991). In their pioneering studies Hyvärinen & Poranen (1974) and Mountcastle et al. (1975) already described classes of neurons in the posterior parietal cortex associated with saccadic eye movements, pursuit eye movements, directed ocular fixations to particular parts of body-centred space and reaching movements of the arm.

Mountcastle et al. described the sensory and motor properties of neurons in area 5 and stated that neurons in area 5 seem to have an important role in somatosensory exploration, and in reaching and manipulation of objects. Interestingly, natural combinations of positions in several joints constituted optimal stimulation for many neurones in area 5. For example, they described a neuron in area 5 that was activated by elbow flexion when the shoulder was kept anteriorly elevated. Kalaska & Hyde (1985) found that 71% of the neurons they tested in area 5 were responsive to somatosensory stimulation. They showed that neural activity also reflected the direction of arm movements. Mountcastle et al. reported that neurons activated by visual stimuli are rare in area 5.

This is in clear contrast to neurons in area 7a and LIP. Most neurons of area 7a and LIP are related to vision and/or eye movements. For example, neurons have visual responses and react to stimuli in certain parts of the visual field (Andersen, Essick, & Asanuma, 1985; Gottlieb, Kusunoki, & Goldberg, 1998). Neurons are also

activated during goal-directed saccades (Andersen & Buneo, 2002; Robinson, Goldberg, & Stanton, 1978) and when monkeys fixate stationary targets (Ben Hamed, Duhamel, Bremmer, & Graf, 2002; Lynch, Graybiel, & Lobeck, 1985; Snyder, Batista, & Andersen, 1997). Neural activity in this region that changes in advance of saccades and during spatial shifts in attention has also been reported (Colby & Goldberg, 1999; Constantinidis & Steinmetz, 2001).

Somatosensory signals, in addition to visual and visual-motor signals can, however, still modify the response of IPL neurons. Although about 2-5 % of area 7a neurons also respond to vestibular stimulation (Grüsser & Landis, 1991), bimodal or multimodal neurons seem to be predominantly located in area 7b and AIP. Leinonen & Nyman (1979) and Sakata, Taira, Kusunoki, Murata, & Tanaka (1997) for example reported cells in area 7b that are sensitive to visual and cutaneous stimuli. Colby (1999) observed that neurons in area AIP code for grasp related spatial representation and Robinson & Burton (1980) reported that 79% of the cells from which they recorded in area 7b were responsive to somatosensory stimulation. Therefore, area 7b and the adjacent AIP region (Sakata, et al., 1999) is presumably involved predominantly in the visual and sensorimotor representation of the grasping space and the actions within that space, while areas 7a and LIP, in contrast, seems to process visual and oculomotor aspects of space.

Recently, much research has investigated neuronal responses from the intraparietal areas and parietal areas on the medial surface. Colby & Goldberg (1999) suggested that the intraparietal areas MIP and VIP differ in their framework of spatial representation. She observed that neurons in areas VIP seem mainly to be concerned with head-centred spatial representation; neurons in area MIP could support an arm-centred and reaching related spatial representation. Cavada et al.

(2000) report that areas V6 and V6a contain visual neurons whose responses are related to the orientation and direction of moving stimuli. V6a contains complex units that include neurons with craniotopic receptive fields and neurons related to attention. V6a and MIP are sometimes lumped together as the parietal reach region (PRR) (Batista, Buneo, Snyder, & Andersen, 1999; Buneo, Jarvis, Batista, & Andersen, 2002; Snyder, Batista, & Andersen, 1997). Only area V6 shows retinotopic organisiation (Galletti, Fattori, Battaglini, Shipp, & Zeki, 1996; Galletti, Fattori, Gamberini, & Kutz, 1999; Galletti, Fattori, Kutz, & Gamberini, 1999). Neurons in area 7m (Caminiti, et al., 1999; Cavada & Goldman-Rakic, 1989a; Cavada & Goldman-Rakic, 1989b) are involved in the interaction between gaze angle and hand position in the visual field during hand reaching tasks.

### *1.4.3 Lesion experiments in animals*

Recordings from neurons tell us about the firing behaviour of single or multiple neurones in one or several brain areas in relation to certain stimuli. These recordings can only give information about associations, while studies in which a whole brain area is inactivated or removed can elucidate the causal contribution of one area and its connexions. As with recordings, most discrete lesion studies have been done in monkeys. In general, parietal lesions led to an impairment in their ability to locate objects, oculomotor disorders and aiming deficiencies (Grüsser & Landis, 1991). Deficits in visuospatial attention have also been observed after removal of the posterior parietal cortex (Lawler & Cowey, 1987). Stein (1991) reports that lesions in SPL cause tactile agnosia (a deficit in recognising objects by touch), impaired weight discrimination and uncoordinated manipulatory and palpatory movements of

the contralateral arm. This shows clearly that the SPL is involved in representing limb- and body-centred co-ordinates.

After lesions or cooling of the inferior parietal lobule, however, different deficits have been reported: extinction (Lynch & McLaren, 1989; Schwartz & Eidelberg, 1968), impairment of visually guided grasping (Ettlinger & Kalsbeck, 1962; Faugier-Grimaud, Frenois, & Peronnet, 1985; Faugier-Grimaud, Frenois, & Stein, 1978; Gallese, Murata, Kaseda, Niki, & Sakata, 1994) and gaze-control defects (Stein, 1978).

Animals with extinction show attention only towards the stimulus in the extra-personal space ipsilateral to the parietal lobe lesion in simultaneous bilateral visual stimulus display conditions. Lynch & McLaren (1989) trained monkeys to report whether a target appeared on the left or the right side of a screen. In catch trials targets appeared on both sides at the same time. The researchers then removed area 7 and the lower bank of the IPS in one hemisphere. On catch trials the lesioned animals only reported the target on the side ipsilateral to the lesion. They thus clearly showed that inferior parietal lesions produce extinction in monkeys.

Lynch & McLaren (1983) reported reduced eye movements to the contralateral part of the extra-personal space as well as an impairment in saccade latencies and pursuit eye movements after removal of area 7 (area 7a in particular).

In general, results from lesion studies support the view that area 5 deals with somatic functions which are also dealt with in area 7b and that visual information is present throughout area 7 but is more prominent in the more posterior divisions, area 7a and LIP.

### *1.4.4 Homologous posterior parietal areas in humans*

It is somewhat controversial how far the human posterior parietal lobe is homologous to the monkey posterior parietal lobe. As mentioned above, in monkeys Brodman (1909) identified area 5 as an area comprising most of the superior parietal lobule and area 7 as covering the complete inferior parietal lobule. In contrast for humans he located both area 5 and 7 in the superior parietal lobule and described "human-specific" areas 39 and 40 in the inferior parietal lobule. This fundamental reorganisation of the parietal cortex from the monkey to the human brain supposes that in evolution homologous areas shifted from one side of the intraparietal sulcus to the other, while new areas developed in the IPL.

Other anatomists have been less convinced that there has been such dramatic reorganisation and have suggested that human areas 5 and 7 are homologous to superior parietal cortex in monkeys (i.e. area 5a and 5b). Area 7a and 7b in monkeys are believed to have homologues in area 39 and 40 of human PPC (Eidelberg & Galaburda, 1984; von Bonin & Bailey, 1947).

Recently, more and more evidence supports the latter view. Passingham (1998) writes that the cytoarchitecture of areas in the inferior parietal cortex are similar in the macaque, chimpanzee and human brain. Several imaging studies on humans (Bremmer, et al., 2001; Rushworth, Paus, & Sipila, 2001) strongly suggest some equivalences between human and monkey intraparietal and inferior parietal areas. For example, Bremmer, et al. (2001) and von Bonin & Bailey (1947) found an area in the depth of human IPS that reacts to moving visual, tactile or auditory stimuli in the same way as neurons in macaque area VIP. In addition, results from Rushworth, Paus & Sipila (2001) are consistent with a scheme in which IPS divides parietal cortices in a similar way in both monkey and people (von Bonin & Bailey,

1947; Eidelberg & Galaburda, 1984) rather than a scheme in which IPL is regarded as a novel structure (Brodmann, 1909).

### *1.4.5 Functions of the human parietal lobe*

In a recent review of neuroimaging studies in humans Culham & Kanwisher (2001) underlined the heterogeneity of stimuli and tasks that produce parietal activation. Parietal activation has been reported for visuomotor control, attention, eye movements, motion processing, stereo vision, spatial and non-spatial working memory, mental imagery, mental rotation, response inhibition, task switching, alertness, calculation and functions not typically attributed to parietal cortex such as pain processing, swallowing and meditation (Culham & Kanwisher, 2001).

There is clear evidence that the parietal lobe is important for attention. Many patients with brain damage in the parietal lobe show visual inattention and neglect (Vallar & Perani, 1987). Bisiach & Luzatti (1978) described a remarkable example of patients with hemineglect. They asked Italian patients with left neglect who were living in Milan to recall the features of Piazza della Scala in Milan, first from the perspective of standing at one end of the square and then from the other end. In both descriptions the patients omitted the features on the left. Neglect in patients can occur in all sensory modalities (Bisiach & Valler, 1988; Heilman, 1979). Although the basic pathophysiological principles leading to spatial neglect are still an issue of lively debate (eg. Halligan & Marshall, 1994; Milner & Goodale, 1995; Karnath, 2001), there is evidence that the most frequent anatomical correlate of visuospatial hemineglect in humans is damage to the inferior parietal lobule at the temporo-parietal junction (Vallar & Perani, 1986).

Strong evidence for the importance of the posterior parietal lobe for attention stems also from neuroimaging studies on normal subjects. Wojciulik & Kanwisher

(1999), for example, observed overlapping activations in the parietal lobe in a variety of tasks that all shared an abstract component of attention orienting. Futhermore, Culham & Kanwisher (2001) showed that not all attentional activations of the parietal lobe reflect a spatial component and not all such activations can be accounted for in terms of engaging the eye movement system (Nobre, Gitelman, Dias, & Mesulam, 2000). Attention-related activation has been reported throughout the parietal lobe, specifically in the IPS, the postcentral sulcus, SPL, IPL and temporo-parietal junction (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Perry & Zeki, 2000; Wojciulik & Kanwisher, 1999). Parietal regions have not only been indicated in visual but also in auditory (Pugh, et al., 1996) or haptic (Burton, et al., 1999) attention tasks.

But the parietal lobe has been implicated in many functions other than attention. Patients with lesions in the caudal superior parietal lobe and IPS are often impaired in tactile perception and cross-modal matching (Stein, 1991). Many show optic ataxia, a disorder of reaching movements performed with the hand under visual guidance (Perenin & Vighetto, 1988). In neuroimaging studies areas within the IPS are reported to be activated in association with saccades (Corbetta & Shulman, 1999) and reaching movements (Kertzman, Schwarz, Zeffiro, & Hallett, 1997). The anterior IPS is active during visually guided grasping (Faillenot, Toni, Decety, Gregoire, & Jeannerod, 1997), tactile manipulation of objects (Binkofski, et al., 1999a; Binkofski, et al., 1999b), observation of others' hand movements (Iacoboni, et al., 1999) and during passive viewing of graspable objects, namely tools (Chao & Martin, 2000; Devlin, et al., 2002). Binkofski et al. (1998) showed in both patient and neuroimaging studies the important role of the anterior lateral bank of the IPS for the co-ordination of finger movements for object grasping.

Subregions that differ in their pattern of activation have also been described within the inferior parietal lobule. For example, Roland & Friberg (1985) showed that the angular gyrus but not the supramarginal gyrus is active during a visuospatial memory task. In another imaging study, Jenkins et al. (1994) made subjects learn to perform sequences of finger movements in the absence of visual targets. They found a significant increase in activation of area 40 compared with rest, while at the same time the activity in area 39 decreased below that found in the rest condition. These findings suggest that the angular gyrus in humans, like area 7a in monkeys, may be important for visuospatial representations that support reaching movements while the human supramarginal gyrus, like area 7b in monkeys, might be important for limb centred representation of a reaching movement.

Dyslexia, dysgraphia and acalculia have also been described after inferior parietal lobe damage and seem to be more common after left hemisphere damage. These findings suggest the parietal lobe is involved in higher cognitive functions such as reading and calculating (Critchley, 1953). In section 1.5 the literature on acalculia will be reviewed in detail. The wide variety of tasks that activate the parietal lobe was again shown in a recent fMRI study by Simon et al. (2002). They set out to describe the topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Ten subjects were scanned while they performed six different tasks: grasping, pointing, saccades, attention, calculation and phoneme detection. A large patchwork of activations comprising parietal, lateral frontal and mesial frontal regions was observed. Only activations in the parietal lobes will be discussed here. They found no parietal region that was activated by pointing alone or phoneme detection alone. For grasping alone they reported bilateral supramarginal gyrus and postcentral activation. For saccades alone the

superior parietal lobe and the posterior segment of IPS were bilaterally active. They observed bilateral precuneus activation for attention alone and the left IPS for calculation alone. An overview of these activations is given in figure 1-5.

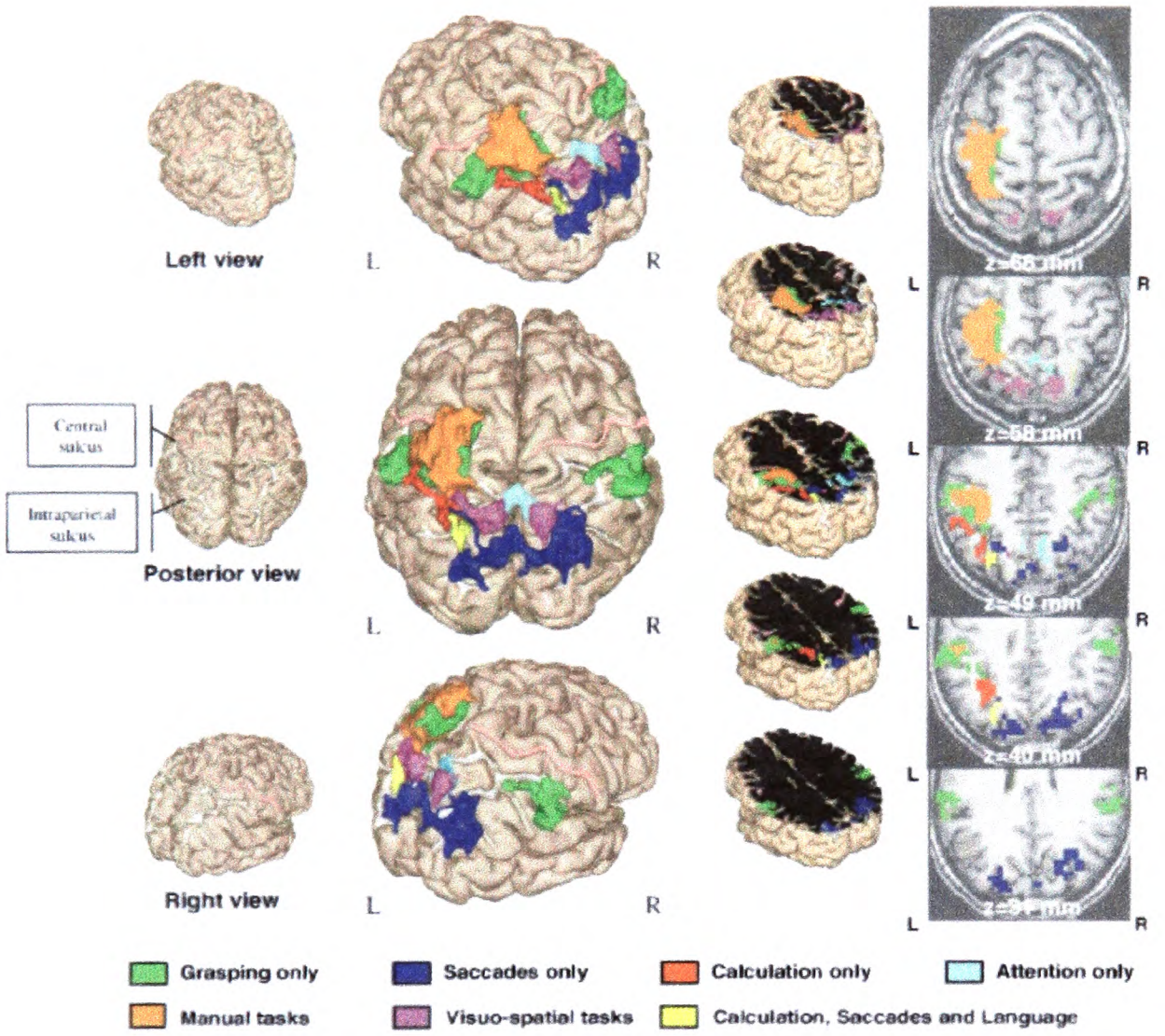



**Figure 1-5:** Localisation of parietal activations specific to grasping only, saccades only, calculation only, attention only, manual tasks, visuospatial tasks and calculation, saccades and language. Left: three-dimensional view on a transparent brain as seen from a superior posterior viewpoint; right: axial slices in MNI space. The figure is taken from Simon et al. (2002).

Selective activation for grasping and pointing was reported in the left anterior IPS extending into the SPL and postcentral sulcus with a posterior extension into the horizontal segment of IPS and an anterior extension into the central sulcus. Bilateral activation of the SPL, dorsal to the posterior horizontal segment of the IPS was common to all visuospatial tasks (grasping, pointing, saccades and attention). Interestingly, they also detected an area of overlap between the calculation and the phoneme detection task in the left posterior segment of the IPS.

Several recent studies have investigated the role of the parietal lobes in number representation and calculation. Pinel, Dehaene, Riviere, & LeBihan (2001) for instance showed a patchwork of areas including the intraparietal sulci that were active in a number comparison task. The neuroimaging literature on calculation will be reviewed in detail in chapter 7.

### *1.4.6 The role of the posterior parietal cortex in humans*

In summary, the posterior parietal cortex combines signals from different modalities including vision, audition and somatosensation as well as signals derived from vestibular apparatus and signals indicating eye position and eye velocity. Although attention may be a major part of its function, the posterior parietal cortex is not only devoted to the direction of attention in space. Rather, it seems to play a role in many other cognitive functions such as eye movements, motion processing, spatial and non-spatial working memory, mental imagery, mental rotation, alertness and calculation, to name only a few.

Furthermore, within the posterior parietal lobe there is evidence for regional specialisation. The superior parietal lobe has been implicated in limb and body representation while the inferior parietal lobe seems to be of great importance for visuo-spatial representation. Also, within the inferior parietal lobe the supramarginal gyrus (and anterior part of IPS) is often activated by motor related tasks in contrast to the more posterior angular gyrus (and posterior IPS) that is mainly activated by visuospatial tasks.

## *1.5 Acalculia*

As mentioned above, brain damage to the parietal lobes can lead to an impairment in number processing and/or calculation abilities. Acalculia is the term given to this

deficit. As Boller & Grafman (1983) point out, the term acalculia actually stands for a complete inability to calculate. However, in most reported cases of acalculia the ability to calculate is not totally lost and therefore strictly speaking the term dyscalculia would be more appropriate. Nevertheless, the term acalculia will be used here, as generally in the literature, for any disturbance of number processing or calculation.

Acalculia has not only been reported after parietal injuries but also after lesions in other brain areas such as the frontal lobes (Delazer & Butterworth, 1997), temporal lobes (Warrington, 1982), the thalamus (Cohen & Dehaene, 1995) or basal ganglia (Hittmaier-Delazer, Semenza, & Denes, 1994). Nevertheless, as early as 1918 Peritz suggested that areas in the parietal lobes play a key role in representing numbers and calculations. In general, this has been supported by data from patients and by recent neuroimaging studies.

This section will give a brief overview of the history of acalculia. It will then show that numerical skills can indeed be independent of other cognitive skills. Subsequently, patients will be presented in whom various subcomponents of numeracy skills are impaired, thus shedding light on the potential cognitive architecture of number processing. The section will close with evidence for parietal involvement in number representation and calculation solely drawn from patients.

### *1.5.1 History of Acalculia*

Jackson & Warrington (1986) estimated that between 7 and 20 % of patients show acalculic symptoms following cerebral lesions. Despite this frequency, the systematic study of acalculia commenced much later than the study of patients with aphasia. One reason suggested by Boller & Grafman (1983) might be that "until fairly recently the ability to calculate remained a luxury monopolised by a restricted

elite of highly educated persons and by the merchants" (p.206). Also, acalculic symptoms, while debilitating, are often less obvious without testing than language impairments. Another reason might have been the general belief that an impairment of calculation abilities is secondary to an impairment in some other cognitive functions. This belief was widely accepted at the turn of the 19th century. Pierre Marie (1906) (Boller & Grafman, 1983), for example, pointed out that an impairment or complete loss of calculation abilities is found as a normal accompaniment of aphasia. Around the same time, however, Lewandowsky & Stadelmann (1908) reported a patient who had almost completely lost his ability to perform oral arithmetic operations such as 4+7 or 11-7 while he could still speak, read, write and understand numbers. Other acalculic patients were soon described by Poppelreuter (1917), Sittig (1917) and Peritz (1918).

Peritz was also the first person who specifically proposed the left angular gyrus as the "calculation centre". Interestingly, he investigated the role played by visualisation or optic mental representation in the process underlying calculation. He suggested a "quasi-spatial" determination of numbers and inferred that the process of calculation must always be visually based. At the same time he did not consider defects of spatial visualisation or visuospatial-constructive deficits themselves as relevant factors in acalculia.

The Swedish neurologist Henschen (1919, 1920) was the first to employ the term "acalculia" in the context it is used today. He differentiated between disturbances of number recognition, number meaning, number sense and a deficit in carrying out arithmetical operations. According to Henschen, calculation deficits are clearly related to an inability to copy and to agraphia for numbers. Henschen was the first researcher to identify different components of calculation disturbances.

Furthermore, he postulated specific centres for pronunciation of numbers, reading numbers and writing numbers. For instance he pointed out the significance of the left angular gyrus for agraphia and acalculia.

One of the most important early researchers on acalculia is Hans Berger. He (1926) described two forms of acalculia: (1) primary or pure acalculia, which is not clearly related to other cerebral disturbances and (2) secondary acalculia caused by an impairment of attention, a loss of immediate or delayed memory or language disturbances.

In 1936, Guttman reported a patient who knew multiplication tables and could carry out simple arithmetical calculations, but had great difficulty with number estimation and number knowledge. He concluded that calculation deficits might be due to some disruption in the fundamental processes of quantity and magnitude estimation which had become perturbed as a result of structural or functional anomalies affecting visual brain regions. In contrast to this visually based theory of calculation deficits, researchers such as Krapf (1937) suggested the importance of sensory-motor elements for calculation.

Gerstmann (1924) described a patient with acalculia, a writing disability (agraphia or dysgraphia), an inability to distinguish right from left, and an inability to identify fingers (finger agnosia). Gerstmann then proposed in 1930 that these four deficits (acalculia, finger agnosia, agraphia and right-left disorientation) did not appear together by accident, but constituted a syndrome, an internally coherent combination produced by disorders of the body schema that specifically involved the hands. This syndrome was subsequently termed Gerstmann's syndrome, and acalculia was often treated as a subcomponent of this syndrome (Kinsbourne & Warrington, 1962; Strub & Geschwind, 1974). The unity and utility of Gerstmann's

syndrome are still debated today. A brief summary of this debate will be given in section 1.5.2.

In 1961, Hécaen and his colleagues described three different types of acalculia: alexic and/or agraphic acalculia, spatial acalculia and anarithmetia. Alexic and/or agraphic acalculic patients have difficulties in writing and reading of numbers and are thus impaired in arithmetic operations. Patients with spatial acalculia show problems with the spatial organisation of written numbers involving difficulty in aligning numbers and carrying them from one column to another. Hécaen (1961) found spatial acalculia to be 12 times more frequent in patients with right hemisphere lesions than in those with left hemisphere disease suggesting some possible correspondence with spatial neglect. Anarithmetia is any case of acalculia that is not clearly related to one of the impairments explained above and seen as the only primary deficit in arithmetical operations. Although written reports by Hécaen and his colleagues do not contain any information on their research methods and therefore their work is of almost an entirely descriptive nature, their contribution was nevertheless remarkable. Boller & Grafman (1983) summarised several main conclusions of Hécaen. First there is often a dissociation between language and calculation abilities. Second there are strong associations between alexia and agraphia for numbers and difficulty in calculation. And thirdly, many acalculic patients had unilateral lesions in the parietal area.

Interestingly, Luria (1966), who described primary acalculia in patients after lesions of their left inferior-parietal division, again favoured a visual approach to acalculia. He suggested that disintegration of visuospatial synthesis may directly lead to marked arithmetical malfunctioning. During the following years, acalculia was mostly perceived as being secondary to disturbances of language. Benson &

Denckla's article (1969), for example, discusses the methodological problem of ascertaining the very existence of calculation disturbances which might often be erroneously diagnosed while the true underlying defect is aphasia. Collignon, Leclercq & Mahy (1977) even state that calculation deficits can always be attributed to disruption in other functions, e.g. language disorders or constructional apraxia.

Today, it is clear that calculation skills can be seen as largely independent of general intellectual skills such as language (Cipolotti & van Harskamp, 2001). The evidence for independent numerical skills will be discussed in section 1.5.3.

### *1.5.2 Gerstmann's syndrome*

Gerstmann (1924) worked as a neurologist in the Viennese university clinic when he first introduced the concept of a disturbed "body schema" ("innere Anschauung des eigenen Körpers", page 1010), i.e. a disturbed internal representation of one's own body. Gerstmann argued that knowledge of one's own body was necessary in order to understand another body. In 1924, Gerstmann described a 52 year-old woman with finger agnosia, agraphia, left-right disorientation and acalculia. He was convinced that the underlying disturbance in acalculia and the three other elements of this tetrad is a disturbed body schema. Among the symptoms of Gerstmann's syndrome acalculia was in fact the last to be included and is the one for which the relationship with the concept of "body schema" appears least obvious. Interestingly, Gerstmann (1924, 1930) suspected that a disturbance in body schema leading to the four symptoms described above is caused by a focal lesion in the area of the left angular gyrus, thus leading to a high diagnostic value of Gerstmann's Syndrome. It is remarkable, that Gerstmann reached this focal anatomical conclusion at a time when there was very little general knowledge about the functions of the parietal lobe, and despite having a rather inadequate patient sample, came to this focal

anatomical conclusion. Today, it is universally accepted that functions of PPC include not only the representation of external space but also that of personal space, i.e. the disposition of a subject's own limbs and body.

In the past Gerstmann's syndrome has been much debated on several grounds. First, some researchers such as Stengel (1944) supported Gerstmann's view of one basic underlying deficit ("Grundstörung"), but suggested that the underlying deficit was a spatial disorientation rather than a disturbance of the body schema.

Furthermore, whether Gerstmann's syndrome with its four symptoms is a distinct entity has been much debated. Several authors (Benton, 1961; Poeck & Orgass, 1966) have questioned its very existence and have tried to cast doubt on its diagnostic value and theoretical importance. They found that incomplete combinations of the Gerstmann symptoms are far more frequent than the full syndrome. Poeck & Orgass (1966), for example, examined 50 patients, in which all of Gerstmann's symptoms were strongly associated with aphasia. Consequently they claimed that the associations between the four symptoms are no closer than associations between symptoms and other deficits lying outside the syndrome.

The neuroanatomical basis of the Gerstmann's syndrome, and thus its diagnostic value, has often been questioned. Benton (1959), Critchley (1966) and Brusa et al. (1960) showed that the syndrome can be produced by lesions in non-parietal areas of the brain. However, Heimburger, DeMyer & Reitan (1964), demonstrated that all patients with the full Gerstmann syndrome invariably had large lesions which involved the superior temporal and supramarginal gyri as well as the angular gyrus of the left hemisphere.

More recently several case reports of Gerstmann's syndrome patients have been published (Roeltgen, Sevush & Heilman, 1983; Varney, 1984; Mazzoni,

Pardoni, Giorgetti, & Arena, 1990), all clearly indicating a lesion in the territory of the left angular and supramarginal gyri. Additionally, Morris et al. (1984) in their cortical stimulation study of an epileptic patient produced an isolated Gerstmann's syndrome by stimulating an area located in the transition between the angular and supramarginal gyri. There is now strong evidence supporting Gerstmann's assertion from more than 70 years ago that lesions in the left inferior parietal lobe, particularly in the angular gyrus, can lead to Gerstmann's syndrome (Benton, 1992).

Mayer et al. (1999) reported a pure case of Gerstmann syndrome with a subangular lesion. Interestingly, their patient HP was also impaired on mental rotation. Thus, Mayer et al. (1999) concluded that the common cognitive denominator of Gerstmann's syndrome is an impairment in the mental manipulation of images and not in the body schema. Although the neuroanatomical foundation of Gerstmann's syndrome has been verified, the debate about the nature of the cognitive deficit continues.

Recently, the existence of a developmental Gerstmann's Syndrome has been suggested in children (Fayol, Barrouillet, & Marinthe, 1998). Generally, children classified as having this disorder exhibit poor handwriting and spelling skills, and difficulty with math functions, including adding, subtracting, multiplying, and dividing. Most cases are identified when children reach school age, a time when they are challenged with writing and mathematical exercises. An inability to differentiate right from left and to discriminate among individual fingers may also be apparent.

### *1.5.3 Evidence that numerical skills are independent of other cognitive skills*

For a long time, calculation abilities were seen as a subcomponent from general cognitive skills. But several individuals with very limited intelligence who display exceptional calculation skills have been described in the literature ('savant

syndrome'; Kelly, Macaruso, & Sokol, 1997), thus showing that calculation skills can be largely independent of general cognitive skills.

The short review of the history of acalculia showed that for a long time the main recurrent argument against the independence of numerical skills of other cognitive abilities was its frequent association with aphasia. Acalculia is indeed often accompanied by aphasia (Poeck & Orgass, 1966). However, cases of acalculia without aphasia have been reported (Cipolotti & van Harskamp, 2001) and there is ample evidence that calculation skills can be independent of general spoken language skills.

Hermelin & O'Connor (1990), for example, describe a case of an autistic boy with total developmental aphasia. He was unable to speak or understand spoken language, but could write and read numerals, add, subtract, multiply and divide large numbers. He also displayed a remarkable ability to generate and recognise factors and primes far more quickly than an adult with a mathematics degree. This case shows that verbal abilities are unnecessary for the development of even a high level of number skills.

Additionally, several patients with semantic dementia and with preserved number processing skills have been presented. In general, patients with semantic dementia manifest a loss of the meaning of words, they make semantic errors and their speech often lacks content. Cappelletti, Butterworth, & Kopelman (2001) for example described a 65 year-old former banker who was severely impaired in verbal tests assessing semantic memory while his numerical understanding was intact. This highlights the independence of numerical knowledge from other categories in semantic memory. Interestingly, the opposite pattern has been reported as well. Cipolotti, Butterworth, & Denes (1991) for instance reported a patient with a

complete loss of meaning for numbers larger than 4 who nevertheless showed preserved knowledge for a large number of other semantic categories at the same time.

Furthermore, calculation skills seem to be largely independent of short term memory skills. For instance, Butterworth, Cipolotti, & Warrington (1996) reported a patient with impaired auditory short term memory who nevertheless showed normal performance in auditorily presented addition and subtraction problems. This suggests that auditory short term memory span has little influence on calculation abilities.

In summary, there is evidence for numerical skills being independent of general cognitive skills, short term memory, semantic memory and language ability, thus strongly supporting the view that acalculia can be regarded as a primary deficit caused by specific forms of brain damage.

### *1.5.4 Subcomponents of numeracy skills*

Research on patients with impairment in their numerical processing has not only shown that acalculia can appear as a primary impairment following brain insult. It has also highlighted that there are subcomponents of numerical skills that can be impaired selectively in patients. In this section a brief overview of acalculic patients who are impaired in certain subcomponents will be given.

There is strong evidence from neuropsychological studies that numeracy skills can be divided into two functionally independent subcomponents: number processing and calculation. Several studies (e.g. Cipolotti & de Lacy Costello, 1995; Warrington, 1982) report patients who were severely impaired in calculation, but who had preserved number processing. On the other hand Cipolotti & Butterworth (1995) described a patient with spared calculation skills who was unable to read

numerals aloud, to write numerals to dictation and to transcode from written number names to Arabic numerals. This clearly shows that number processing and calculation skills can be impaired independently. Therefore these impairments will be discussed here separately. Additionally, patterns of impaired processing as well as patterns of impaired calculation can be further subdivided. This section will follow the classification of impairments used by Cipolotti & van Harskamp (2001).

*1.5.4.1 Patterns of impaired number processing*

According to even a basic information processing approach an impairment can either be caused on the input or the output side of a computational process. For higher cognitive functions such as language skills this dichotomy is exemplified by a distinction between impairment of language comprehension and production. With respect to numerical processing there is evidence that both number production and number comprehension can be impaired selectively and independently.

A large body of research is concerned with number reading and writing and transcoding between the different formats of numbers (Arabic digits, written number words, spoken numbers, groups of dots, Roman format). McCloskey et al. (1986, 1990), for example, described several patients (HY, JG, RR and AT), who showed high error rates in reading aloud written Arabic numerals while their understanding of Arabic numerals, as shown for example in number comparison tasks, was unimpaired.

Cipolotti et al. (1994) reported a patient (DM) who was impaired in writing Arabic numerals to dictation. For example, when he heard "one thousand nine hundred and forty five", he wrote 1000,45. His number reading, however, as well as his number comprehension was intact. Several authors (e.g. Deloche & Seron, 1982; McCloskey, Sokol, Goodman-Schulman, & Caramazza, 1990) have studied

extensively the types of errors made by patients impaired in number production. These analyses led to the development of models suggesting separate routes for number processing which will be discussed in section 1.6.

Research on patients with impairment of number comprehension began much later than research on impaired number production. Nevertheless, several patients have been reported with severe difficulties in understanding numbers (Cipolotti & van Harskamp, 2001). Cipolotti et al. (1991) for example asked their patient (CG) her age and all she could answer was "*I am a middle aged woman.*" (pg. 2628). Another patient (NR, Noël & Seron, 1993) showed very impaired performance in matching spoken number names to the corresponding Arabic numerals and in number comparison. Interestingly, he also performed very poorly when he was asked to indicate the magnitude of an Arabic numeral on an analogue scale, thus indicating that he did not understand the meaning of the numbers.

There have been several reports suggesting that loss of number comprehension might be modality specific (Cipolotti & van Harskamp, 2001). For instance, Cipolotti (1995) described a patient (BAL) who was severely impaired in reading aloud single Arabic numerals while at the same time he could read aloud letters, words and written number names.

Current research is investigating whether number comprehension impairments could be selective for certain subsets of numbers. Patients have been reported who displayed particular difficulties with certain numbers or number ranges. Patient CG (Cipolotti et al., 1991) for example could not deal with numbers larger than 4 while JC (Weddel & Davidoff, 1991) exhibited difficulties particular to numbers 7 and 9.

Table 1-2 is taken from Cipolotti & van Harskamp (2001) and gives an overview of patients with number processing impairment from whom neuroradiological data were reported and who were not suffering from progressive degenerative conditions.

**Table 1-2:** Summary of patients with number processing impairment (adapted from Cipolotti & van Harskamp, 2001)

| **1. Number production impairments** | | | |
|---|---|---|---|
| | Patient | ✋ | Lesion site |
| ***Impairments in Reading aloud Arabic numerals*** | HY (McCloskey, Sokol, & Goodman, 1986) | R | L temporo-parietal CVA |
| | JG (McCloskey, Sokol, & Goodman, 1986) | R | L temporo-posterior CHI |
| | AT (McCloskey, Sokol, Goodman-Schulman, & Caramazza, 1990) | R | L CVA |
| | YM (Cohen & Dehaene, 1991) | R | L temporal tumour extending into the L parietal lobe and the lower part of the splenium |
| | JS (Sokol & McCloskey, 1988) | R | L temporo-parietal CVA |
| | JE (McCloskey, Sokol, Goodman-Schulman, & Caramazza, 1990) | R | L parieto-occipital CVA |
| | JE (Cohen, Dehaene, & Verstichel, 1994) | R | CHI, involving lateral aspect of the posterior half of L hemisphere |
| | GOD (Cohen & Dehaene, 1995) | R | L PCAI, affecting calcarine cortex, lingual and fusiform gyrus |
| | SMA (Cohen & Dehaene, 1995) | R | L PCAI, affecting calcarine cortex, lingual and fusiform gyrus and L thalamus |
| | ZA (Delazer & Girelli, 1997) | R | Large L MCA CVA |
| | ZA (Benson & Denckla, 1969) | R | L CVA |
| | ZA (Benson & Denckla, 1969) | R | L posterior parietal tumour |
| ***Impairments in Writing Arabic numerals*** | DM (Cipolotti, Butterworth, & Warrington, 1994) | R | L parietal CVA |
| | CK (Delazer & Denes, 1998) | R | L fronto-temporo-parietal and perisylvian CVA |
| **2. Number comprehension impairments** | | | |
| | Patient | ✋ | Lesion site |
| | RH (Macaruso, McCloskey, & Aliminosa, 1993) | L | L parietal tumour with mass effect toward the temporal horn and body of the L lateral ventricle |
| | STH (Warrington, 1982) | L | L posterior temporal and L occipito-temporal CVA |
| | BAL (Cipolotti et al., 1995) | R | L parietal AVM |
| | JC (Weddel & Davidoff, 1991) | R + L | CVA, involving mildly dilated L lateral ventricle and possibly R parietal |
| | CG (Cipolotti et al., 1991) | R | L fronto-parietal CVA |
| | SE (Delazer & Butterworth, 1997) | ? | L frontal infarct |

Table only includes patients from whom neuroradiological data were reported and who were not suffering from progressive degenerative conditions. L : left; R: right; ✋: handedness ; CVA : cerebrovascular accident; CHI : closed-head injury; MCA : middle cerebral artery; PCAI : posterior cerebral artery infarct; AVM : arteriovenous malformation; ? : not reported

*1.5.4.2 Patterns of impaired calculation*

As mentioned above, not only number production and/or comprehension can be impaired after brain insult, but calculation skills can also be compromised. Again, most researchers suggest that calculation skills can be fractionated into different and functionally independent components (Remond-Besuchet et al., 1999; Cipolotti & van Harskamp, 2001). Warrington (1982), for example, stated that the arithmetic fact system, calculation procedure system and calculation symbol processing system can be disrupted selectively. She therefore divided calculation into three major components: operational processing, arithmetic facts and calculation procedures. Patients have been described whose calculation performance could be construed to reflect selective deficits to each of these major aspects of calculation.

Caramazza & McCloskey (1987), for example, described two patients (WF, DL) with difficulties in processing operational signs who did not show an impairment in understanding numbers, retrieving arithmetic facts or carrying out calculation procedures. Laiacona & Lunghi (1997) reported a patient (EB) who was unable to differentiate between arithmetical signs.

While patients with difficulties in understanding arithmetical signs are relatively rare, many parietal lobe patients present with an impairment in arithmetical fact retrieval. Warrington (1982) first described a patient (DRC) who, after a left parietal intra-cerebral haematoma, still possessed an intact concept of quantity but his performance of simple addition was severely impaired. His performance of subtraction and multiplication was equally bad. Warrington was the first to conclude from this case that knowledge of arithmetical facts (e.g. of single-digit multiplication) can be impaired separately from knowledge of arithmetical operations.

Recently several reports on patients seem to indicate that the four different basic arithmetic procedures (addition, subtraction, multiplication, division) can be impaired selectively. Delazer & Benke (1997), for instance, described patient JG. After developing a left parietal glioblastoma, she was diagnosed with Gerstmann's syndrome. While she was fine with multiplication, she showed impaired addition, subtraction and division.

Van Harskamp & Cipolotti (2001) investigated a patient (FS) after a left cerebral vascular incident. His number transcoding skills were intact, but he was severely impaired in carrying out simple addition, while multiplication and subtraction was flawless. Table 1-3 gives an overview of patients with selective impairments of arithmetical facts.

**Table 1-3:** Selective impairments/preservations of arithmetical facts (adapted from Cipolotti & van Harskamp, 2001)

| | **Patient** | ∗ | - | + | ÷ |
|---|---|---|---|---|---|
| ***Subtraction impairment*** | MAR (Dehaene & Cohen, 1997) | ✓ | × | ✓ | × |
| ***Subtraction preservation*** | RG (Dagenbach & McCloskey, 1992) | × | ✓ | × | - |
| | (Lampl, Eshel, Gilad, & Sarova-Pinhas, 1994) | × | ✓ | × | × |
| | BB (Pesenti, Seron, & Van Der Linden, 1994) | × | ✓ | × | - |
| | HAR (McNeil & Warrington, 1994) | × | ✓ | × | - |
| ***Multiplication impairment*** | GC (Grafman, Kampen, Rosenberg, Salazar, & Boller, 1989) | × | ✓ | ✓ | - |
| | SB, AB, HM, MD, SC, TM (McCloskey, Aliminosa, & Sokol, 1991) | × | ✓ | ✓ | - |
| | BOO (Dehaene & Cohen, 1997) | × | ✓ | ✓ | - |
| ***Multiplication preservation*** | JG (Delazer & Benke, 1997) | ✓ | × | × | × |
| ***Division impairment*** | CB (Cipolotti & de Lacy Costello, 1995) | ✓ | ✓ | ✓ | × |
| ***Addition impairment*** | FS (van Harskamp & Cipolotti, 2001) | ✓ | ✓ | × | - |

∗ : Multiplication; - : Subtraction; + : Addition; ÷ : Division; ✓ : spared; × : impaired; - : not tested.

As can be seen in table 1-3, patients have been described with impairment in subtraction (Dehaene & Cohen, 1997), multiplication (Grafman et al., 1989), addition (van Harskamp & Cipolotti, 2001) and division (Cipolotti & de Lacy Costello, 1995). Moreover, patients with selective preservation of subtraction (Pesenti et al., 1994; Lampl, Eshel, Gilad, & Sarova-Pinhas, 1994) and

multiplication (Delazer & Benke, 1997) have also been observed. On the basis of these dissociations between operation types, several researchers (e.g. Cohen & Dehaene, 2000) have claimed separate or at least different neuronal routes for different operations. Based on their model suggesting separate routes for multiplication and subtraction, Cohen & Dehaene (2000) predicted that it should not be possible to find a patient with impaired multiplication and subtraction with preserved addition; nor should it be possible to have a selective impairment of addition relative to multiplication and subtraction. Various models of numerical processing will be discussed in more detail in section 1.6.

Contrary to the wealth of research on impairment of arithmetical facts there are few studies focussing on selective impairment of arithmetical procedures. Delazer & Butterworth (1997) for example described a patient (SE) who, three weeks after an infarct, could answer simple additions by counting, but was unable to apply a basic principle of addition. He could readily name the next number in the sequence, but he could not add one. Interestingly, he also showed an inverse distance effect in a number comparison task. The authors concluded that this case study implies that numbers have different meanings that can be impaired selectively. Caramazza & McCloskey (1987) reported four patients (VO, DL, WV and HY) with an impairment in multi-digit calculations. They attributed their impairment to defective knowledge of calculation procedures.

Table 1-4 gives a summary of patients with impaired calculation and shows their lesion sites.

**Table 1-4:** Summary of anatomical lesions in patients with arithmetical facts and arithmetical procedures impairments (adapted from Cipolotti & van Harskamp, 2001)

| | Patient | ✋ | Lesion site |
|---|---|---|---|
| **1. Impairments of arithmetical facts** | | | |
| ***Impairments of arithmetical facts***<br><br>(∗): only multiplication was tested;<br><br>(+, ∗): only addition and multiplication were tested;<br><br>(∗, ÷) : only multiplication and division were tested; | DRC (Warrington, 1982) | R | L posterior parieto-occipital haematoma |
| | PS (Sokol & Ruzecki, 1991) (∗) | R | L CVA |
| | GE (Sokol, McCloskey, Cohen, & Aliminosa, 1991) (+, ∗) | R | L frontal CHI |
| | JB (McCloskey, Aliminosa, & Sokol, 1991) (+, ∗) | ? | L CVA |
| | JG (McCloskey, Aliminosa, & Sokol, 1991) (+, ∗) | ? | L CVA |
| | JG (Cohen & Dehaene, 1994) (+, ∗) | R | L parieto-temporalAVM |
| | BE (Hittmaier-Delazer, Semenza, & Denes, 1994) (∗,÷) | R | L basal ganglia CVA |
| | DA (Hittmaier-Delazer, Sailer, & Benke, 1995) | R | Extensive white matter lesions |
| | TA (Girelli, Delazer, Semenza, & Denes, 1996) (∗, ÷) | ? | Wide perisylvian CVA |
| | TL (Girelli et al., 1996) (∗, ÷) | ? | Wide perisylvian CVA |
| | MC (Whetstone, 1998) (∗) | R | L parietal tumour, extending to the splenium |
| ***Selective impairment of subtraction facts*** | MAR (Dehaene & Cohen, 1997) | L | R inferior parietal CVA |
| ***Selective preservation of subtraction facts*** | RG (Dagenbach & McCloskey, 1992) | R | Large L posterior CVA |
| | HAR (McNeil & Warrington, 1994) | R | L parieto-occipital glioma |
| | HAR (Lampl, Eshel, Gilad, & Sarova-Pinhas, 1994) | R | L parieto-temporal CVA |
| ***Selective impairment of multiplication facts*** | SB (McCloskey, Aliminosa, & Sokol, 1991) | ? | R frontal CHI |
| | AB (McCloskey, Aliminosa, & Sokol, 1991) | ? | L CVA |
| | HM (McCloskey, Aliminosa, & Sokol, 1991) | ? | L CVA |
| | MD (McCloskey, Aliminosa, & Sokol, 1991) | ? | R CVA |
| | SC (McCloskey, Aliminosa, & Sokol, 1991) | ? | L CVA |
| | TM (McCloskey, Aliminosa, & Sokol, 1991) | ? | L CVA |
| ***Selective preservation of multiplication facts*** | BOO (Dehaene & Cohen, 1997) | R | L capsulo-lenticular CVA, affecting L lenticular nucleus, head of caudate, internal capsule and insula |
| | JG (Delazer & Benke, 1997) | R | L parietal glioblastoma |
| ***Selective impairment in division*** | CB (Cipolotti & de Lacy Costello, 1995) | R | L parietal & L posterior frontal CVA |
| ***Selective impairment of addition facts*** | FS (van Harskamp & Cipolotti, 2001) | R | Large L CVA involving L middle temporal lobe and left parietal area; extensive damage particularly in the parietal areas including the angular and supramarginal gyri. Only the posterior/superior part of the L parietal lobe is spared. |
| **2. Impairments of arithmetical procedures** | | | |
| | Patient | ✋ | Lesion site |
| | (Luchelli & De Renzi, 1993) | ? | L medial frontal CVA, involving areas 10, 11, 16, 14, 23, 6 and 4 and anterior half of CC |
| | MT (Girelli & Delazer, 1996) | R | L fronto-temporo-parietal CVA |
| | MM (Semenza, Miceli, & Girelli, 1997) | ? | Large hydrocephalus, enlargement of the ventricles, R upper parietal and R dorso-frontal |

Table only includes patients from whom neuroradiological data were reported and who were not suffering from progressive degenerative conditions. L: left; R: right; ✋: handedness ; CVA : cerebrovascular accident; CHI : closed-head injury; AVM : arteriovenous malformation; CC : corpus callosum; ? : not reported

*1.5.4.3 Approximate calculation*

It has been debated whether approximate calculation/estimation could also be an independent subcomponent of calculation abilities that could be impaired selectively. In 1967, Warrington and James asked 29 patients with right hemisphere lesions, 20 patients with left hemisphere lesions and 15 control patient with peripheral nerve lesions to estimate the number of dots tachistoscopically presented to them. The performance of the right hemisphere cases was significantly worse than control patients and no significant differences were found between the left hemisphere and control groups.

In 1982 Warrington investigated patient DRC who, although inefficient and inaccurate at calculation, was unimpaired in tasks involving arithmetical estimation. Dehaene & Cohen (1991) described a patient (NAU) with severe impairment on numerical problems. However, NAU gave responses "approximate" to the correct response in a number knowledge task. On calculation verification task with slightly or grossly incorrect answers he tended to select the slightly incorrect answer. Dehaene & Cohen (1991) interpreted this finding as evidence that the patient had a preserved approximate calculation system and an impaired exact calculation system. Both fMRI studies and ERP studies (Dehaene et al., 1999; Cohen et al., 2000; Stanescu-Cosson, et al., 2000) with normal subjects supported this interpretation showing different patterns of brain activation during approximation than during exact calculation. In addition, normal individuals sometimes show strong discrepancies between arithmetical estimation and exact calculation (Dowker, 1995).

However, so far no patient with the opposite pattern of impairment (spared exact calculation with impaired approximation) has been documented. Furthermore, on the basis of two separate systems one for exact calculation and another one for

approximation/estimation it is difficult to explain why ability in calculation and estimation normally tend to correlate with one another, both in children and adults (Dowker, 1997; Dowker, 1995). Cipolotti and van Harskamp (2001) are likewise cautious about a system for approximate calculation, because to them it is unclear at a theoretical level whether the approximate and the exact calculation system are really functionally separable.

### *1.5.5 Evidence from patients for the role of the left posterior parietal lobe in number representation and calculation*

This short review of the literature on acalculia has made it clear that numerical processing is not a homogenous function. Therefore it would be surprising if there were just one brain area involved in numerical processing. Nevertheless, there is clear evidence for the importance of specific brain regions, the left posterior parietal lobe in particular, in number representation. Grafman, Passafiume, Faglioni, & Boller (1982) for example tested 102 subjects with left anterior, left posterior, right anterior or right posterior lesions on addition, subtraction, multiplication and division. Both left and right hemisphere-damaged patients performed significantly worse than controls for total numbers of problems answered correctly, but those with left posterior lesions performed significantly worse than the other groups.

Several other studies have replicated the finding of left hemisphere lesion predominance in acalculia (Collignon et al., 1977; Dahmen et al., 1982; Jackson & Warrington, 1986). The majority of patients with impairments in number comprehension as well as with deficits in retrieving arithmetical facts in table 1-2 and table 1-4 also presented with lesions involving the left parietal cortex (Cipolotti

& van Harskamp, 2001). These findings clearly indicate the importance of the left posterior cortex for number comprehension and calculation.

## *1.6 Models of number representation and simple arithmetic*

These findings of selective impairments of mathematical subcomponents together with research on numerical processing in general have inspired several models of number processing. These models can be broadly divided into models of number transcoding and models of numerical processing.

### *1.6.1 Models of number transcoding*

The majority of models of number transcoding distinguish between lexical and syntactical processing in number production. They differ markedly, however, in the way in which they suggest that different number formats are transcoded. In models of number transcoding proposed by Cohen & Dehaene (1991) and Deloche & Seron (1982, 1987) transcoding from Arabic to verbal numerals can occur through a direct connection, no abstract code is thought to be necessary. The models have therefore been classified as single "asemantic" route models.

Multi-route models put forward by Cohen, Dehaene, & Verstichel (1994), Cipolotti (1995) and Cipolotti & Butterworth (1995), however, propose independent "semantic" and "asemantic" transcoding routes for number processing. Cipolotti et al. state that transcoding tasks preferentially activate the asemantic transcoding route. Additionally the activation of one of the two routes is thought to inhibit the function of the other route.

### *1.6.2 Models of numerical processing*

The distinction between single and multiple route models also applies to models of numerical processing. Models for numerical processing disagree on whether number

transcoding and calculation are based on a single semantic route or on multiple semantic and asemantic routes. Additionally, they have divergent views on whether the semantic representations are abstract or modality specific.

*1.6.2.1 McCloskey's single semantic route model*

McCloskey (1992) and McCloskey, Caramazza, & Basili (1985) proposed a very influential single semantic route model. In this model, number processing relies on a single amodal representation and three functionally distinct modules. Dedicated mechanisms exist for each type of notation (Arabic, spoken or written verbal numerals). A central calculation system is accessed in all calculation processes independently of the input's format (see figure 1-6). All number formats are converted into modality neutral abstract representations which specify the magnitude of the number and serve as input for the calculation system.

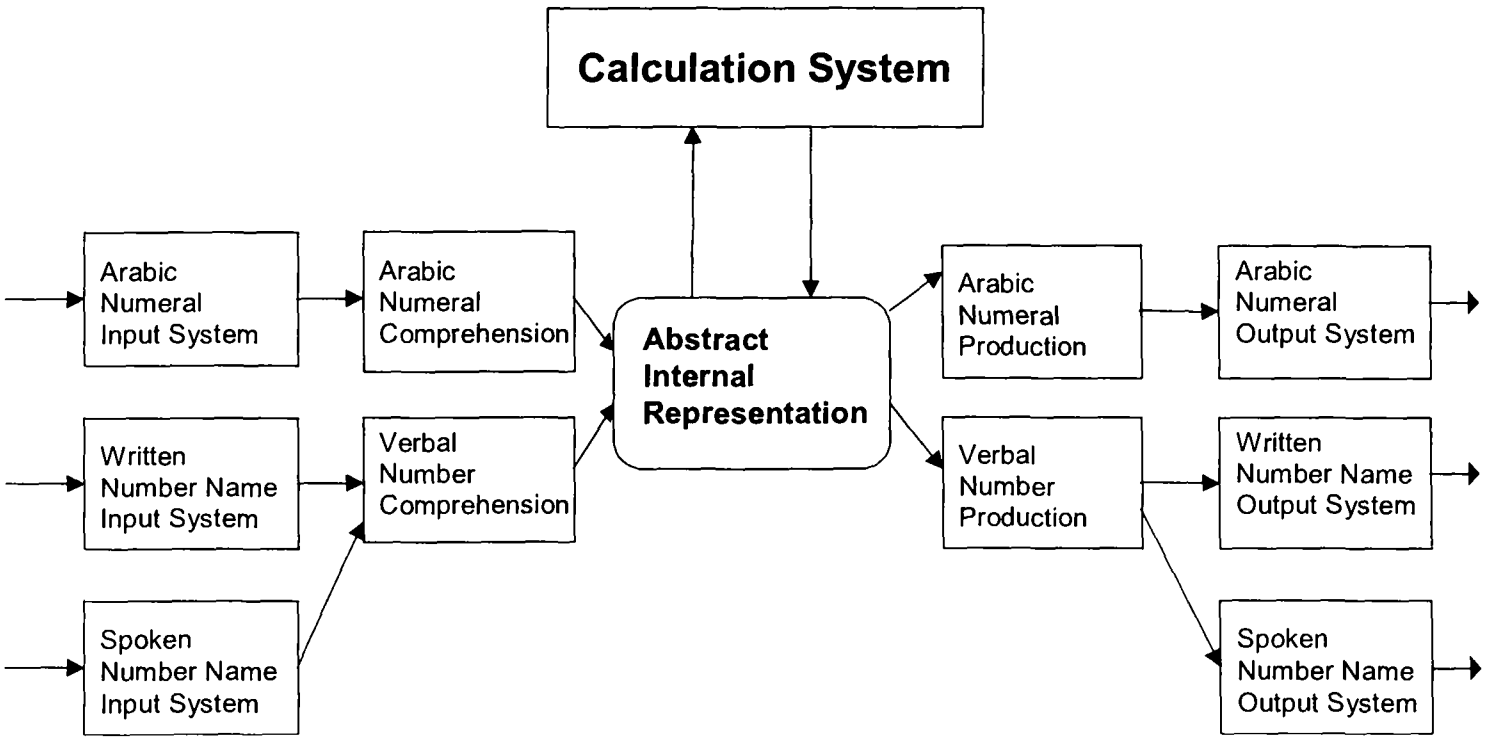



**Figure 1-6:** Schematic representation of McCloskey's (1992) model (redrawn from Cipolotti & van Harskamp, 2000)

The abstract internal representation is supposed to express the basic quantities within a number in a proposition-like language by using powers of ten. In this model, the

Arabic numeral 1989, for example, and the verbal numeral one thousand nine hundred eighty nine both have the same mental abstract representation formally expressed as {1}10EXP3, {9} 10EXP2, {8} 10EXP1, {9} 10EXP0.

One of the main assumptions of this model is that these abstract representations underlie all numerical processes including number transcoding and calculation. This assumption has been refuted by several empirical studies (Deloche & Seron, 1982; Dehaene, 1992) showing that number transcoding tasks do not seem to require a semantic representation. Delazer & Butterworth (1997) criticised McCloskey's model on the grounds that it cannot describe qualitative changes in understanding number meaning. Furthermore, it makes assumptions neither about the conceptual basis of calculation processes nor about the relation between transcoding, calculation and basic numerical abilities such as counting.

*1.6.2.2 Multi-route model by Cipolotti & Butterworth (1995)*

Cipolotti & Butterworth (1995) proposed a multi-route model based on the basic architecture of the McCloskey model, but attempt to overcome its central criticisms by positing an alternative asemantic route for number transcoding (see figure 1-7). This models describes at least four different possible routes for numerical processing, a "semantic" route requiring the mediation of abstract internal representations and three "asemantic" routes that do not involve the generation of a number semantic representation. Which route is activated depends on the task demands (Cipolotti, 1995; Cipolotti & Butterworth, 1995). All routes in figure 1-7 have inhibitory links with each other. Thus, activation of a particular route will automatically inhibit the other routes.

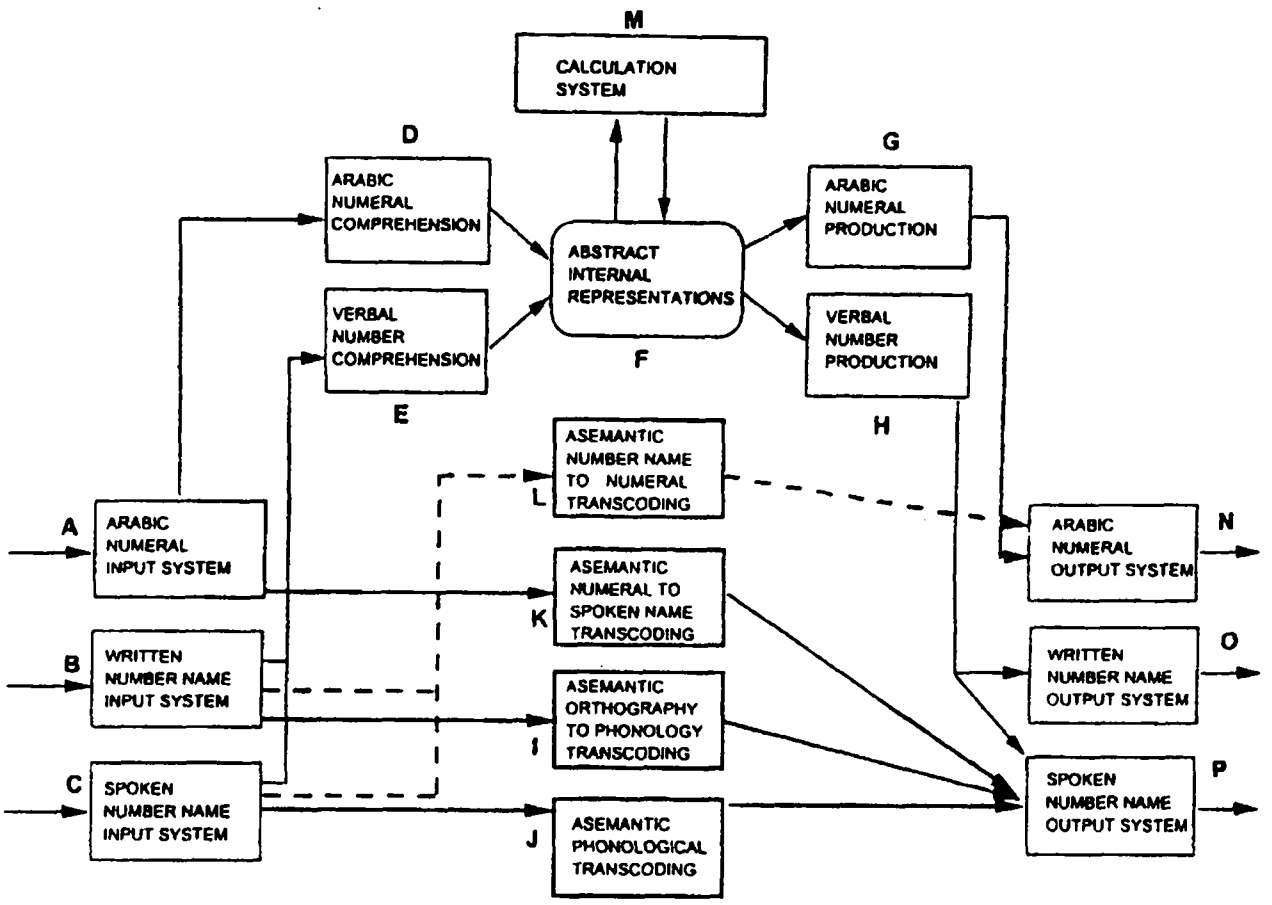



**Figure 1-7 :** Schematic representation of the model of Cipolotti and Butterworth (1995), (taken from Cipolotti & van Harskamp, 2000)

Both, Cipolotti & Butterworth's model (1995) and McCloskey's model (1992) have been challenged, because of their common assertion that the internal representations of numbers are abstract. Several studies, however, present evidence for format-specific instead of abstract representations of numbers (McNeil & Warrington, 1994; Gonzales & Kolers, 1982; Gonzales & Kolers, 1987).

*1.6.2.3 Models with format-specific representations of numbers*

Campbell & Clark (1992) and Campbell (1995) introduced a model with format-specific internal representations based on the encoding complex hypothesis. According to this hypothesis, number transcoding and calculation are based on several modality specific number codes such as verbal, visual and visuospatial codes that can be directly translated without the mediation of an abstract code (see figure

1-8). The evidence supporting this interactive view is, however, still inconclusive (McCloskey, 1992).

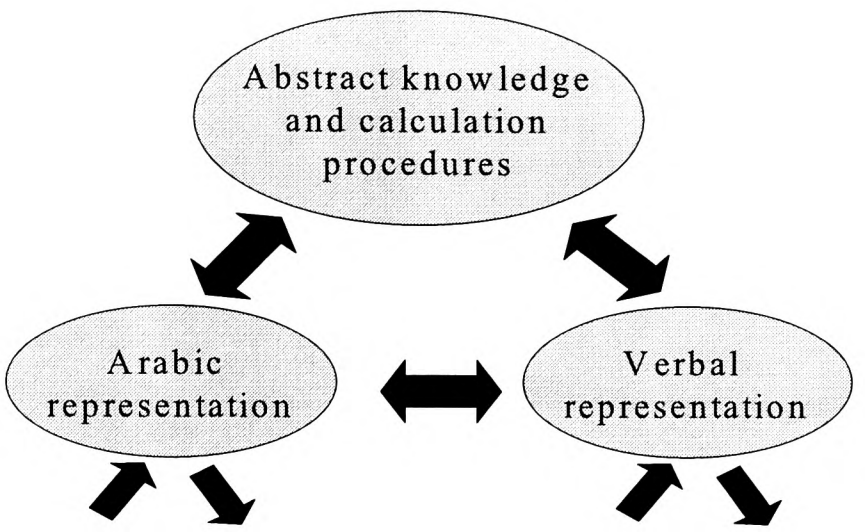



**Figure 1-8:** Schematic representation of the encoding complex hypothesis by Campbell & Clark (1992), redrawn from Dehaene (1992)

Campbell & Clark explicitly consider individual differences in their model. According to them the complex of codes used for a particular task depends on individual preferences.

This approached is echoed by Noël & Seron's (1993, 1995) preferred entry code hypothesis. Noël and Seron reported a patient (NR) who transcoded all numerals initially into a verbal code through which he then accessed his number-related knowledge and quantity representation. This led to their preferred entry code hypothesis claiming that abstract knowledge and calculation procedures are accessed via a unique notation to which all the numerals are initially transcoded (see figure 1-9). This unique notation (for example auditory or visual) varies between individuals.

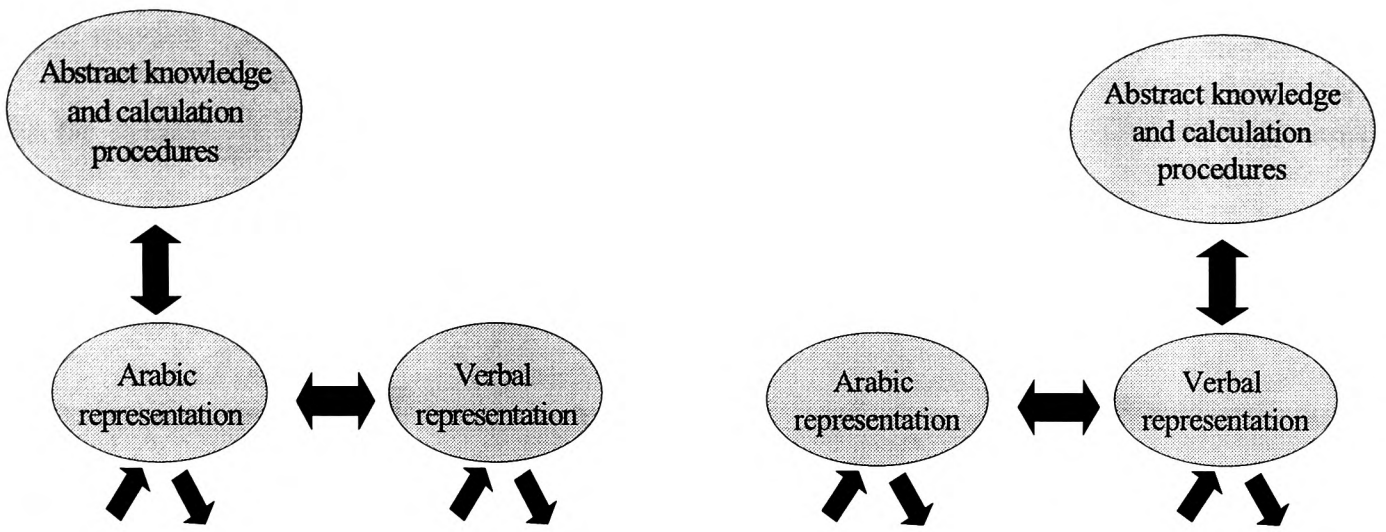



**Figure 1-9:** Schematic representation of the preferred entry code hypothesis by Noël & Seron (1993), redrawn from Dehaene (1992)

*1.6.2.4 Triple code model (Dehaene, 1992; Dehaene & Cohen, 1995)*

The idea of format-specific codes that are involved in more than one numerical operation and activate one another without the mediation of an abstract, modality independent code is consistent with some of the assumptions of an influential model (Dehaene, 1992), the triple code model (see figure 1-10).

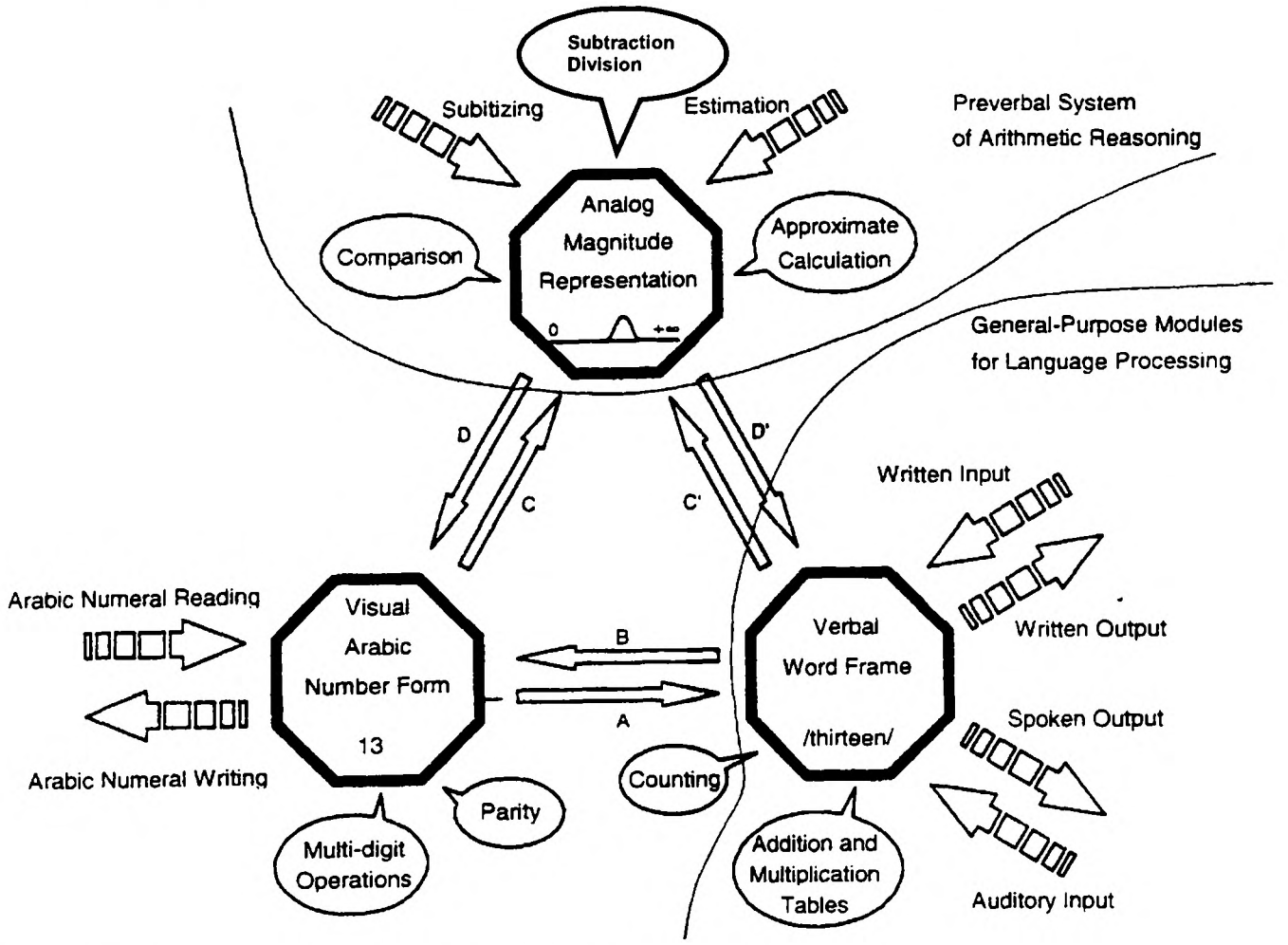



**Figure 1-10:** Schematic representation of the triple-code model by Dehaene (1992), taken from Dehaene (2000), slightly altered

This model is called the triple code model because numerical information is thought to be coded in three formats: an analogical representation, a verbal format and a visual Arabic number form.

In the analogical representation of quantities numbers are represented as distributions of activations on a number line (Dehaene, 2000). The visual Arabic number form is representing numbers as a string of digits (e.g. 15) and in the verbal format numbers are represented as strings of words (e.g. fifteen). These three codes are seen as being directly interconnected, so that transcoding procedures can translate directly from one code to the other.

Each number-processing task is assumed to be based on a fixed set of input and output codes. Number comparison and processes for simple subtraction and division, for example, are thought to operate on the analogical representation along with subitizing, estimation and approximate calculation. The visual Arabic number representation is thought to subserve multi-digit calculation and parity judgement. The verbal word frame is described as the obligatory code for the retrieval process of rote arithmetical facts such as simple addition and multiplication.

Although there is no abstract semantic component assumed in this model, the analogue magnitude component is thought to have a semantic function. Dehaene & Cohen (1997) suggested two basic routes for simple arithmetic problems: firstly, a direct asemantic route specialised for storing and retrieving rote verbal knowledge of arithmetic tables (multiplication problems and single digit addition); secondly, an indirect semantic route, specialised for quantitative processing (such as subtraction, division and complex addition). This suggestion is based on evidence of a double dissociation in two acalculic patients (BOO and MAR). BOO was impaired in multiplication by rote memory while his subtraction was preserved (Dehaene &

Cohen, 1997). In contrast, MAR displayed an impairment of subtraction and other quantity manipulation tasks as compared to multiplication (Dehaene & Cohen, 1997).

The status of addition and division in the triple code model is in principle more ambiguous. For addition, two parallel circuits are claimed to be available: rote verbal retrieval or strategical quantity manipulations. Therefore Cohen & Dehaene (2000) put forward the claim that it should never be possible to find a patient with impaired multiplication and subtraction, yet relatively preserved addition nor should it be possible to have a selective impairment of addition relative to multiplication and subtraction. Van Harskamp, Rudge, & Cipolotti (2002), however, report a patient (SS) with an impairment of subtraction and simple addition problems with preservation for multiplication facts. The authors interpret this case as contradicting the predictions of the triple code model.

The triple code model has generated a wealth of studies not least because it associates tentative anatomical circuits to each function (see figure 1-11). Cohen & Dehaene (1996) speculate that the inferior occipito-temporal sectors of both hemispheres are involved in the visual identification processes that give rise to the Arabic number form. For the verbal representations of numbers they propose an important role of the left perisylvian areas, while they are convinced that the analogical quantity representations rest upon inferior parietal areas in both

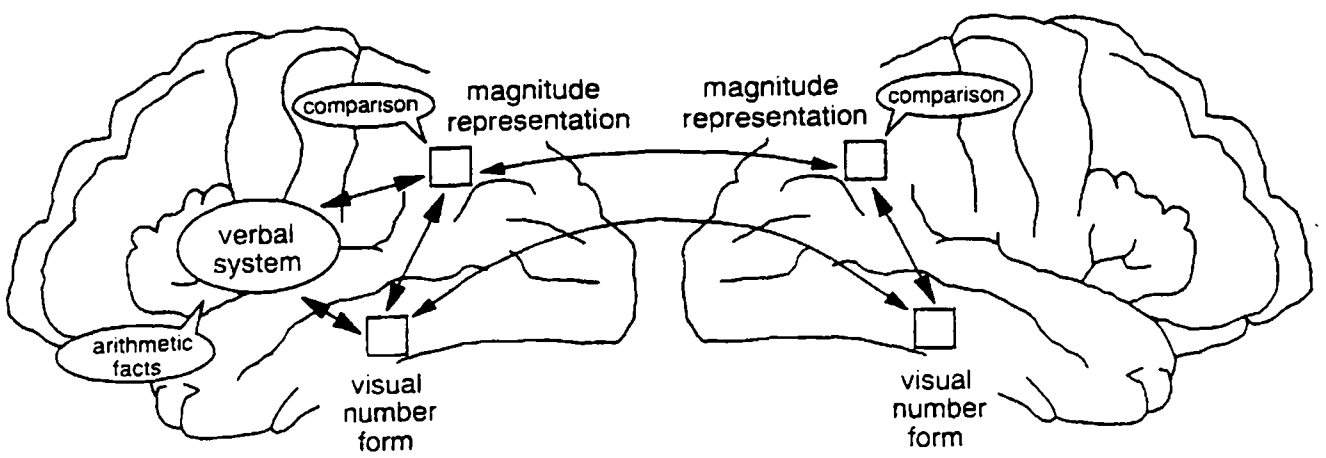



**Figure 1-11:** Schematic diagram of the anatomical substrates of the triple-code model of number processing (taken from Dehaene, 2000)

hemispheres. The assumption of *bi*lateral inferior parietal lobe involvement in magnitude representation seems to be in contradiction to patient data which provide evidence that *uni*lateral inferior parietal lobe lesion can lead to acalculia (see section 1.5). Dehaene (2000), however, is fully aware of this "superficial paradox " (pg. 994) and explains that according to his model most calculation abilities depend upon the verbal code and only the left hemispheres have access to the verbal code. This is supported by evidence from split-brain patients whose right hemispheres can compare numbers which cannot be read aloud (Cohen & Dehaene, 1996; Gazzaniga & Smylie, 1984). Such a pattern also occurs in some children, especially among those with specific language impairments (Donlan & Gourlay, 1999).

### *1.6.3 Evaluation of the contribution of models of numerical processing*

Although many of the models presented above have provided the framework for considerable and important research, the debate on the procedures involved in numerical processing is far from being resolved. None of the models can be seen as a complete and all encompassing model of number processing and calculation. Number processing and calculation procedures, although often perceived as the "easy" part of mathematics in general, are complex procedures based on a large knowledge base of cognitive strategies and principles (Karmiloff-Smith, 1992). Models of numerical processing have to reduce and simplify these varieties of knowledge (Cipolotti & van Harskamp, 2001). Therefore they cannot, and perhaps should not be expected to, account fully for all findings from patient data, imaging studies and cognitive experiments with adults and children.

## *1.7 Summary*

As shown in this general introduction, numerical processing and calculation have a long history. Systematic research on numerical processing and calculation, however, only started a century ago. An important role of areas in the inferior parietal lobes in number processing was soon suggested after studies of patients with difficulties in numerical tasks. This suggestion has been supported more recently by evidence from both studies on patients and neuroimaging experiments. Findings from patient studies have also led to the development of several cognitive models of numerical processing and calculation. In some cases suggestions have been made for neural implementations of these models. Perhaps the most neuroanatomically detailed proposal is Dehaene's (1992) triple code model. An important role for the inferior parietal lobules is central to the model.

This thesis will use the wealth of research on acalculic patients and the parietal lobes as a starting point. It will proceed to investigate the neural foundations of the representation of numbers in normal subjects by using two techniques: transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI).

# 2. Introduction to Methods

In this chapter two neuroimaging methods will be described: functional Magnetic Resonance Imaging (fMRI) and Transcranial Magnetic Stimulation (TMS). These two methods have only recently been developed. Both are based on the usage of magnetic fields. TMS is used to stimulate brain tissue; with fMRI a measure of local brain activity can be obtained.

The history of magnetism is much longer than that of either TMS or MRI. The ancient Greeks and Chinese discovered that certain rare stones, called lodestones, naturally attract small pieces of iron and always point in the same direction when allowed to swing freely suspended by a piece of string (Livingston, 1996). The term magnetism was coined to explain the phenomenon whereby these stones attract iron. Archimedes who lived in the 3$^{rd}$ century BC in Greece is reputed to have used powerful lodestones to pull the nails out of enemy ships thus sinking them.

For many centuries magnetism was considered as a curious natural phenomenon. It was widely used for navigation and it is probably some 4500 years since a precursor to a compass was first developed by the Chinese (Livingston, 1996). Travellers used to carry small portable lodestones that they suspended freely in order to locate north.

Long before magnetism became a tool for research methods and also before the study of magnetic properties became an active field of physical research in the 20$^{th}$ century, magnetism as a "natural power" was used as a "treatment". Since the days of Paracelsus it was believed that magnets possessed specific healing properties (Waxman, 1986).

In the 18th century the Viennese jesuit and astronomist Maximillian Hell treated people with a magnetic steel plate (Livingston, 1996). But it was his student Franz Anton Mesmer who became famous for healing with magnetism. Mesmer was born in 1734 near Lake Constance. He received a medical education and at the age of 40, then in Vienna, he became interested in the effects of magnets on the human body. Mesmer believed in Hell's magnetic therapy and posited that it works because there is a very subtle magnetic fluid flowing through everything which sometimes gets disturbed and needs to be restored to its proper flow (Waxman, 1986). This idea clearly differs from physical magnetism, because Mesmer believed that non-ferromagnetic substances such as paper and glass can be "magnetised". Mesmer eventually discovered that he got the same results without the magnets and concluded that he himself could act as the magnet. Mesmer first came to public attention in Vienna, when he healed Maria Theresa Paradis, daughter of the private secretary to the Empress of the Holy Roman Empire, from blindness (Forrest, 2000). But this triumph was only short-lived. He could not give scientifically satisfactory reasons for Maria's blindness or for the effectiveness of his treatment. Shortly afterwards Maria lapsed back into blindness, Mesmer's popularity declined and he left for Paris. There he re-established himself so successfully as a magnetic healer that King Louis XVI set up a Royal Commission under the presidency of the newly appointed United States Commissioner to France, Benjamin Franklin, to investigate Mesmer's methods (Forrest, 2000). The verdict returned by the Royal Commission was that "the imagination does everything, the magnetism nothing" (Waxman, 1986). Mesmer left Paris and retired to the German countryside. But although his treatment had no scientific basis, his ideas remained influential throughout Europe in

the 19th century and Mesmer is sometimes considered to be the father of hypnosis (Forrest, 2000).

## *2.1 Functional magnetic resonance imaging (fMRI)*

### *2.1.1 History of NMR*

In 1946 the physicists Felix Bloch and Edward Purcell discovered the physical basis of magnetic resonance imaging: nuclear magnetic resonance (NMR). They observed that when certain nuclei were placed in a magnetic field they absorbed energy in the radio-frequency range of the electromagnetic spectrum and re-emitted this energy when the nuclei were tranferred to their original state. Felix Bloch and Edward Purcell were awarded the Nobel Prize in Physics in 1952 for the discovery of NMR (Levinovitz & Ringertz, 2001).

During the 1950s and 1960s NMR was mainly used for spectroscopy, an important non-destructive analytic method in the study of the composition of chemical compounds. It was not until the late 1960s and early 1970s that NMR was used to study tissue and its rise as an important technique in medical diagnosis began (Rinck, 1993).

### *2.1.2 Principles of nuclear magnetic resonance and MRI*

NMR is the behaviour of atomic nuclei in a stable magnetic field when a second magnetic field is applied. One of the fundamental physical properties of the subatomic particles protons and neutrons is that they possess an angular momentum which is often referred to as "spin". Only very specific quantized values of the angular momentum of protons and neutrons are possible. All atomic nuclei have a net angular momentum that is determined by the number of constituents and neutrons. Any nucleus with an even atomic mass number and an even charge number has no spin.

Hydrogen-1 has one of the strongest of all nuclear moments and therefore is an excellent candidate for biomedical spectroscopy and imaging (Jezzard & Clare, 2001). For the hydrogen nucleus in a stable magnetic field (B0) only two energy states exist: parallel and anti-parallel to the magnetic field. The time it takes the nuclei to align themselves with the stable magnetic field (longitudinal magnetisation) is called T1 (Rinck, 1993).

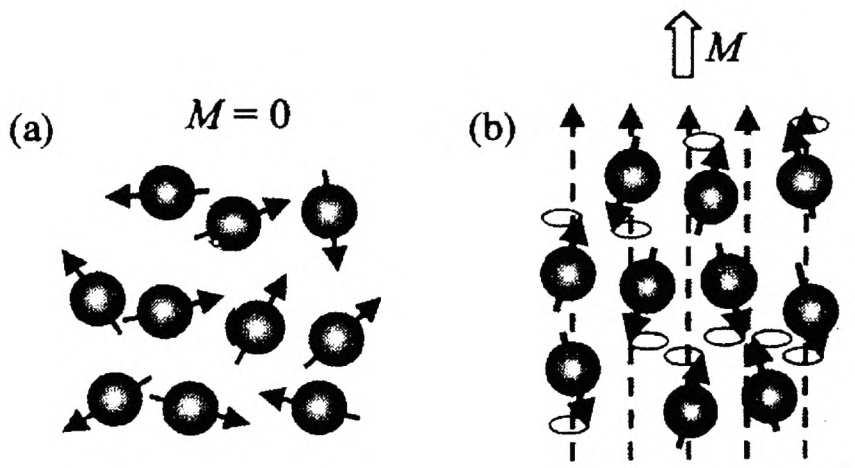



**Figure 2-1:** Alignment of spins in a magnetic field (adapted from Jezzard & Clare, 2001)

In NMR a radio frequency pulse (RF pulse) is applied that produces a second magnetic field (B1) thus changing the spin of the nuclei and perturbing the net magnetisation (M0). According to the classical model, the RF pulse tips M0 by 90 degrees with respect to B0. When the excitation pulse is switched off, the spins start returning to their equilibrium and a signal can be detected (Rinck, 1993). The signal that is received from a homogenous sample in a homogenous magnetic field typically appears as shown in figure 2-2a. It is called free induction decay (FID) of the system. If the magnetic field is not homogenous, different parts of the sample experience different field strength and thus different parts of the sample will resonate at different frequencies (figure 2-2b).

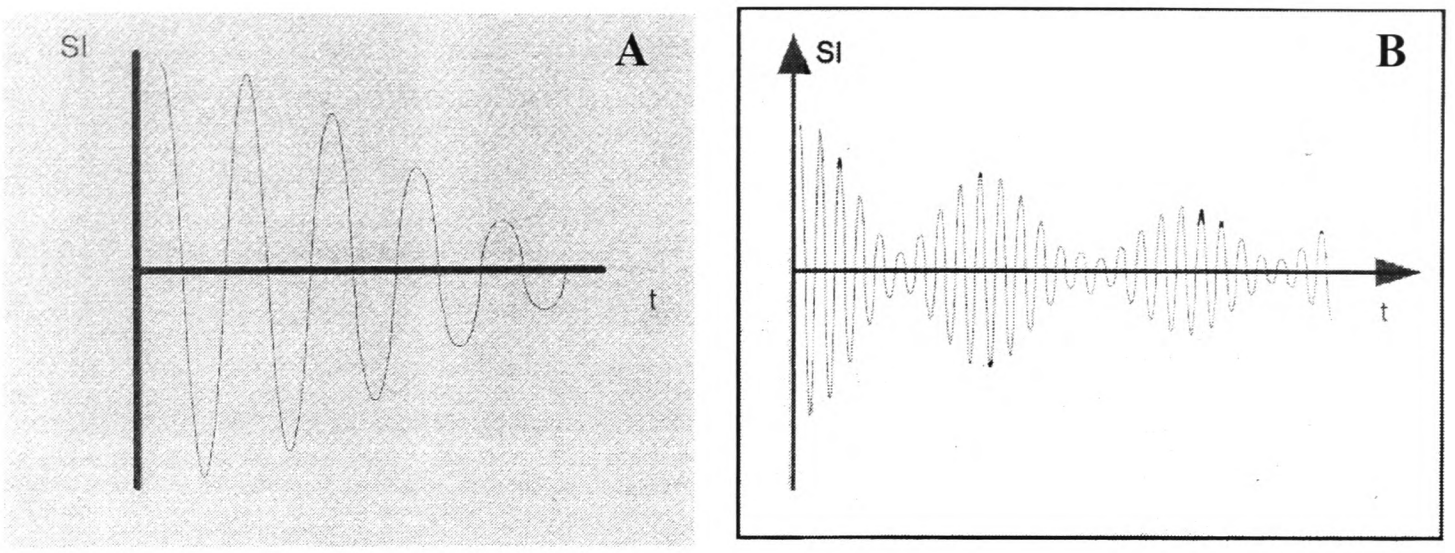



**Figure 2-2:** free induction decay (FID) of homogeneous (A) and inhomogeneous (B) sample (SI = signal intensity; t = time) (from Rinck, 1993)

This resonance frequency (the Lamor frequency) is specific for each type of nucleus and changes with the strength of the magnetic field, e.g. Hydrogen-1 nuclei will resonate at 64 MHz in 1.5 Tesla and at 128 MHz in 3 Tesla (Jezzard & Clare, 2001). The detected signal is analysed for its frequency components by use of a Fourier transform and can then be used to plot the distribution of certain nuclei in a substance.

### *2.1.3 Contrasts*

Various magnetic resonance image contrasts can be used to detect differences in tissue distribution. A proton density structural magnetic resonance image (MRI), for example, involves the measurement of the distribution of the single proton nucleus of hydrogen-1. Variations in the relative concentrations of water protons provide contrast between structures thus allowing, for example, clear discrimination between bone (little water, i.e. low MR signal) and brain (approximately 70% water, i.e. high MR signal) (Matthews, 2001) or types of tissue that differ in water content. An example of an image obtained with the proton density contrast is shown in figure 2-3a.

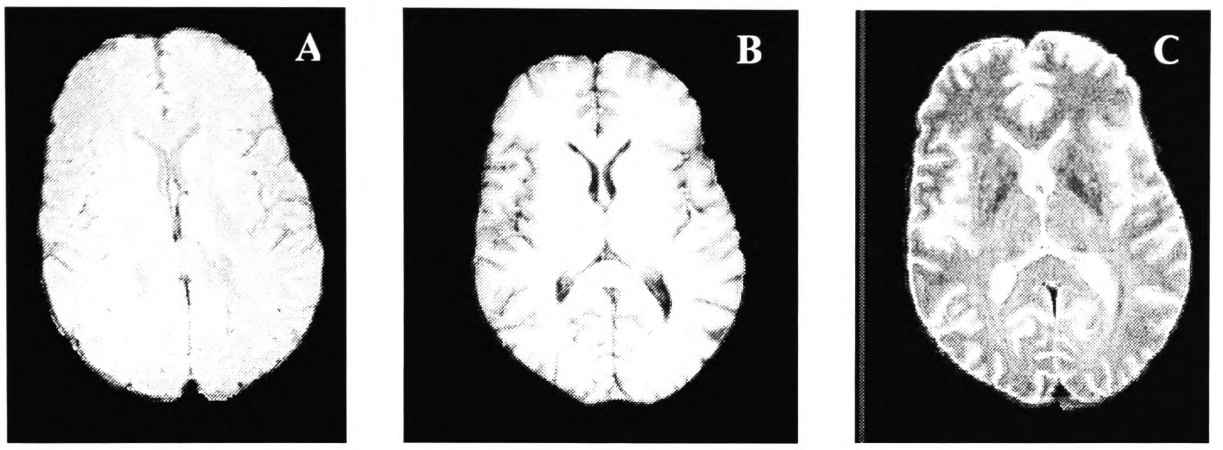



**Figure 2-3:** Examples of proton density image (A), T1-weighted image (B) and T2-weighted image (C)

Useful contrast in MR images comes not just from density of hydrogen-1 but from contrasts caused by fundamental NMR processes known as relaxation. After excitation by the RF pulse the dephased spins will tend to return to their equilibrium distribution (M0) in which there is no magnetisation orthogonal to the stable magnetic field B0 (no transverse magnetisation) and the longitudinal magnetisation (i.e. alignment with the stable magnetic field B0) is at its maximum value. It is observed that in the absence of the radio frequency pulse the transverse magnetisation decays toward zero with a characteristic time constant T2 and the longitudinal magnetisation returns towards the equilibrium value M0 with a characteristic time constant T1 (Rinck, 1993). This process is called relaxation. T1 contrast results from differences in T1 relaxation time between different tissue types, while T2 contrast results from differences in T2 relaxation times (see figure 2-4).

T1 and T2 values are fixed for a given nucleus in a given environment. They vary with field strength of B0. At 3 Tesla, for example, it takes grey matter 1200 ms but white matter only 860 ms to reach T1 relaxation; T2 relaxation times at this field strength are 110 ms for grey matter and 80 ms for white matter (Jezzard & Clare, 2001).

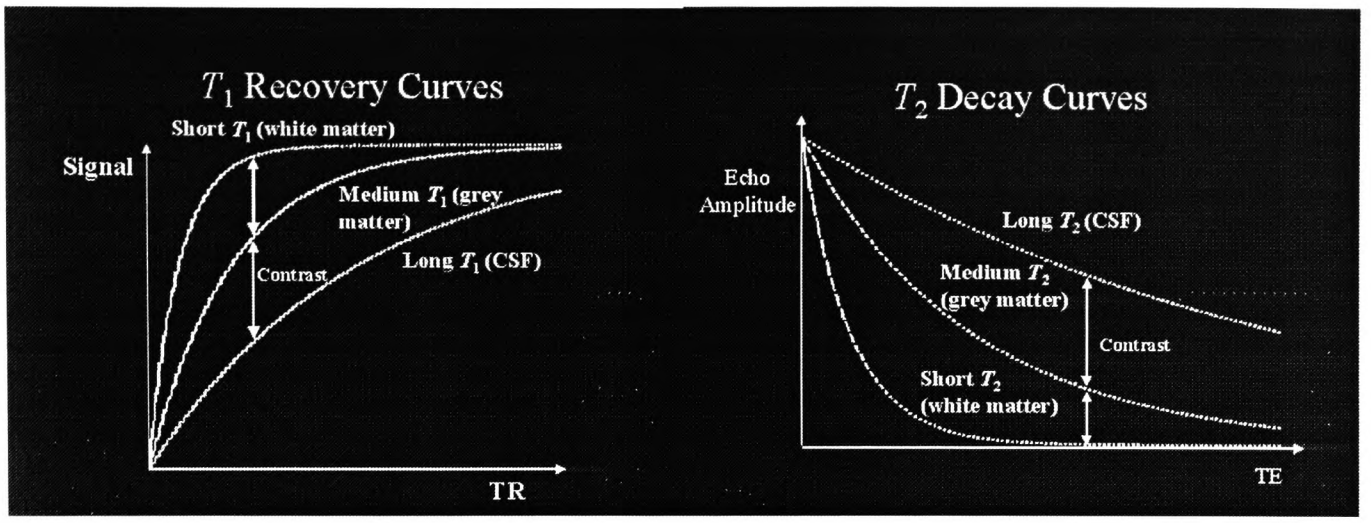



**Figure 2-4:** T1 recovery curves and T2 decay curves for white and grey matter and cerebrospinal fluid (CSF)

There is a third relaxation time called T2* which can be observed in a so-called spin echo sequence. In this sequence the nuclei aligned along B0 first get excited by a radio frequency pulse of 90° (figure 2-5a), i.e. its magnetic field is orthogonal to B0. In consequence the spins de-phase (figure 2-5b; clockwise movement of the small black arrows). Then the system is exposed to a second radio frequency pulse lasting twice as long as the first pulse, called the 180° pulse. It results in a magnetic field that is also orthogonal to B0, but its direction is opposite to the field generated by the 90° pulse.

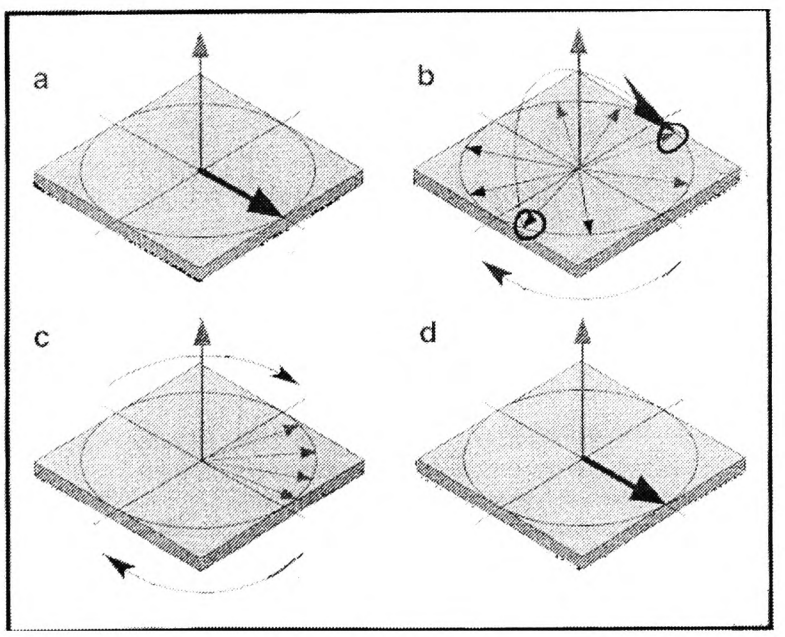



**Figure 2-5:** Schematic spin-echo sequence (from Rinck, 1993)

The spins are refocused by this 180° pulse (figure 2-5b; curved arrow shows the refocusing of one spin; refocused spins: small grey arrows). The faster spins are first behind the slower spins, then catch up with them (figure 2-5c). The spins line up

again and a net magnetisation results. This recovery of the initial magnetisation is termed an electron spin echo (figure 2-5d) (Rinck, 1993).

This 90°-180° pulse sequence is called a spin echo (SE) sequence. In multi-echo sequences (see figure 2-6) several 180° pulses are transmitted, thus creating echos of decreasing amplitude. Echo time (TE) is defined as the time of the second echo.

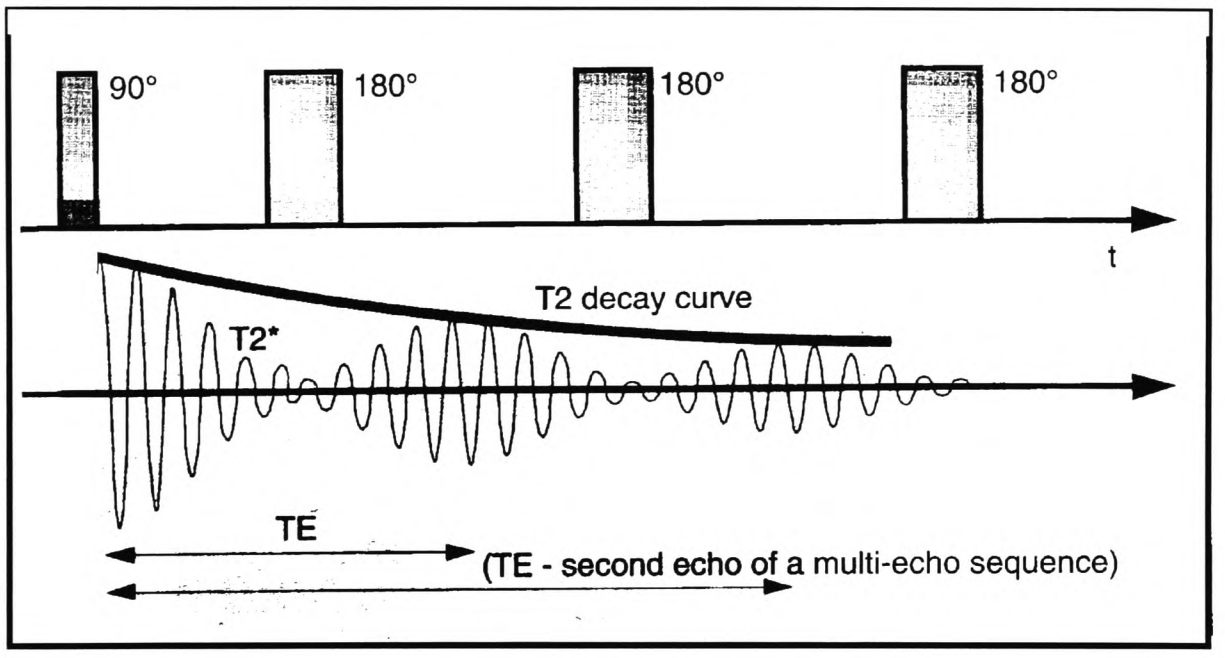



**Figure 2-6:** The value of T2* can be obtained from FID while T2 is calculated from the echo amplitudes. Several 180° pulses create echoes of decreasing amplitude (multi-echo sequence) (from Rinck, 1993)

The value of T2* can be obtained from the free induction decay (FID) after the 90° pulse while T2 is calculated from the echo amplitudes (Rinck, 1993) (see figure 2-6).

### *2.1.3.1 BOLD contrast*

While MRI is used to image the anatomical structure of brains, the aim of fMRI is to image changes in brain activity that are related to various cognitive tasks. Local neuronal activity consumes energy that is mainly produced by oxidation of glucose. Therefore maps of local glucose or oxygen consumption, or maps of local blood flow providing oxygen can in principal provide information about neuronal activity in a brain region.

Early imaging experiments showed a change in regional cerebral blood flow while subjects performed a cognitive task (e.g. during mental arithmetic, Roland & Friberg, 1985). Such early experiments measured the distribution of injected or inhaled short half-life radioactively labelled compounds. FMRI, however, is based on measurements of the distribution of molecules intrinsic to the blood. Ogawa et al. (1990) first described a BOLD (Blood Oxygenation Level Dependent) contrast imaging experiment with a report that MR images of cat brain showed signal loss around blood vessels when the animal was made hypoxic. Today most of the fMRI experiments use a contrast related to the amount of oxygen in the blood, the BOLD contrast, to image brain activity. This contrast is not directly based on the density of oxygen but on the distribution of a larger iron-containing molecule in blood: haemoglobin. Using haemoglobin has several advantages. The presence of iron atoms in this molecule means that haemoglobin has very good magnetic properties. When oxygen is bound to haemoglobin the molecule alters from being paramagnetic (having significant magnetic effect on its environment) to being diamagnetic (having little effect) (Pauling & Coryell, 1936) (see figure 2-7).

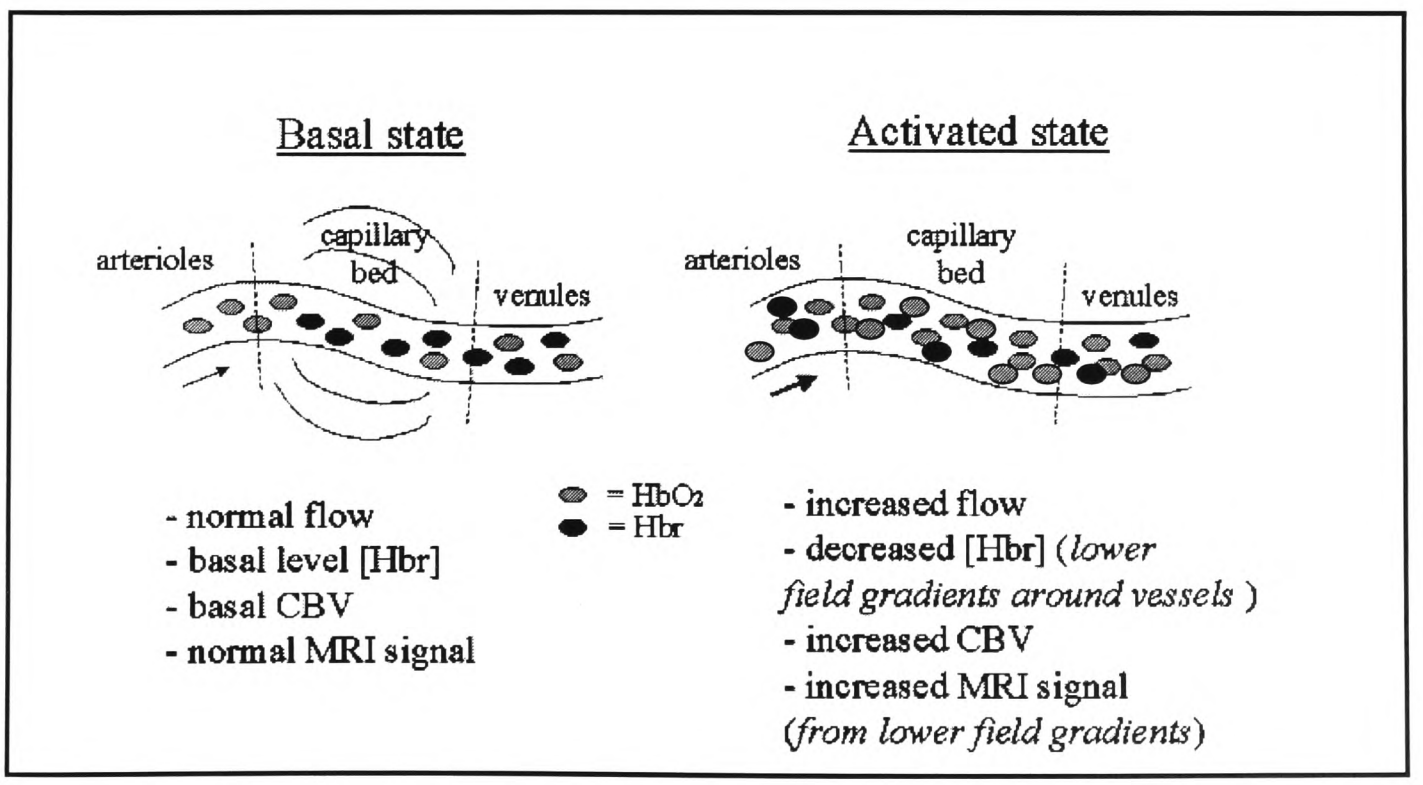



**Figure 2-7:** fMRI BOLD rapid overview

A change in haemoglobin oxygenation therefore leads to changes in the local distortions of a magnetic field. If the oxygenation level of the blood decreases (or more specifically, if fewer oxygen molecules are bound to haemoglobin) it causes the relaxation times of blood (T2* and to a lesser extent T2) to decrease, resulting in slightly lower signal in a T2* weighted image.

BOLD signal changes occur both in the tissue (extra-vascular BOLD effect) and within the vasculature (intra-vascular BOLD effect) (Jones, Brookes, & Moonen, 2001). Although the BOLD signal is widely used, it is, however, still debated how exactly this signal is related to neuronal brain activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). This will be discussed in the next section.

### *2.1.4 BOLD signal and neuronal activity*

Information is transmitted in the brain by neuronal activity. Activation of neurones and establishment of ion potentials in brain cells requires a supply of energy. This energy is used to pump the sodium ions, that enter for membrane depolarisation, out of the cell against an electrochemical gradient to restore the resting membrane potential. Energy is supplied in the form of adenosine tri-phosphate (ATP) generated in the mitochondria. Both short- and long-term regulatory mechanisms are used to maintain a constant concentration of ATP. There are three known ways of ATP production, only one consumes oxygen (Gjedde, 2001). First, ATP can be directly re-synthesised by a biochemical process called hydrolysis of phosphocreatine. This is only efficient for very short time-periods (5-10 s). ATP can also be produced from glucose; this process is called glycolysis. In glycolysis 2 ATP molecules are produced from one glucose molecule by a partial breakdown of glucose to pyruvate. Under aerobic conditions the pyruvate can be oxidised. This process is called

oxidative phosphorylation and it leads to further production of ATP. Oxidative phosphorylation is the most efficient way of energy production; it can produce up to 36 ATP molecules per one glucose molecule. Therefore it can be concluded that the vast part of energy used by neurones is produced by oxidative phosphorylation. This process needs oxygen which is supplied by blood perfusing the tissue. The change in blood oxygenation gives rise to the BOLD (Blood Oxygenation Level Dependent) signal. The measured changes in this signal reflect the changes in energy produced for synaptic activity or a combination of synaptic and dendritic electrical changes, but they do not measure neuronal activity directly (Gjedde, 2001). Two main questions about the origin of the BOLD fMRI signal remain unsolved: first, the quantitative relationship between neural activity and the BOLD contrast, and, second, the nature of the biological mechanism underlying that relationship (Bandettini & Ungerleider, 2001). Increases in blood flow have been shown to be proportional to increases in neural activity (Raichle, 1998). But the BOLD effect reflects changes in blood flow, blood volume and blood oxygenation (Menon, 2001). Recently several groups have found a predominantly linear correlation between neuronal activity and haemodynamic responses (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Rees, Friston, & Koch, 2000). But the BOLD signal might reflect not only the firing rates of the local neuronal population, but also subthreshold activity, simultaneous excitation and inhibition or modulatory inputs that might not evoke spikes (Heeger & Ress, 2002). Logothetis et al. (2001) simultaneously recorded neural and haemodynamic responses (i.e. local field potentials, single- and multi-unit spiking and the BOLD response) in the visual cortex of anaesthetised monkeys. Their findings suggest that BOLD activation might reflect the neural activity related to the input and local processing in an area rather

than the spiking activity commonly thought of as the output of the area. Additionally they showed that the sensitivity of the BOLD signal to changes in neural activity is less than to the local field potential at high levels of neuronal activity (but perhaps not at low levels, see Bandettini & Ungerleider, 2001). Thus, we might only be looking at the tip of the iceberg of brain activity when using BOLD fMRI.

Inhibitory synaptic activity might actually modulate the BOLD response by changing metabolic demand (Arthurs & Boniface, 2002). While Waldvogel et al. (2000) reported inhibitory activity did not result in a BOLD signal at the site of inhibition, Heeger et al. (2000) observed fMRI BOLD signals under conditions that appear to involve inhibitory interactions. Clearly, more work is needed to clarify the coupling of haemodynamic response and neuronal activity.

### *2.1.5 Temporal and spatial resolution of BOLD fMRI*

The potential temporal and spatial resolution of each BOLD fMRI experiment depends on various factors, not the least of which is the experimental design. Other factors to be taken into account are the temporal and spatial dynamics of the BOLD response, potential sources of noise and the limitations of the scanner itself.

#### *2.1.5.1 Temporal resolution of fMRI*

FMRI has been used primarily to map human brain areas that are responsible for sensory and cognitive tasks. Menon & Kim (1999) believe it is possible to study the temporal processing in the brain at the second and sub-second time scale. Miezin et al. (2000) estimated from their data that timing offsets of as little as 100 ms were detectable with fMRI in theory.

The BOLD response itself sets limitations in time. Even for a brief stimulus duration the time from initial changes in BOLD signal to the final return to baseline is typically between 12 and 18s. In order to understand the temporal limitations that

go along with using the BOLD contrast it is important to know the temporal dynamics of the BOLD signal itself.

According to Hoge & Pike (2001) the haemodynamic response to neural activity is biphasic (see figure 2-8). Optical imaging (Malonek & Grinvald, 1996) has shown that subsequent to the onset of neural activity the amount of deoxyhaemoglobin in tissue is heightened by an increase in local oxygen consumption which precedes any change in blood flow or volume resulting in a brief hypoxic state. This early hypoxic phase is termed the "initial dip". Recently it has been suggested that the initial dip should be used for imaging, because this might lead to higher temporal and spatial resolution (Kim, Duong, & Kim, 2000). But even at a magnetic field strength of 4T this initial dip reaches only 10% of the amplitude of the familiar positive BOLD signal. The existence of this initial dip, an early negative BOLD response is still controversial in the optical imaging and fMRI literature, because it has not always been found (Menon, 2001).

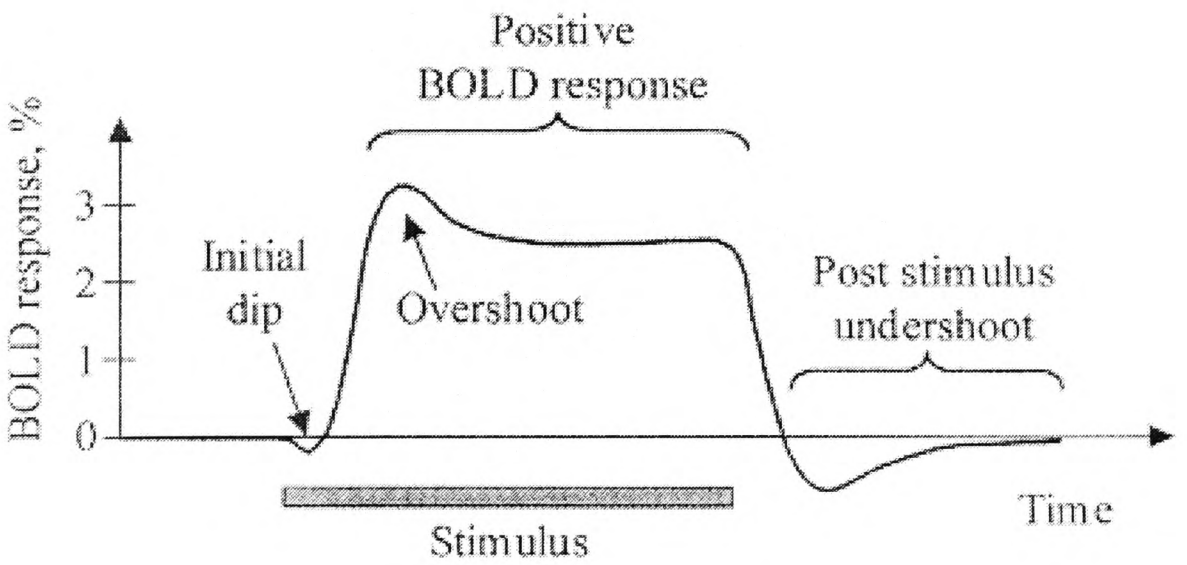



**Figure 2-8:** Schematic representation of the temporal dynamics of the fMRI BOLD response to a period of stimulation (from Hoge & Pike, 2001)

The BOLD response evolves the early "dip" over the first second following a stimulus and subsequently increases progressively over the next 2 to 4 s. Then there

is a vasodilation of the arterioles which results in a large fractional increase in cerebral blood flow (CBF). This CBF increase overcompensates for the increase in local oxygen consumption and leads to blood hyper-oxygenation and the standard positive BOLD response. After the stimulus is removed the BOLD signal decreases over a few seconds to a level below the initial baseline ("undershoot") from which it slowly recovers over a couple of seconds. Thus even for a brief stimulus duration the time from initial changes in BOLD signal to the final return to baseline is typically between 12 and 18 s (Matthews, 2001). As long as the shape of the haemodynamic response can be accurately estimated the lag does not need to dictate the useful temporal resolution of the technique, as the expected time course can simply be convolved with the expected haemodynamic response function (HRF).

There is, however, evidence that the temporal dynamics of the BOLD signal might vary between subjects and between regions. Miezin et al. (2000) suggested that vascular responses might not be completely consistent between different brain areas. Additionally, the time it takes the BOLD signal to peak varies in part depending on how far the BOLD signal is rising. Menon & Goodyear (2001) suggest that if time-dependent modulation occurs (such as learning, alterations in strategy, errors and habituation), the time to peak can actually vary from 1 s to 6 s. It is therefore the variability in haemodynamic response latency rather than the lag itself that limits the temporal resolution of fMRI (Bandettini, 1999).

Ogawa et al. (2000) suggest that using the amplitude differences of the BOLD response can help to extract timing information about processing in the brain and might lead to higher temporal fMRI resolution.

The importance of temporal resolution of fMRI depends partly on the paradigm design chosen. In a conventional block design (see section 2.1.8.1), for

example, the BOLD signal is averaged over blocks of typically 20 - 40 s. In an event-related design, however, the aim is to detect signal changes to single events separated in time (see section 2.1.8.2). Limits of temporal resolution therefore apply largely to event-related designs. As the fMRI experiment in this thesis, described in chapter 7, uses a block design, the optimal event-related paradigm design for maximal temporal resolution will not be discussed here (for details see Friston, Zarahn, Josephs, Henson, & Dale, 1999).

*2.1.5.2 Spatial resolution of fMRI*

The spatial resolution of each fMRI experiment depends on at least two factors: the chosen resolution of the scan and the spatial resolution of the haemodynamic response.

Currently an in-plane resolution of 2-5 mm is commonly used with a slice thickness between 2-10 mm. This results in a volume element (voxel) being interrogated that is between 8 and 250 $mm^3$. Menon (2001) states that typically there might be $10^5$ neurons and $10^8$ synapses in a 1 $mm^3$ voxel, thus fMRI measures the net activity of large populations of neurons.

Unfortunately, the haemodynamic response is not spatially very specific to the areas of neural activity. Malonek & Grinvald (1996) used the metaphor of the brain "waters the whole garden for the sake of one thirsty flower". The desired response is that of capillaries embedded within the cortex which are well co-localised with the site of neural activity. But large BOLD signal changes seem often to be associated with large draining veins, while tissue areas have low BOLD signal changes (Kim, Tsekos, & Ashe, 1997). These larger draining veins spatially "blur" the activation responses, because they may be up to several millimetres away from the site of neural activity. Recently, Duong et al. (2001) showed for orientation

columns in the visual cortex that the perfusion signal is precisely restricted to the neural site of activity, and that the extended point spread function reported with optical imaging and the hyperoxygenation phase of BOLD likely indicates the effect of large draining veins.

These limits of the potential spatial resolution depend on the signal to noise ratio of each measurement and the spatial scale of the vascular supply. This vascular supply is not regulated at the scale of individual neurons and might be limited to 0.5 to 1.5 mm in humans depending on field strength (Menon & Goodyear, 1999).

Also, Menon & Goodyear (2001) argue that the lateral connections in the horizontal layers of the cortex as well as the vascular density should be expected to limit the resolution in fMRI and these can vary in different areas of the brain. On top of these anatomical differences between brain areas there is strong evidence that the spatial scale of functional specialisation varies between regions (Churchland & Sejnowski, 1988).

Despite all these limitations Engel et al. (1997) argue that the fMRI signal could be localised to within 1.1 mm at a magnetic field strength of 1.5 Tesla. And Menon and Goodyear (1999) were successful in resolving ocular dominance columns within human visual cortex by fMRI.

### *2.1.6 BOLD signal reliability*

There is some variability in the exact form of the BOLD response from one subject to the next and from one brain region to another. Nevertheless the signal used in BOLD fMRI seems to be reliable enough to justify general conclusions. For instance, Ojemann et al. (1998) demonstrated reproducible patterns of activity associated with a speech production task in a comparison across studies produced in multiple labs employing both fMRI and PET (Positron-Emission-Tomography).

Also, Miezin et al. (2000) showed that the BOLD response for an individual subject within a fixed region is highly reproducible in timing, shape and amplitude within the same experimental session.

### *2.1.7 Susceptibility effects*

There are possible sources for artefacts both in the stable and applied magnetic field. First, the magnet may not be completely homogenous. Second, there may be effects of geometry and composition of the sample being imaged on the local magnetic field, e.g. in the human head. There are regions of greatly varying magnetic susceptibility, i.e. even if a perfectly uniform static magnetic field is applied to the head the nuclei in different regions within the head will not at all experience the same field. This effect is particularly severe at the boundaries between sample components with very different magnetic susceptibilities such as the air/tissue interfaces near the sinuses and can generate image artefacts (Frackowiak, 1997).

### *2.1.8 Experimental design*

There are several potential problems for imaging studies in comparison to behavioural experiments that should be considered carefully when designing an fMRI experiment. First lying relatively still in a scanner for 30-60 minutes might generate significant fatigue and boredom that might effect the results. Also the scanner itself provides a peculiar physical environment for the subject.

Second, each imaging system generates considerable acoustic noise when acquiring the images. In a scanner with a magnetic field strength of 3 - 4 Tesla the noise level might rise to 90 - 120 dB (120 dB is the sound of a jumbo jet turbine recorded at a distance of five meters). For safety reasons subjects have to wear

earplugs and headphones. This acoustic noise, however, will still distract the subject and can cause brain activation on its own.

There are two general approaches to designing an fMRI experiment (see figure 2-9). Many early fMRI experiments followed the design of PET studies and used block designs.

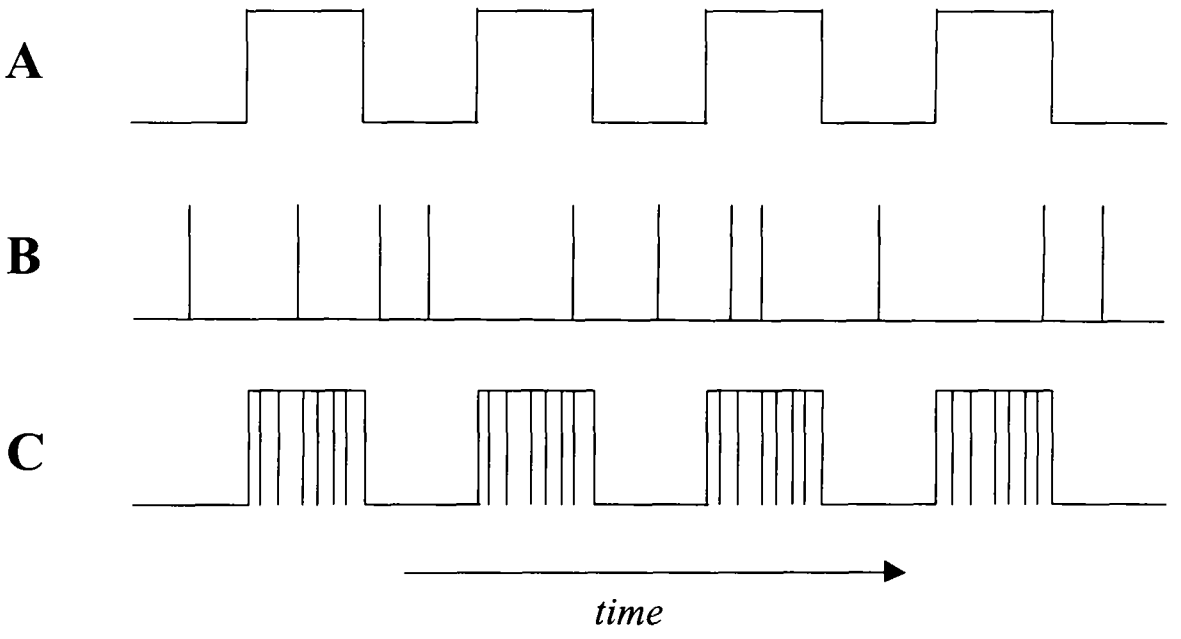



**Figure 2-9:** Schematic representation of three different design options for fMRI experiments
A: block design, B: event related design, C: mixed design

*2.1.8.1 Block design*

In a block design two (or more) different types of trials are presented in blocks (a simple example might be a visual display either on or off for a given time interval). The activations will then be averaged across each block of trials and subsequently these averaged activations between different blocks will be compared (cognitive subtraction; see Friston, 1997). There are, however, several problems with this approach. Due to the averaging across periods in a block design any comparisons made between periods will be confounded by sustained as well as transient changes in activity. fMRI methods are currently limited to finding relative changes between task comparisons. So the crucial question is how to best design task comparisons in a given study. The resting state of the human brain (i.e. simple fixation or eyes closed)

often used as comparison with the task of interest might involve a specific set of mental operations itself (Gusnard & Raichle, 2001).

*2.1.8.2 Event-related design*

Traditionally cognitive neuroscientists have employed procedures that enable measurement of individual trials (such as reaction times) or even sub-components of individual trials. Recently an increasing number of fMRI studies have tried to mimic this approach by using an event-related design (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). In this design different types of trials are intermixed on a trial by trial basis. The data are then averaged according to stimulus trial types revealing activity that is time-locked to the onset of individual trial events. This approach only became possible after Dale & Buckner (1997) demonstrated that the BOLD response is predictable and relatively stable across events, even when there is an overlap in the responses to successive events (see figure 2-10). There are several advantages of an event-related design over the traditional block design, including its proximity to traditional cognitive behavioural experiments. Additionally, time-locked averaging should result in an increase of the signal to noise ratio, because the signal of interest is systematically associated with the time-locked event and invariant across trials, while background noise is random (Donaldson & Buckner, 2001).

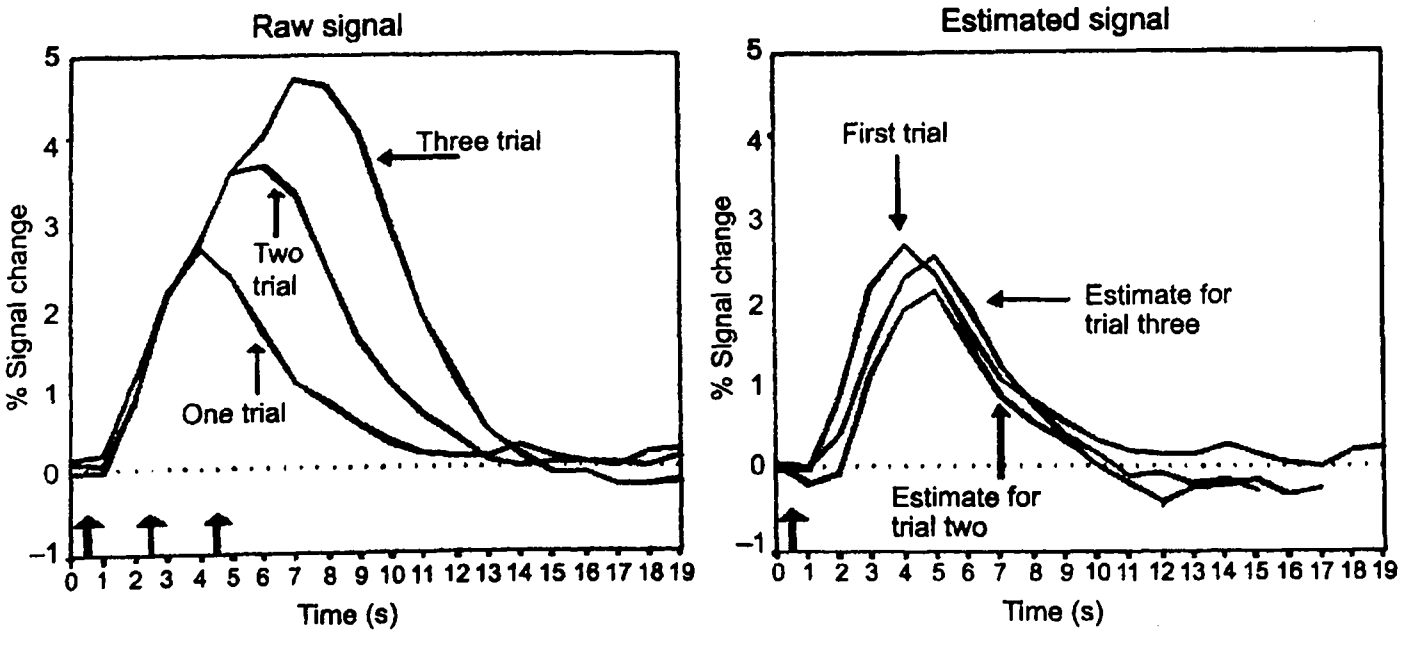



**Figure 2-10:** Linear summation of the BOLD signal. Event-related fMRI data show linear summation of the haemodynamic response in early visual cortex for closely spaced trials (2 s apart) of a 1 s visual checkerboard stimulus (adapted from Dale & Buckner, 1997).

*2.1.8.3 Mixed design*

The cost of using an event-related procedure, in terms of functional meaning of signal changes, is that it is more likely to miss activity that spans across successive trials and that would form part of the summated activity in a block design. Therefore, Donaldson & Buckner (2001) have suggested using a mixed design that combines the advantages of both block and event-related designs (see figure 2-11).

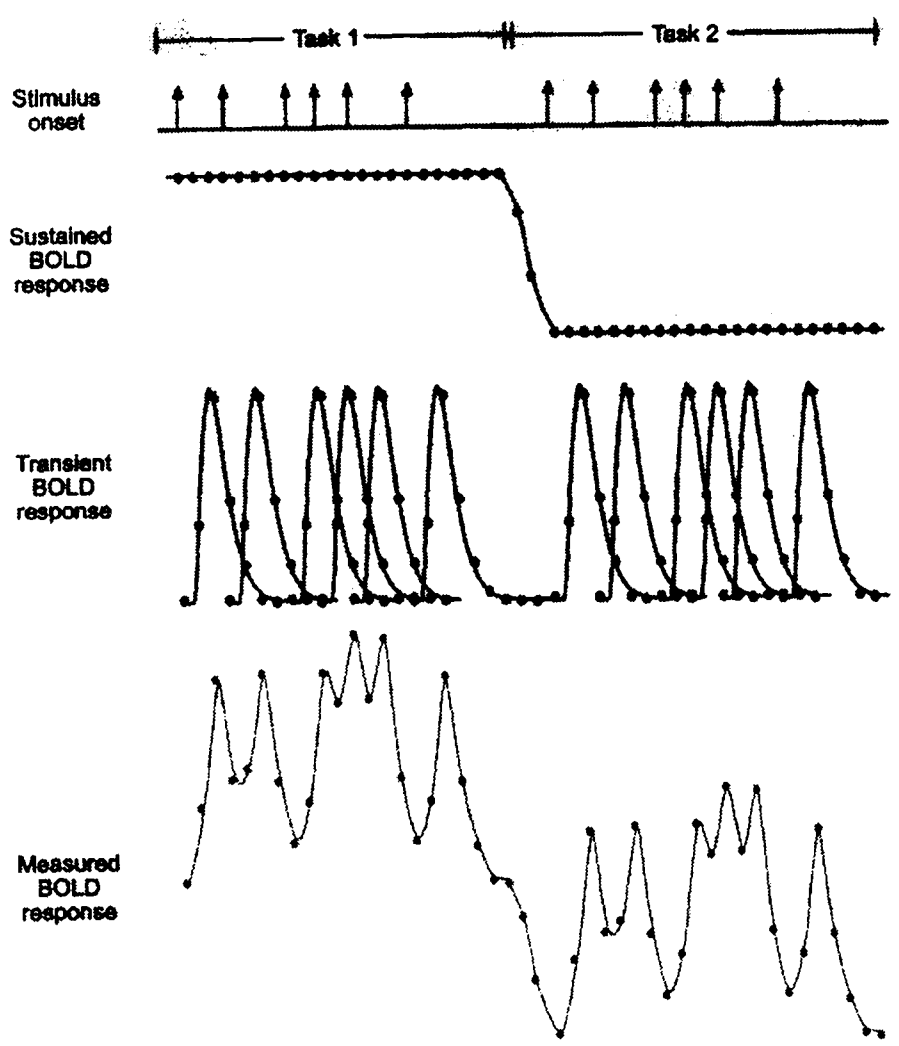



**Figure 2-11:** A representation of the signal measured in a mixed blocked and event-related paradigm. Stimuli are presented in two separate blocks (task 1 and task 2). Two distinct kinds of correlates of activity may occur, a sustained BOLD response that is modulated across the two tasks, and a transient BOLD response that is associated with the individual stimuli. The measures BOLD response will be a linear summation of these different signal changes (from Donaldson & Buckner, 2001).

In a block design any comparisons made between blocks will be confounded by sustained and transient changes in activity while event-related paradigms are typically designed to be sensitive only to transient signal changes. Only with a mixed design is it possible to investigate the role of both transient and sustained activity in supporting the cognitive processes of interest to the experimenter.

*2.1.8.4 Parametric design*

Recently several fMRI studies have used parametric designs. These experiments were typically designed to identify brain areas in which BOLD response changes systematically co-vary with certain characteristic of the stimulus (e.g. the size of a number). This approach circumvents concerns about the validity of "rest conditions" (Owen, Epstein, & Johnsrude, 2001).

### *2.1.9 Safety issues*

There are several safety issues to be considered when carrying out an fMRI experiment. The noise in the scanner from gradient switching can reach levels of 90 to 120 dB thus exceeding safety limits. Currently subjects have to wear earplugs and headphones to reduce the noise level to below the safety threshold. There are two main safety issues in the scanner room itself. Because of the strong stable magnetic field ferromagnetic objects are not allowed into the scanner room. They would fly into the scanner at high speed, possibly injuring the subject severely and potentially also damaging the scanner. For the same reason, subjects with metal parts in their body have to be excluded from the study. Secondly, because considerable electromagnetic radiation is generated in the scanner, conduction loops can generate substantial heat and must therefore be kept away from subjects to avoid burns. A detailed overview of all safety issues to consider in any fMRI study is given elsewhere (Shellock & Kanal, 1996).

### *2.1.10 Image analysis*

In fMRI, data for one volume of the whole brain are acquired not in one three dimensional image, but by scanning successive two dimensional slices through the brain; these slices can be acquired at different angles. Each of the slices is first

processed separately. A single scan volume is made up of individual cuboid elements called voxels (see figure 2-12).

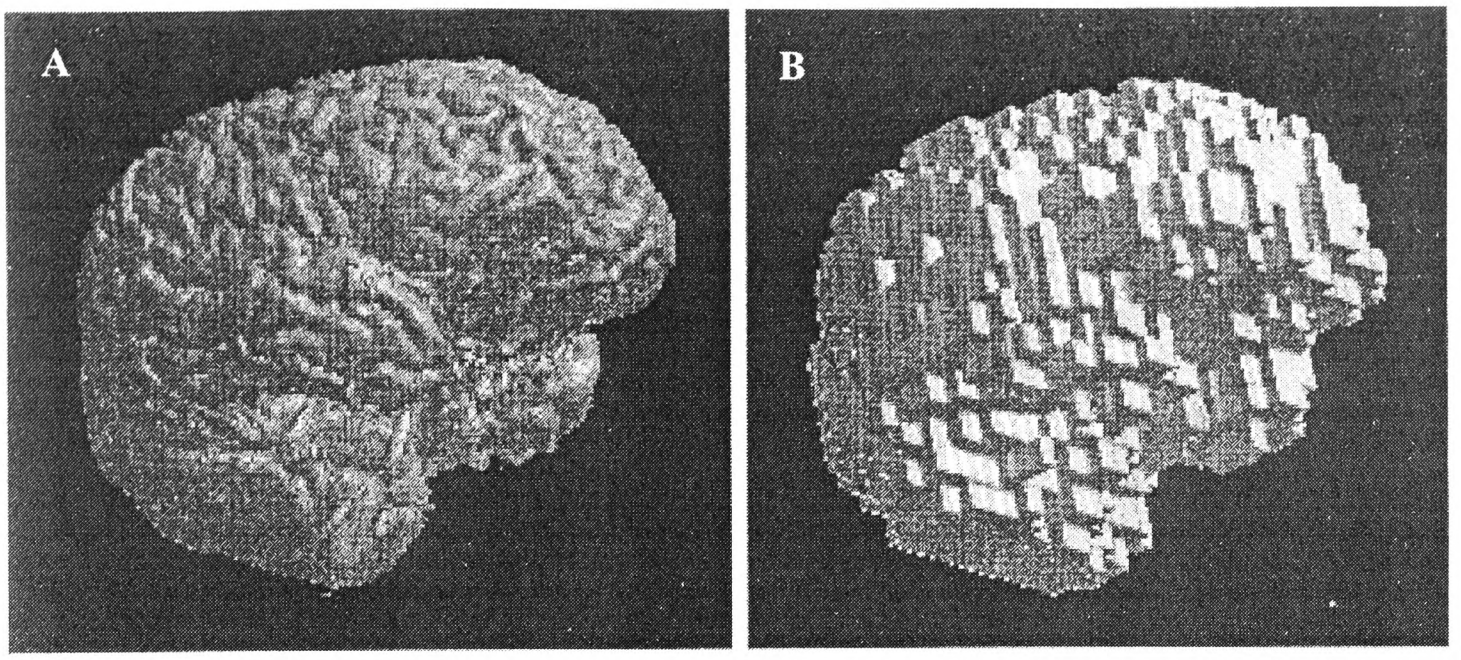



**Figure 2-12:** Surface renderings of 3 D brain images: a) high resolution image with small voxels (1mm × 1mm × 1.5mm); b) low resolution image of the same brain with large voxels (7mm × 7mm × 10 mm)

The size of one voxel is typically somewhere between 2 mm × 2 mm × 2 mm and 5 mm × 5 mm × 10 mm. The aim of fMRI analysis is to identify in which voxel's time series the signal of interest is significantly greater than the noise level.

*2.1.10.1 Pre-processing*

Before each voxels' time series is analysed statistically the acquired data are subject to several pre-processing steps (Smith, 2001b). The purpose of this pre-processing is to remove artefacts in the data. Typically the first step in pre-processing of fMRI data is *slice-timing correction*. Because each slice in each volume is acquired at slightly different times, it is necessary to adjust the data so that it appears as if all voxels within one volume had been acquired at exactly the same time.

Most significant artefacts for fMRI come from its extreme susceptibility to movement either of head or brain. Even very small movements of the head on a scale of less than a millimetre can be a major source of error in fMRI analysis if not identified and treated correctly, because the signal from an individual voxel may then not correspond to the same point in the brain throughout the experiment.

Therefore *motion correction* is extremely important. There are several effective motion correction procedures (see Brammer, 2001).

The next step of pre-processing is *spatial blurring* of each volume in order to reduce noise, hopefully, without significantly affecting the activation signal. Typically the change in signal intensity due to stimulation is between 0.5% and 5% of the average intensity and the noise level is between 0.5 % and 1% (Smith, 2001b). Spatial blurring of a signal can enhance the signal-to-noise ratio, because the noise values in the neighbourhood will tend to cancel each other out.

Next, each volume's overall intensity level is adjusted so that all volumes will have the same mean intensity (*intensity normalisation*). This step is extremely important for between-subject comparisons, but can lead to problems if strong activations are present. If a volume contains a strong signal then its mean intensity will be high and consequently it will be rescaled by a large factor and so activations may begin to show up as deactivations. Typically the last step of pre-processing is reduction in low and high frequency noise (*high and low pass filtering)* e.g. physiological effects like heartbeat or breathing or scanner-related drift. High pass filtering attempts to remove all slowly varying unwanted signals in each voxel's time series, while low pass filtering attempts to reduce high frequency noise in each voxel's time series. Low pass filtering might be inappropriate for some event-related experiments, because there the signal of interest might change very rapidly. Low-pass filtering would then reduce the signal itself. In these cases no low-pass filtering should be used. An alternative approach involves estimating the amount of temporal smoothness in the data and removing the temporal autocorrelations during the statistical analysis stage (so called "prewhitening"; Woolrich et al., 2001).

*2.1.10.2 Single subject analysis*

After the pre-processing activation images are analysed statistically to determine which voxels are activated by the stimulation. This can be done by correlation analysis or more advanced modelling of the expected haemodynamic response to the stimulation (although there are also model-free approaches, see McKeown et al., 1998). For analysing the fMRI experiment described in chapter 7 an approach based on the general linear model (GLM) was used. The following section describes the principles of the general linear model for an individual voxel.

2.1.10.2.1 Principle of the general linear model for an individual voxel

In model-based analysis a model of the expected response of each voxel is generated and compared with the data. The most commonly used model is a General linear model (Friston, et al., 1995) in which, for each voxel in a data set, the expected response is estimated by representing each time point in the data set by a linear equation:

$$y(t) = \beta^* x(t) + c + \varepsilon(t) \qquad \textit{(Equation 2-1)}$$

y is the observed data (over time t) from one voxel. x is the model; it describes the state of one parameter during the experiment that is expected to be related to changes in the data (such as on/off for a stimulus) and is often called the explanatory variable (EV). $\beta^*$ is the parameter estimate, c is a constant and $\varepsilon$ is the error in model fitting. If there are two types of explanatory variables, the model would be:

$$y(t) = \beta_1^* x_1(t) + \beta_2^* x_2(t) + c + \varepsilon(t) \qquad \textit{(Equation 2-2)}$$

Formulated in matrix notation the GLM is

$$y = \beta^* \mathbf{X} + c + \varepsilon \qquad \textit{(Equation 2-3 )}$$

In equation 2-3 all of the $\beta$ parameters are grouped together into a vector $\beta^*$ and all of the model time-courses are grouped together into a matrix **X** which is often called design matrix.

2.1.10.2.2 Convolution of the model by a haemodynamic response function

The brain's haemodynamic response is a delayed and blurred version of the input time-series, so in order to get the best possible fit of the model to the data the design matrix (in its simplest form a sharp on/off waveform) is convolved with the haemodynamic response function (HRF) thus creating a delayed and blurred version which will better fit the data (see figure 2-13).

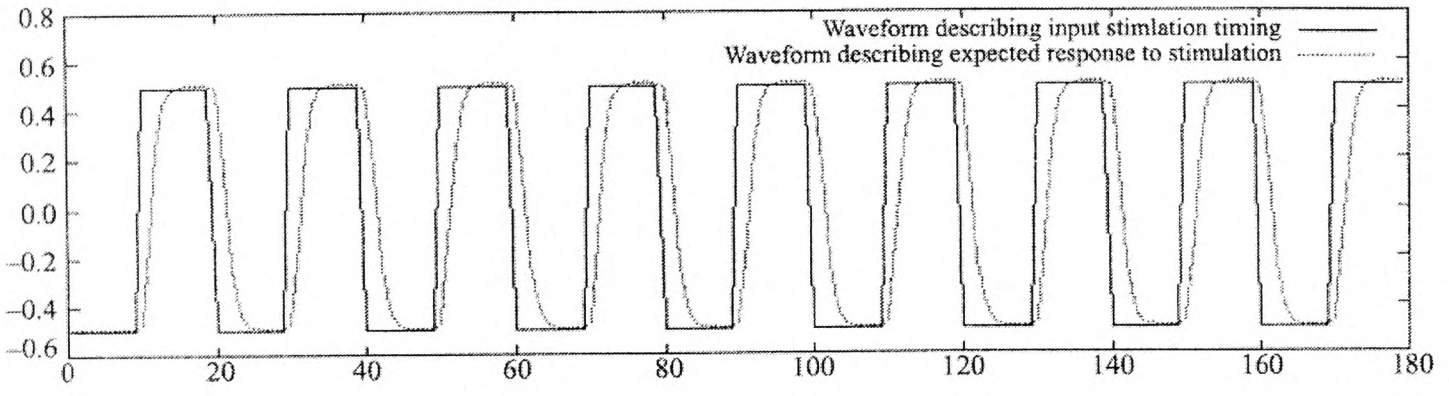



**Figure 2-13:** Model waveform formation: the square waveform describes the input stimulation timing; the smoothed waveform results from convolving the first with the haemodynamic response function, a transformation which leaves the model looking much more like the measured data (from Smith, 2001)

2.1.10.2.3 Statistical parameters at single voxel level

When the general linear model is fitted separately to the data at each voxel an estimate of the goodness of fit of each column in the model to that voxel's time course is made. Then the parameter estimate $\beta^*$ is converted into a useful statistic, which is called the T-value. The T-value is calculated by comparing the parameter estimate $\beta^*$ with the uncertainty in its estimation, i.e. with its standard error SE. The T-value therefore is computed as $T = \beta^* / SE(\beta^*)$. If the parameter estimate $\beta^*$ is low relative to its standard error then the fit is not significant and vice versa. The T-value can then be converted into a probability or a z -statistic by standard statistical transformation. T-values as well as z-values describe how strongly each voxel is related to each explanatory variable (EV). The parameter estimate $\beta^*$ can be also used to test whether one EV is more relevant to the data than another by formulation specific contrasts between the explanatory variables (Smith, 2001a).

2.1.10.2.4 Inference: Thresholding the statistical map

The T- or z-values of each voxel state how well the model of that voxel's behaviour fits its activation time series. In order to be able to classify whether that fit is significant, the simplest way is to select a significance threshold (p) that indicates how likely it is to explain the same amount of variance just by chance. Generally, in fMRI the main interest lies in finding areas consisting of large numbers of voxels that are activated significantly. Therefore, in *voxel-based thresholding* many tests for many voxels are carried out (Smith, 2001a). The more tests are carried out the higher are the chances of finding a significant result just by chance (this is called the multiple comparison problem). For instance, if 10 000 voxels are tested at a significance level of $p < 0.01$ it is expected that 100 will activate by chance. Consequently, the p-threshold has to be corrected for the number of comparisons made. Because there is a large number of voxels in the brain most ways of correcting for multiple comparisons result in an overly conservative p-threshold.

Another way of thresholding the statistical map is by *cluster analysis* (Roland et al., 1993). In this method a Z-statistic threshold is used to define contiguous clusters of voxels. A significance level for each cluster is estimated by using Gaussian Random Field Theory (Worsley et al., 1996). Subsequently, this estimated significance level is compared with the cluster probability threshold. Significant clusters are then used to mask the original Z-statistic image for later production of colour blobs. This alternative to voxel-based correction is normally more sensitive to activation (Smith, 2001a). Therefore cluster analysis was used to threshold the statistical maps reported in chapter 7.

*2.1.10.3 Multiple subjects statistic – group analysis*

Generally, the aim of an fMRI experiment is to yield results that can be generalised to the whole population. Therefore it is common to run an experiment several times with several different subjects and to look for significant activations common to all subjects. Before combining statistics across different subjects it is important to align the brain images from all subjects into some common space. This process is called *registration* and will be explained in the next section. Group analyses are strict tests as they require not only that most of the subjects show an activation in a particular brain region but also that the voxels showing the activation overlap once the individual brains have been co-registered. This requirement might be more easily fulfilled by large, diffuse areas of activation.

After the data have been aligned there are several statistical tools for combining results across a group of subjects (Worsley, 2001). In group statistics, in contrast to the single subject approach, two types of effects can be found: fixed effects and random effects. A *fixed effect analysis* is only sensitive to within-subject variation, while *random effects* additionally consider the variation between subjects. Only the results of a random effect analysis can validly be generalised for the whole population from which the group of subjects is drawn, but this type of analysis generally gives more conservative results and requires more subjects than a fixed effect analysis.

### *2.1.11 Registration*

Registration is used to align the low-resolution fMRI images of a subject to his or her high-resolution structural image. Additionally, because brain anatomy between subjects can differ significantly, it is important in a group analysis to register subjects' individual high-resolution structural images to a common brain. This

common brain (the template) is typically based on an average of many brains (such as the MNI 305 average; Collins, Neelin, Peters, & Evans, 1994) which have all been registered into a standard co-ordinate system. Different common brain spaces may have different shapes so that there are different relations between specific structures and co-ordinate positions depending on which co-ordinate system is used. The most widely used co-ordinate system is based on the atlas produced by Talairach & Tournoux (1988). For a detailed description of the concepts and procedures used for registration see Jenkinson (2001).

### *2.1.12 FMRI Expert Analysis Tool (FEAT)*

The fMRI data presented in chapter 7 has been analysed by using the FMRI Expert Analysis Tool (FEAT). FEAT is part of a software library that has been developed especially for analysing fMRI data at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), the FMRIB Software Library (FSL). FEAT is a tool for model-based fMRI analysis for all steps of image analysis and registration, as discussed in 2.1.10 and 2.1.11. It comprises data preprocessing, first-level GLM analysis with time-series prewhitening, registration to structural and standard space and fully generalised group analysis. Like Statistical Parametric Mapping (SPM; Friston et al., 1995b), FEAT uses the general linear modelling explained in section 2.1.10.2.1. However, FEAT and SPM deal differently with the fact that the intensity at any given time point is likely to be closer to its neighbours' values than values elsewhere in the time series (positive autocorrelation). In FEAT the data is 'prewhitened' within the statistical analysis (Woolrich et al., 2001) while SPM employs 'precolouring' (Worsley, 2001). FEAT and SPM also use different registration methods. While the registration method employed by FEAT uses the Correlation Ratio (Jenkinson & Smith, 2001), registration in SPM relies on a set of

modality-specific templates and Mean Square difference (Friston et al., 1995a). However, FEAT and SPM give very similar answers in most situations (Worsley, 2001). As such the choice of FEAT as image analysis tool for the fMRI experiment described in chapter 7 was mainly determined by local resources and expertise.

### *2.1.13 Applications*

In the last two decades fMRI has developed into one of the most dominant research methods for human cognitive neuroscience (Menon, 2001). It has contributed to many research questions from specialisation in the visual cortex (Tootell et al., 1998) to the role of the frontal lobes in memory (Owen, Epstein, & Johnsrude, 2001). In addition, fMRI has various clinical applications. It can be used for mapping language and motor areas prior to surgery, it may have a diagnostic role (e.g. Alzheimer's disease) and it is also used to observe the brain changes occurring during rehabilitation therapy (Thulborn & Gisbert, 2001). The combination of fMRI and electrophysiological techniques has already yielded exciting results (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Other developing areas of interest include the extraction of brain connectivity and animal fMRI (Matthews, 2001).

## 2.2 Transcranial Magnetic Stimulation (TMS)

### 2.2.1 History

For more than 2000 years it has been known that electricity can influence biological processes (McNeal, 1977). Reilly (1992) reports that as early as 46 AD electrical discharges of the torpedo fish were used to treat pain, but it wasn't until much later that this knowledge was used for systematic enquiries into the interaction between electricity and physiology. In 1658 Swammerdam, an early Dutch microscopist, discovered the twitching of frogs' legs under an electrical stimulus (Thompson, 1881). This phenomenon was subsequently re-discovered and described by Galvani, an Italian physician, in 1786 (Galvani, 1894). Galvani got interested in "animal electricity", because he observed motion in severed frogs' legs when he touched them with metallic wires.

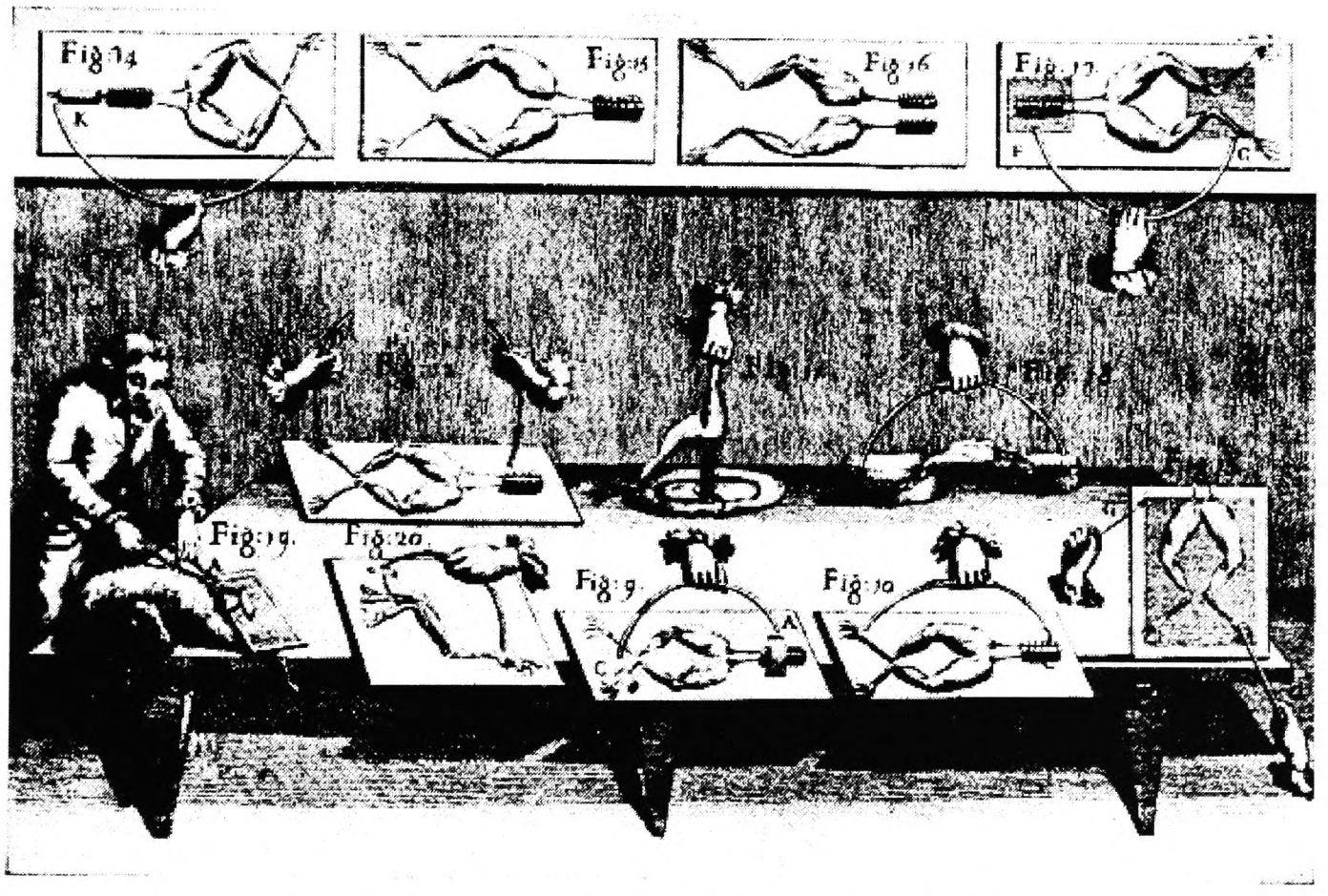



**Figure 2-14:** Galvani's experiments on "Animal Electricity"

In the 1790s Galvani and his fellow Italian physician Volta went on to show that a magnetic field generated by electric current causes ionic changes which results in

tissue stimulation but that the magnetic field itself does not directly stimulate the tissue (Barker, 1996). In 1832, Faraday showed that a moving magnetic field induces an electric current in a nearby circuit (law of induction). Ferrier is the first person reported to have used that law of induction to magnetically induce currents in the cortex, albeit only in animals (Ferrier, 1875; Ferrier, 1876). He worked on dogs and monkeys.

In 1896 d'Arsonval produced the percept of spots or flashes of light, called phosphenes, in humans by magnetic stimulation. Although the generation of magnetically induced phosphenes was replicated several times in the first decade of the 20$^{th}$ century (by Beer in 1902 and later by Thompson in 1910; see Barker, 1991), magnetic stimulation in humans came to a halt because of technological difficulties. Only in the 1980s did it become technically possible to produce large, rapidly changing magnetic fields safely (Walsh, 1998).

In 1950 Penfield & Rasmusssen extended the technique of electrical stimulation to human subjects. They applied electrical stimulation to the cortex of patients while the patients were undergoing neurosurgery. In contrast to electrical stimulation magnetic stimulation in humans did not evolve further until 1982, when Polson et al. succeeded in magnetically stimulating peripheral nerves in humans. In 1985 the current era of TMS finally began when Barker et al. stimulated the human motor cortex magnetically and thereby produced movements of their subjects' hands without causing them any discomfort.

The development of repetitive TMS (rTMS) required the designers of stimulators to solve a number of additional technical problems, not the least of which was the heating of the coil by the passage of frequent high currents. It was only in 1987/1988 that rTMS became possible.

### *2.2.2 Principles of Transcranial Magnetic Stimulation*

All current-carrying devices produce magnetic fields, but under most conditions these magnetic fields are far too small to stimulate excitable tissue (Reilly, 1992). In Transcranial Magnetic Stimulation (TMS) several capacitors discharge a large brief current into a coil of wire (the magnetic coil) which is held above the subject's head. The current in the coil is required to be large enough (up to several kA) to generate a magnetic field below the coil of sufficient intensity that, after passing unattenuated through skin and scalp, induces an electric field in the cortex which results in neural activity.

As can be seen in figure 2-15 the magnetic field is produced with the lines of flux passing perpendicular to the plane of the coil. According to Roth (1991) the induced field has two sources: the induction effect from the current in the coil and the negligible accumulation of charge on the scalp or between the scalp and the skull. The first source is usually meant when discussing TMS (Walsh & Rushworth, 1999).

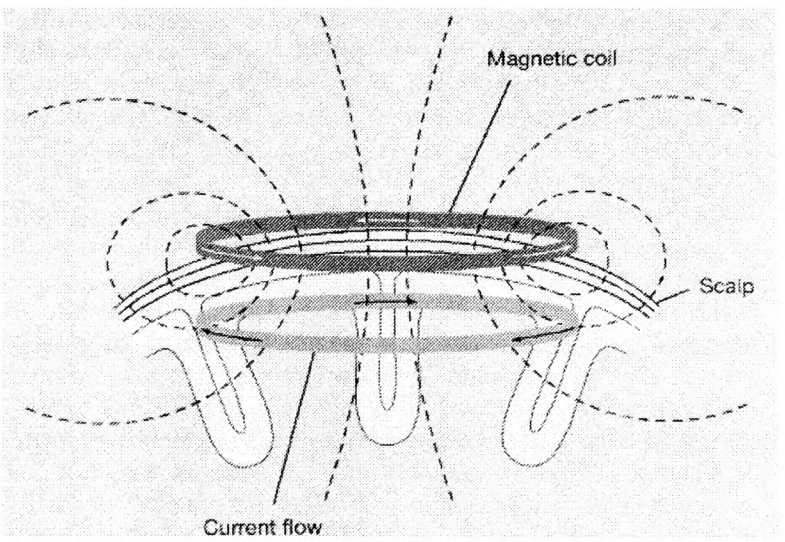



**Figure 2-15:** A magnetic field is produced with lines of flux passing perpendicularly to the plane of the coil (from Hallett, 2000)

An electric field is induced perpendicular to the magnetic field. The Principle of mutual induction states that the strength of the magnetic field is proportional to current running through the coil and the current induced in the tissue is proportional

to the rate of change of the magnetic field. In a homogeneous medium the electric field will cause a current to flow in circles parallel to the plane of the coil. The circles with the strongest current will be near the circumference of the coil itself. The current loops become weaker near the centre of the coil and there is no current at the centre itself. According to Reilly (1992), for induction in living subjects, however, the calculation of the current distribution is complicated by the widely differing conductivities of various body components.

There are differently shaped coils. Round coils are relatively powerful (figure 2-16a). Figure-eight-shaped coils are more focal, producing maximal current at the intersection of the two round components (figure 2-16b).

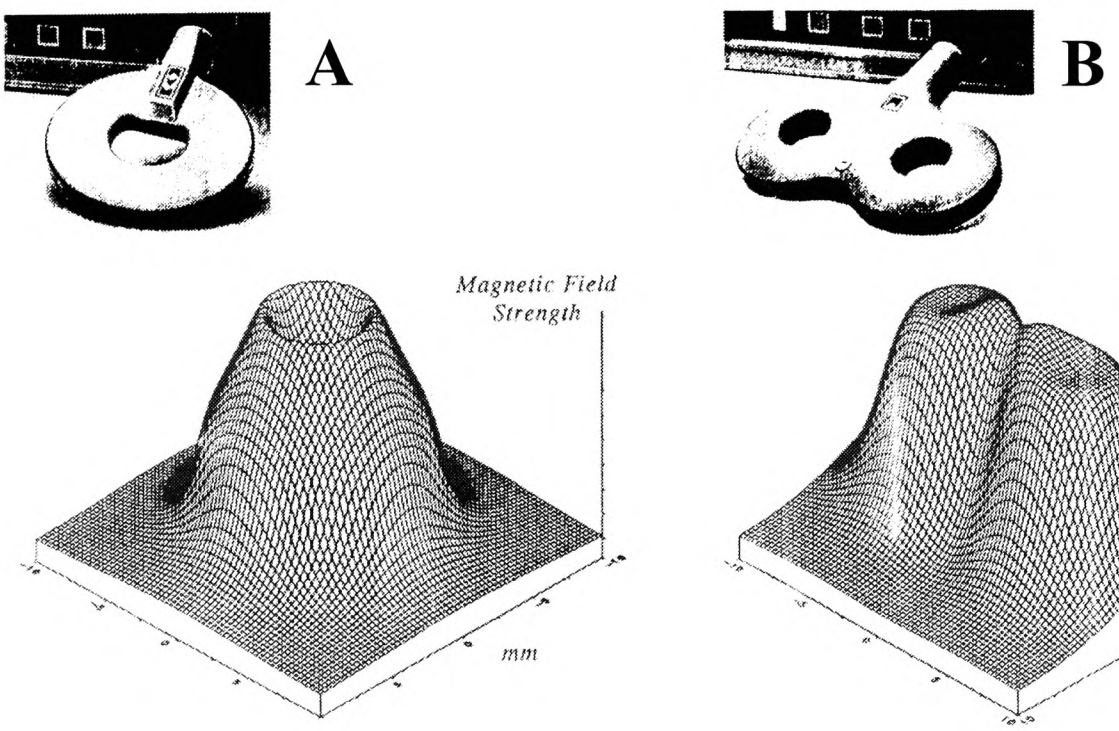
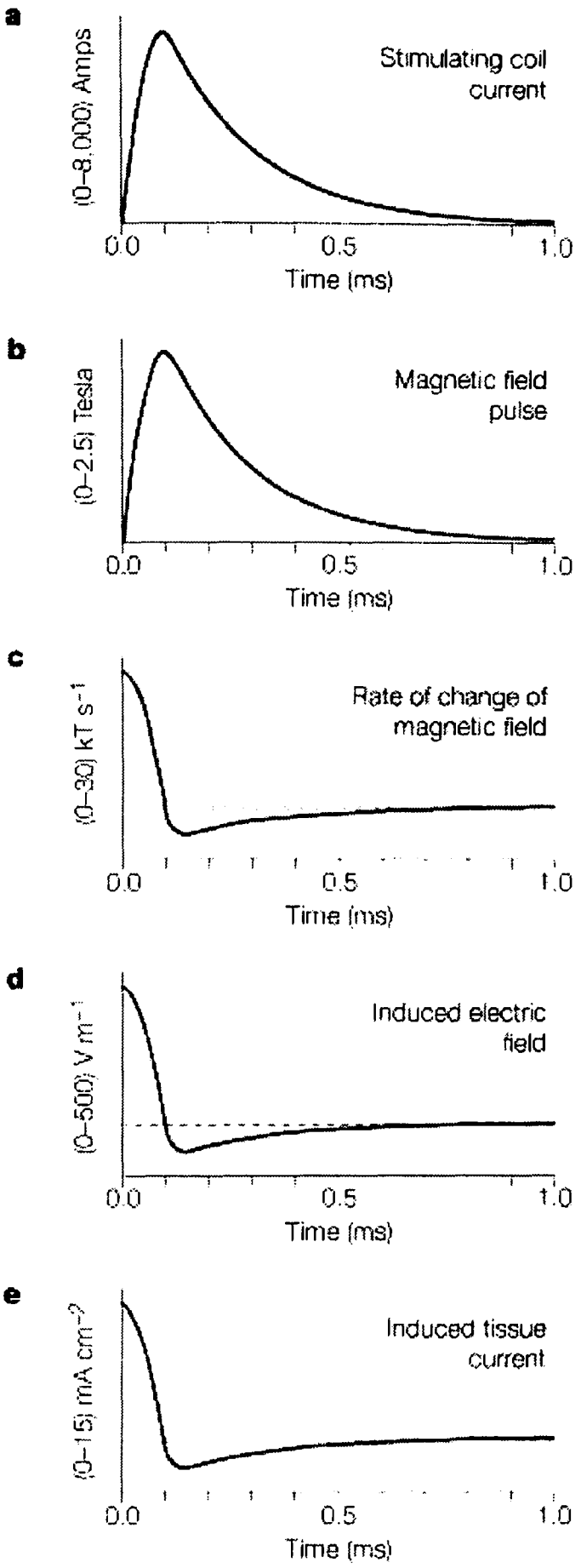



**Figure 2-16:** The 3D magnetic field profiles for A) a circular 90mm coil and B) a figure-of-eight 70mm coil

It is not possible to design a coil that would allow for absolute focal stimulation with a completely pre-specified desired location, depth and orientation of the induced current, because coil current, geometry and the tissue boundary conditions determine the pattern of the induced current (Reilly, 1992).

The following figure shows the cycle of events in a single pulse stimulation with a MagStim 200 with a 70 mm circular coil:




A large current (8 kA in this example) is required to generate a magnetic field of sufficient intensity to stimulate the cortex. The electric field induced in the cortex is dependent upon rate of change as well as on the intensity of the magnetic field. To achieve this latter requirement the current is delivered to the coil with a very short rise time (approximately 200 μs) and the pulse has an overall duration of approximately one millisecond. The net change in charge density in the cortex is zero.

**Figure 2-17:** Sequence of events that occur with a single TMS pulse. A rapidly changing electrical current of up to 8kA is passed through the coil (a), inducing a magnetic field of up to 2.5T (b), that has a very steep rate of change (c), and so generates an electrical field (d) that induces a current in the underlying tissue. Figure adapted from the Magstim Company Guide to Magnetic Stimulation for Walsh and Cowey (2001).

In addition to single pulse stimulation, current stimulators can also produce trains of pulses called repetitive TMS (rTMS) in which small magnetic fields may be applied over a period of several hundred milliseconds at a rate of up to 50 Hz.

### *2.2.3 Cortical Effect of Transcranial Magnetic Stimulation*

The electrical field generated by transcranial magnetic stimulation excites neurones and/or their axons located within the stimulated volume and thereby leads to physiological and biochemical disruption of normal neuronal activity. Nerve cell bodies, axons and dendrites are depolarised at points where current leaves them and hyperpolarised where current enters. Efficacy of the TMS pulse therefore depends on the orientation of the underlying cell bodies and fibres with respect to the flow of the induced current (Barker, 1996). If the depolarisation exceeds a certain level then a propagating action potential will be triggered. The degree of depolarisation depends not only upon the intensity of the current flowing but also on its duration. The shorter the duration of the current pulse the greater the current must be for excitation to occur. The threshold for excitation varies for different neural components (e.g. axons are different from cell bodies). Synchronous depolarisation of neurones is followed by a period of inhibition, but the specific actions of TMS pulse on individual classes of neurones and the duration of the inhibition period are less well characterised. The TMS effect can be excitatory or inhibitory depending on the population of neurones stimulated. Also, Schluter et al. (1999) report that at high levels of stimulation the TMS effect might be partly due to the direct stimulation of axons rather than overlying cortex.

### *2.2.4 Spatial Resolution of TMS*

Statements about the spatial resolution of TMS must be made with care. The physical size of the magnetic field produced by TMS is not spatially focal and theoretically infinite. But what determines the spatial resolution of TMS is not the physical size of the induced magnetic field, but the size of its physiological effect, i.e. where the electrical field induced by the magnetic field is sufficient to disrupt the

normal pattern of activity in underlying neurons. This has not been measured directly. Roth (1991) used a three layer (scalp, skull, cortex) spherical model of the head and calculated that when using a figure-of-eight coil the magnitude of the induced electric field drops to about 75% of the peak field within 10 mm and thus affects about 600 $mm^2$ of the brain tissue located under the coil. Walsh (in press) states that the estimated magnetic field produced with a standard figure of eight coil covers an area of approximately 7 × 6 cm at 5 mm below the coil. This area decreases to 4 × 3 cm at 20 mm below the coil. This shows that the use of TMS is very likely to be limited to the study of superficial cortical regions.

It is important to note that not all the area "stimulated" by the pulse is "stimulated" at suprathreshold level. The effective region of stimulation is much less and maybe of the order of 100 to 400 $mm^2$ (Walsh, in press). The *physiological resolution* of TMS may be inferred from studies that have recorded different outcomes after magnetic stimulation at adjacent positions. In studies in which the dependent measure was electromyographic activity recorded in hand and arm muscles, for example, it has been possible to distinguish between the effects of TMS applied at scalp positions 0.5 to 1 cm apart (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992).

Neuroimaging methods such as Positron-Emission-Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) can be used to investigate the spatial effect of TMS. Paus et al. (1997) used PET to analyse the anatomical distribution of the effects of TMS. In their experiments TMS was applied while changes in regional cerebral blood flow (CBF) were measured with PET. They showed that 10 Hz TMS applied over the left frontal eye field with a figure-of-eight coil led to a significant positive correlation between CBF and the number of trains of

TMS pulses administered. Furthermore, TMS-induced changes in blood flow in their study suggest activity changes in an area of 1 to 2 cm in diameter. This physiological resolution has been confirmed by Siebner et al.'s (1998) study. The *functional* resolution of TMS, i.e. the effect of TMS on behaviour, is also important. Studies that use behaviour as a dependent measure, however, have so far not attempted to distinguish the effects of TMS pulses applied less than 2-3 cm apart on the scalp (probably about 2 cm apart in the brain) (Ashbridge, Walsh, & Cowey, 1997; Pascual-Leone, Walsh, & Rothwell, 2000; Schluter, Rushworth, Mills, & Passingham, 1999; Walsh & Rushworth, 1999).

Paus et al. (1997) not only found local changes in the cortex under the coil but also changes in CBF in several cortical regions far away from the stimulation site. They interpreted the observed distal CBF changes as spread of activation from the stimulation site along known anatomical pathways. In 1989 Cracco et al. showed that TMS can elicit activity in distant areas that are anatomically interconnected with the target region. Ilmoniemi et al. (1997) measured EEG responses after applying TMS to the visual or motor cortex and found that resulting changes in electric activity were maximal close to the point of stimulation, but that the effect spread to adjacent areas within 5 to 10 ms and to the other hemisphere within 20-30 ms. It is currently unclear whether these distant physiological changes affect behaviour.

In a concurrent TMS and fMRI study Bohning et al. (1999) showed that stimulation above motor threshold was associated with significantly increased activity both locally and remotely compared to the rest condition and also compared to stimulation below motor threshold. They observed 3 to 4% increases in BOLD signal during stimulation, thus showing a pattern of BOLD response similar to that observed in behavioural fMRI studies.

Although the exact relationship remains to be determined, the TMS effect depends critically on the rate, the length and the intensity of magnetic stimulation. The physiological effect of TMS is not always limited to the site at which the pulse is directed. There is, however, a difference in spatial resolution between physiological TMS effects and functional TMS effects on behaviour.

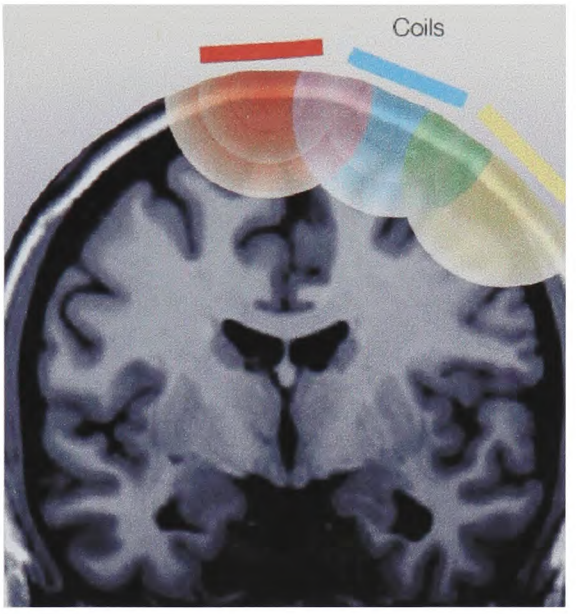



**Figure 2-18:** Subtractive lesion analysis applied to TMS: from models of TMS-induced electric fields one can infer the region of stimulation. By stimulating at neighbouring regions on the scalp the inferences can be refined and notwithstanding the uncertainty of any one field, reasonable functional anatomical attributions can be made. The "coils" and induced fields in this figure are illustrative of the methodological rationale and do not represent real configurations and effects (from Walsh & Cowey, 2000)

### *2.2.5 Temporal resolution*

The critical time for TMS delivery to a human brain area appears to coincide with the time at which single unit responses can first be recorded from the homologous area of the macaque brain (Ashbridge, Walsh, & Cowey, 1997; Corthout, Uttl, Walsh, Hallet, & Cowey, 2000; Schluter, Rushworth, Mills, & Passingham, 1999; Walsh & Cowey, 1998). The critical periods are in general earlier than would be expected on the basis of human scalp recorded event related potentials (ERPs) and can be very brief. Effects of a single TMS pulse may last for up to 70 ms at the site of stimulation, but not all 70 ms are physiologically effective. The resolution of TMS has been shown to be at least 10 ms in behavioural studies (Ashbridge, Walsh,

& Cowey, 1997). Effects in anatomically connected regions can still be seen at at least 30 ms after stimulation when subjects are not performing any task (Ilmonieni et al., 1997; Walsh & Cowey, 1998).




**Figure 2-19:** Defining the problem space of TMS: spatial and temporal resolution as well as interference of TMS in comparison to correlational mode of other neuroimaging methods (from Walsh & Cowey, 2000).

TMS occupies a unique location in what has been described as the "problem space" of cognitive neuroscience (figure 2-19). It has potentially a spatial resolution of less than a centimetre, a temporal resolution of a few milliseconds and the crucial additional feature of enabling interference with processing.

### *2.2.6 Safety and potential long-term effects of TMS*

The use of TMS has to be approved by local ethical committees and there are some precautions that must be taken in all studies using the technique. In TMS experiments subjects are exposed to a strong magnetic field, therefore careful screening is needed to exclude subjects with heart pacemakers, cochlear implants, medical pumps, surgical clips or who have ever undergone a neurosurgery or eye

surgery. rTMS can cause seizures (Dhuna, Gates, & Pascual-Leone, 1991; Pascual-Leone, Gates, & Dhuna, 1991), therefore all subjects who have any neurological or psychiatric conditions, have ever suffered from epilepsy, febrile convulsion, had recurrent fainting spells or have a family history of epilepsy have to be excluded from TMS experiments.

In 1993 Pascual-Leone et al. published safety guidelines for rTMS stating maximal values of safe TMS stimulation intensity and frequency. However, in subsequent TMS experiments using trains of stimulation within this safety guideline rTMS caused seizures in several normal subjects. Relevant parameters to control and to minimize the risk of seizure induction include not only stimulation intensity and frequency and train duration, but also inter-train interval and total number of stimuli and trains. Taking these factors into account Wassermann et al. published new safety guidelines in 1998. Since then one seizure induction by rTMS in a normal subject has been reported, leading to further changes in TMS procedures. Screening procedures now exclude not only subjects in whom there is a possibility that seizure thresholds are permanently lowered (for example after neurosurgery), but also when there is a risk of a temporary lowering of seizure thresholds. Alcohol withdrawal, sleep deprivation, and recreational drugs, for example, lower seizure thresholds. Subjects are therefore asked to refrain from drinking, taking recreational drugs, and to have a reasonable night's rest prior to taking part in an experiment. Additionally, subjects should not participate in more than one TMS experiment in any one day.

*2.2.6.1 Possible histological damage*

It is known from some animal studies that direct cortical stimulation might lead to histological damage. Agnew & McCreery (1990) showed that stimulation of animals with cortical surface electrodes at 50 Hz for up to 8 hours led to some detectable

histological change. However, they could not find histological changes in animals with up to 24 hours of stimulation at only 20 Hz (Agnew & McCreery, 1987). During TMS the figure of charge density per phase (1.1 $\mu C/cm^2$ ) is well below the minimum figure of charge density per phase (40 $\mu C/cm^2$ ) produced with surface electrodes at which Agnew et al. found evidence of neural damage. Gordon et al. (1990) stimulated the anterior lobes of two epileptic subjects subdurally at 50 Hz before surgery. This tissue later showed no evidence of histological damage on investigations with light microscopy.

Studies of animals' brains following rTMS (Sgro et al., 1991) have failed to find any pathological changes. Gates et al. (1992) investigated a resected human temporal lobe which had been exposed to 20 Hz rTMS and failed to find any histological damage.

*2.2.6.2 Neuropsychological effects*

In the first study of the safety of rTMS by Pacual-Leone et al. (1993) subjects were screened with a neuropsychological battery for various types of longer-lasting unintended cognitive effects before and after magnetic stimulation at different frequencies delivered over different sites. No undesirable effects were found. But more recent studies have shown some enhancement effects on motor reaction time, verbal recall and affect. Also, if rTMS is considered as potentially useful in alleviation of depression (George, et al., 1996), it must be conceded that rTMS can have longer term effects on mood.

*2.2.6.3 Hormonal or immunological effects*

Seizures and electroconvulsive therapy are known to be associated with raised serum prolactin levels. Pascual-Leone et al. (1993) therefore investigated the effect of TMS on hormone levels. In serum levels of several hormones (prolactin,

adrenocorticotropic hormone, thyroid-stimulating hormone, leuteinizing hormone and follicle-stimulating hormone) they found no changes following TMS stimulation except for those subjects who had a seizure. George et al. (1996), on the other had, found increases in thyroid-stimulating hormone after rTMS of the right prefrontal area at 5 Hz.

There is also a possibility of immunological effects of TMS. Amassian et al. (1994) reported effects of single-pulse stimulation on a subset of immune cells. These changes, however, resolved within 48 hours and are therefore unlikely to be clinically significant.

*2.2.6.4 Effects on hearing threshold*

The windings of the coil move very slightly when a TMS pulse is generated. This movement produces a brief auditory click and effects on hearing thresholds must be considered. The sound depends on coil size, power level and manufacturing method, but Counter et al. (1990) showed that this acoustic pulse might reach sound pressure levels up to 157dB. In their study they demonstrated a permanent increase in auditory thresholds of animals following single-pulse TMS. Pascual-Leone et al. (1993) reported transient increases in hearing thresholds in humans. The same authors, however, showed that the use of foam earplugs during single-pulse and rTMS prevents changes in hearing threshold.

*2.2.6.5 Uncomfortable muscle movements*

TMS causes direct activation of muscles and nerves near the stimulating coil. rTMS can therefore be quite uncomfortable, especially over fronto-temporal areas. In some individuals it can also cause muscle-tension-type headaches. The discomfort is related to intensity and frequency of stimulation. Allowing subjects to find the most comfortable posture is therefore important.

### *2.2.7 Virtual lesion approach of TMS*

Depending on the rate of stimulation applied to a single area TMS can have either a positive or a negative effect on performance. For example, in an experiment by Pascual-Leone et al. (1999) repetitive TMS over motor cortex at 1 Hz led to a decrease in implicit learning, while TMS at 10 Hz over the same site resulted in an increase in implicit learning.

In TMS experiments in which subjects are stimulated over association cortex, the intention is not to produce a particular movement or perception, but to delay or worsen performance of the task. The induced current operates as "neural noise", which in turn serves to delay or disrupt performance. It is in this sense that TMS has been called a virtual lesion technique (Pascual-Leone, Walsh, & Rothwell, 2000).

TMS has several advantages over traditional studies of patients with lesions. Patients after brain injuries have abnormal brains which may have re-organised to compensate and improve performance. Therefore it is not clear whether the task is being performed as it would be with practice by an intact brain or whether one is studying a re-organised system. Also, a virtual TMS lesion has typically a much better spatial resolution, TMS subjects can serve as their own controls and the lesion is only transient.

### *2.2.8 Design of TMS experiments*

In general it is not good enough to just stimulate a certain brain region and observe an effect. Each TMS experiment should be designed in a way that it can show a TMS effect specific either in time, in location or to the task used.

For the design of TMS experiments it is also important to take into account the peripheral effects of TMS (face twitches or eye blinks produced by stimulating facial muscles). Also, the auditory artefact produced by the coil as well as the concurrent

slightly uncomfortable tactile stimulation where the coil touches the subject's head can lead to intersensory facilitation (Diederich, 1995; Hershenon, 1962; Nickerson, 1973). For example, Dufft & Ulrich (1999) showed that subjects are faster to react to a visual stimulus if it is accompanied by a tone than without the tone even though the tone does not have any relation to the correct clue. Romaiguere, Possamai, & Hasbroucq (1997) showed that TMS over the motor cortex can lead to inter-sensory facilitation and shorter reaction times. Terao et al. (1997) showed inter-sensory facilitation when the coil was discharged near the head or on the scalp regardless of the site where TMS was given. When analysing TMS effects on reaction time it is therefore especially important to be aware of possible inter-sensory facilitation confounds.

### *2.2.9 Applications*

In contrast to other brain mapping techniques TMS can be used to establish the necessity of a brain region for cognitive processes because it is an interference technique. Since its beginnings as a research tool in 1985 TMS has been used for a large variety of research questions. The motor (Mortifee, Stewart, Schulzer, & Eisen, 1994; Schluter, Rushworth, Mills, & Passingham, 1999) as well as the visual system (Corthout, Uttl, Walsh, Hallett, & Cowey, 1999; Masur, Papke, & Oberwittler, 1993) have been explored extensively by using TMS. Research on visual cognition (Ashbridge, Walsh, & Cowey, 1997) and language (Epstein, 1998; Pascual-Leone, Gates, & Dhuna, 1991) has profited from the advent of TMS. TMS has also begun to be used in the research and treatment of conditions such as epilepsy (Caramia, et al., 1996), depression (George, et al., 1999), anxiety disorders (Greenberg, et al., 2000) and stuttering (Ziemann, Paulus, & Rothenberger, 1997). New lines of research into cortical plasticity (Corthout, Uttl, Walsh, Hallet, & Cowey, 2000; Kew, et al., 1994;

Walsh, Ashbridge, & Cowey, 1998), awareness (Cowey & Walsh, 2000) and connectivity/excitability in healthy and disordered brain (Pascual-Leone, Walsh, & Rothwell, 2000; Paus et al., 1997) have recently been developed with the help of TMS.

# 3. 'Causing a virtual Acalculia with TMS'

*Establishing TMS as a Research Tool for Neural basis of Number Processing*

## 3.1 Summary

In this first experiment repetitive transcranial magnetic stimulation was applied over inferior parietal areas and adjacent intraparietal sulci while subjects solved double-digit addition tasks. On addition trials without transcranial magnetic stimulation subjects showed the classical problem size effect with longer reaction times the larger the sum of the two operands. Magnetic stimulation over left inferior parietal areas disrupted performance significantly. This effect was specific to the left hemisphere stimulation. There was no increase in reaction times for TMS stimulation over right hemisphere. The significant effect of TMS specific to left inferior parietal lobe observed in this experiment provides further evidence for the importance of the left inferior parietal lobe, and the angular gyrus in particular, for calculation.

## 3.2 Introduction

A large part of our current knowledge of numerical processing is derived from neuropsychological assessment of patients who present with specific mathematical difficulties following brain injury. The history of research into acalculia goes back at least a hundred years to neurologists such as Pierre Marie or Lewandowsky and Stadelman (see Boller, 1983). The impact of clinical investigations into the development and modification of models of number processing has been tremendous (see for example Cohen & Dehaene, 2000) and most of the current models on number processing such as the Triple Code Model by Dehaene et al. or McCloskey's

model (see section 1.6.2) are explicitly based on single case studies of acalculic patients.

Although research has moved away from claiming "a centre" for calculation in the left inferior parietal lobe, there is a strong agreement that disturbances in arithmetical calculation are more often observed after damage to the dominant (typically left) hemisphere and that the inferior parietal lobe seems to be of particular importance. Grafman, Passafiume, Faglioni, & Boller (1982), for example, tested 102 patients with left anterior, left posterior, right anterior or right posterior lesions on addition, subtraction, multiplication and division. They found that both left and right hemisphere-damaged patients performed significantly worse than controls and that those with left posterior lesions performed significantly worse than the other groups on all tasks.

The important contribution of the left parietal lobe to mathematical performance has also been highlighted by studies on children (Aram & Ekelman, 1988; Martins, Parreira, Albuquerque, & Ferro, 1999). Ashcraft et al. (1992), for example, showed that unilateral left hemisphere damage during childhood yields more pervasive performance deficits in mathematics than do right hemisphere lesions.

Several neuroimaging studies have investigated which brain circuits are active during various calculation tasks. It is clear that the left inferior parietal lobe is active during most calculation tasks (e.g. Cowell, Egan, Code, Harasty, & Watson, 2000; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Zago, et al., 2001). Chochon, Cohen, van de Moortele, & Dehaene (1999) for example reported a larger contribution of the left than right parietal lobe during multiplication. However, the evidence from neuroimaging experiments for hemispheric dominance in calculation

is not as clear cut as one would expect based on the patient data. Often a concomitant activation of the homologous inferior parietal region of the right hemisphere is reported in the same tasks (Kazui, Kitagaki, & Mori, 2000; Dehaene et al., 1996). Dehaene, Spelke, Pinel, Stanescu, & Tsivkin (1999) for example studied exact calculation (addition) relative to an approximation task with fMRI. They revealed a left-lateralised activation in the inferior frontal lobes, but bilateral angular gyrus activation for exact calculation. There thus exists a discrepancy between results from neuroimaging data indicating an important role of both left and right inferior parietal areas in calculation and the patient data suggesting a left hemisphere dominance of calculation abilities. This discrepancy needs to be resolved.

### *3.2.1 Shortcoming of lesion studies*

Without neglecting the important contribution studies of brain-damaged patients have made and will make to further our knowledge about numerical processes, there are certain intrinsic limitations in patient studies. In most patients large areas of the brain are affected, so for developing a detailed anatomical theory of number processing researchers clearly have to rely on complementary methods with better spatial resolution such as fMRI or TMS. Additionally, in most lesion cases not only is the grey matter of a certain brain area damaged but often its connecting fibers are also affected (Mayer et al., 1999). It is then difficult to establish whether it is the disrupted normal functioning of the lesioned area or the damaged connection (input or output) with other brain areas that is causing the impairment. Patients with brain lesions are typically middle-aged or older, and often the large size of their lesions causes impairment on other cognitive, perceptual or motor skills that might interact with their ability to perform well in numerical tests (e.g. impaired writing, speech).

Additionally, every patient presents herself or himself as a single case, so the question of generalisability to a normal population is an important issue (Vallar, 2001).

In interpreting a patient's performance on a task it is assumed that impaired performance reflects damage to a cognitive system that was capable of performing the task successfully prior to the damage, and certainly in most cases this assumption is justified. Nevertheless the possibility of a premorbid difficulty with a task cannot always be completely ruled out, especially with a topic like mathematics which presents difficulties for a significant number of people. An additional difficulty in working with brain damaged patients is that researchers are possibly looking at the function of a reorganised brain that is trying to compensate for the damaged brain areas by using other brain areas or functions of other brain areas (Robertson & Murre, 1999).

### *3.2.2 Advantages of using TMS*

In this first experimental chapter I aim to show that these drawbacks of lesion studies can be partly overcome by using TMS in an experimental setting to cause a virtual lesion in normal subjects. Walsh & Cowey (1998) and Pascual-Leone, Walsh, & Rothwell (2000) pointed out that TMS can be used as a virtual lesion technique. 'Lesion' in this context is just used as a metaphor for temporary disruption. Using TMS comes with the advantage that the virtual lesion can, to a reasonable degree, be experimentally manipulated in time and space. Therefore the virtual lesion typically is of smaller size affecting only certain specified sub-regions of a lobe (for a more detailed discussion of the spatial resolution of TMS see section 2.2.4.1). Subjects usually act as their own controls, the sample size increases from one to typically 6-

10 subjects and last but not least the lesion is transient and so brief that reorganisation in order to compensate is unlikely.

Several experiments in which studies originally carried out on patients have been successfully transferred from the clinic to the experimental laboratory and from patients to normal subjects, show the validity of the method. Pascual-Leone, Gomez-Tortosa, Grafman, & Alway (1994) used rTMS over occipital, temporal or parietal cortices while subjects had to report the appearance of stimuli in either their right or left visual hemifield. Patients with visual neglect who can report the identity of a single stimulus presented in either the right or the left visual hemifield fail to see the stimulus presented in the field contralateral to the lesion when it is accompanied by one in the ipsilateral field (Vuilleumier & Rafal, 1999). Pascual-Leone showed that rTMS over parietal cortex in normal controls increased errors for bilateral but not unilateral stimulus presentation. These normal control subjects thus performed very similarly to patients with visual neglect.

Another example of the virtual lesion approach in TMS studies stems from research on a motion blind patient LM (Walsh, Ellison, Battelli, & Cowey, 1998). She had bilateral V5 lesions, but was nevertheless able to perform form and colour conjunction tasks. Walsh et al. (1998) could replicated this finding in normal controls by stimulating over V5; they impaired performance on form and motion conjunction tasks, but their performance on colour and form conjunction tasks improved.

### *3.2.3 Using TMS to investigate addition*

To my knowledge no one has so far reported using TMS to investigate the cerebral architecture of numerical processing. Therefore the goal of this first experiment was to test the effect of TMS in normal subjects in a well-researched paradigm from the

neuropyschological literature on numerical processing. Normal subjects had to solve addition tasks and TMS was used to investigate the contribution of left and right parietal lobes in this task. Additionally, we looked at the differential contribution of two different areas in the inferior parietal lobe (angular gyrus and supramarginal gyrus) and the adjacent areas in the intraparietal sulcus. In many patients with acalculia both these areas are probably damaged (Cipolotti & van Harskamp, 2001). It is known, however, that at least in animals the homologues of these two regions differ anatomically as well as functionally and evidence is mounting that these two regions in the inferior parietal lobe might also subserve different functions in humans (see section 1.4 of the general introduction).

### *3.2.4 Patients with a deficit in addition*

For our investigation we chose to focus on a calculation task rather than on the more fundamental process of number representation, because numerical transcoding and simple numerical tasks such as number comparison are often well-preserved even in patients with severe acalculia (Cipolotti & van Harskamp, 2001). There are however many cases with impaired calculation in the literature. I will only mention three cases here in pars pro toto to illustrate the clinical deficits most commonly seen.

Warrington's patient DRC (1982) showed inaccurate performance of simple addition after a left parietal intracerebral haematoma. Interestingly, the concept of quantity was still intact as well as knowledge of arithmetical operations. Van Harskamp & Cipolotti (2001) reported a patient (FS) with intact number transcoding skills after a left cerebral vascular incident. He showed a severe impairment in simple addition while his ability to multiply and subtract was flawless. Patient JG described by Delazer & Benke (1997) showed the typical symptoms of a Gerstmann's syndrome after a left parietal glioblastoma. She had no problems

identifying the larger of two Arabic numerals and she was fine with multiplication, but she was impaired on addition, subtraction and division.

Although these are only three out of at least a dozen published cases with impaired addition, it is evident how variable the numerical abilities of these patients are although they show lesions in roughly the same brain area and exhibit a common impairment on addition.

There are also somewhat smaller inter-individual differences in performance in simple addition tasks even between normal adults (LeFevre & Kulak, 1994; Dowker, 1995; Deloche et al., 1999). So far models of number processing have tried less to account for individual differences in number processing seen in the normal population. In contrast most of the calculation models try to account for common behavioural effects seen in normal adults.

### *3.2.5 Problem-size effect*

One behavioural effect that can be consistently observed in normal children and adults solving calculations is the problem-size effect; sometimes also termed problem-difficulty effect. This effect refers to the fact that problems involving large operands (and hence large answers) show longer reaction times and higher error rates. The effect is found for simple addition, subtraction, multiplication and division, in production as well as in verification tasks, and ranges from children to adults and the elderly (Ashcraft & Battaglia, 1978; Groen & Parkman, 1972; Miller, Perlmutter, & Keating, 1984). There exist however, some exceptions to this rule. Ties (e.g. 2 × 2, 3 × 3, etc.) and 5-multiple problems (e.g. 2 × 5) are usually answered much faster and do not present the expected regression slope seen in other size related problems (LeFevre, Sadesky, & Bisanz, 1996). The effect is usually analysed by correlating correct reaction times across problems with one or a number

of different problem-size variables. Typically, these include (e.g. for 6 + 5) the minimum operand (5), the maximum operand (6), the sum (11) or squared sum (121) of the operands, or the product of the operands (30). In the experiment reported here, I will analyse reactions times according to different sum sizes, a measure with an obvious and intuitive appeal in an addition task.

### *3.2.6 Hypotheses*

The objective of this first experiment was to investigate whether TMS can be used to replicate basic patient findings and to tackle discrepancies between patient data and results from neuroimaging studies in an addition task. Along with evidence from patient studies it was hypothesised that left hemispheric TMS stimulation should result in an increase in reaction times in the addition task. However, there should be no effect of right hemisphere stimulation. For trials without TMS stimulation it was expected that the larger the size of the sum of the two operands the longer the reaction times.

## *3.3 Materials and Methods*

### *3.3.1 Stimuli and apparatus*

Subjects sat in a lighted room at a distance of approximately 50 cm from a screen. The experiment was controlled by a PC running SuperLab software version 1.04. Stimuli were presented centrally on a 17-in. colour monitor and appeared as white against a black background. The stimuli consisted of a set of 40 different double-digit addition tasks (ranging from 21+22 to 49+47; ties were excluded). Numbers were displayed using the font Arial (type size = 30 points) and when viewed from the distance of 50 cm they subtended 6.5° of visual angle. Subjects wore rubber bathing caps on which the relevant co-ordinates of the International 10/20 EEG

system (AEEGS, 1991) were marked. For generating the magnetic pulses a Magstim stimulator, Model Super Rapid (The Magstim Company Limited, Whitland, UK) with a 70 mm figure of eight coil was used. The maximal magnetic field strength at the coil surface was 1.8 Tesla. Precise timing of onset of both the visual and the magnetic stimulus was verified using an oscilloscope.

### *3.3.2 Procedure*

In each block, the addition tasks ranged from 21+22 to 49+47. In each addition trial the task (e.g. 22 + 34) was first displayed for 300 ms followed by an inter-stimulus interval of 300 ms. Then a two forced response choice was displayed for 200 ms consisting of the correct answer (i.e. 56) and an incorrect answer (see figure 3-1).

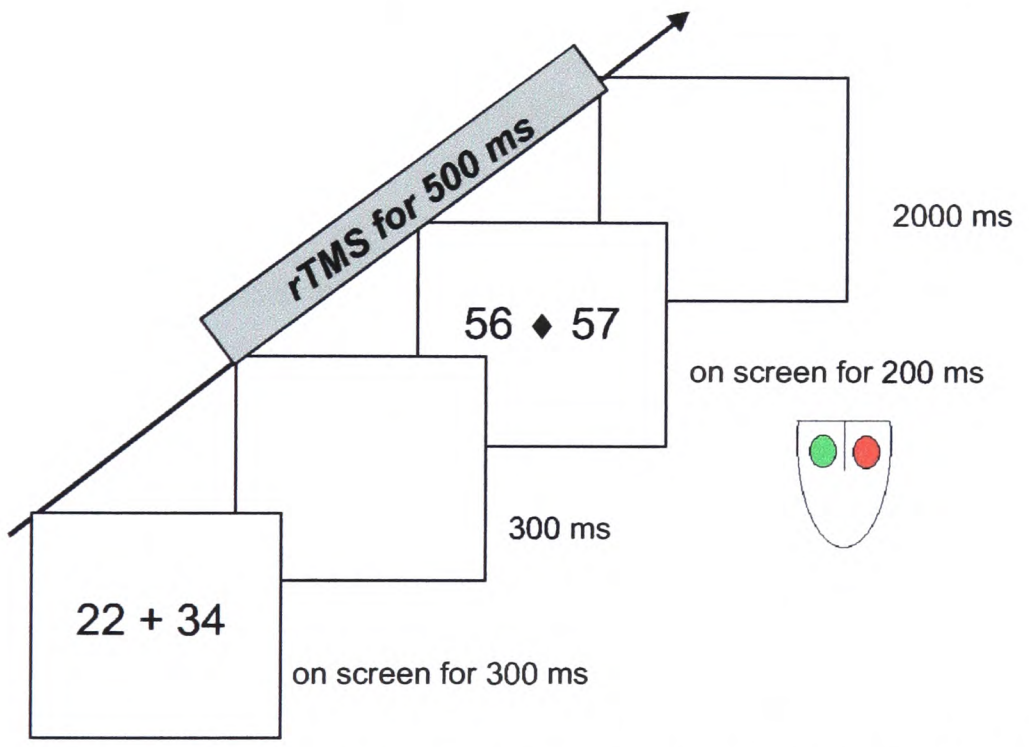



**Figure 3-1:** Addition task. Subjects were presented with addition problems ranging from 21+22 to 49+47. After an interstimulus interval of 300 ms two possible answers were displayed on the screen for 200 ms. Subjects had to indicate with one of two possible key presses the side of the correct answer. On some trials rTMS was applied.

The incorrect answer was always one unit larger or smaller than the correct answer (e.g. the distractor for 56 was 57). Subjects were required to indicate with one of two possible key presses whether the correct response was on the left or the right of the fixation point. The location of the correct answer (left or right from fixation point)

was counter-balanced. The index fingers of the right and left hands were used to indicate the 'right' and 'left' responses respectively. The intertrial interval was two seconds. The order of the addition trials appearing on the screen was pseudo-random within each block. During each session subjects performed 4 blocks of 50 trials, preceded by an initial training block of 50 non-TMS trials. On 10 trials in each experimental block rTMS was applied over the subject's scalp for 500 ms at 10Hz. The rTMS stimulation began with the onset of the inter-stimulus interval and lasted until the onset of the inter-trial interval. It thus spanned the time interval when the solution was presented on the screen. The rTMS trials occurred pseudo-randomly with the constraint that after four blocks each of the 40 addition tasks had been displayed 5 times, one of which had been accompanied by TMS stimulation. During the whole experiment the coil was held in a constant position with reference to the subject's head.

Magnetic stimulus intensity was between 50% and 75% of the maximum stimulator output. The intensity of the magnetic stimulation was set separately for each individual depending on their motor threshold. Motor threshold was defined as minimum percentage of the stimulator output that evoked a visually detectable twitch in a tense muscle of the subject's hand contralateral to the stimulated motor cortex (Pridmore et al., 1998). Frequency, intensity and duration of rTMS were in accordance with the safety guidelines established by Wassermann (1998).

All subjects were checked for TMS exclusion criteria and gave their informed written consent before participating. The procedure was approved by the Ethics Committee of the University of Oxford, Department of Experimental Psychology (OxREC numbers: C99.178, C02.092). Subjects were over 18 years of age, either held or were studying for a university degree, had normal or corrected to

normal visual acuity and were free of any neurological condition. They were reimbursed for travel expenses and time taken to participate in the study.

### *3.3.3 Participants*

Fourteen right-handed volunteers were tested twice, once with stimulation over the angular gyrus and the adjacent posterior part of the intraparietal sulcus (pIPL+S) and once with stimulation over supramarginal gyrus and the adjacent anterior part of the intraparietal sulcus (aIPL+S). In seven subjects stimulation was delivered over the left hemisphere (left aIPL+S and left pIPL+S). In this group two subjects were female and five male. Their ages varied from 19 to 40 years, mean age was 23.9. The remaining seven subjects were stimulated over right aIPL+S and right pIPL+S. Four of these subjects were female, three male. Their age varied from 19 to 35 years, mean age was 24.9.

### *3.3.4 Magnetic resonance imaging (MRI)*

Images of individual subject brain anatomy were determined with high-resolution T1-weighted anatomical scans on a 3 Tesla Varian INOVA MRI system (1.5 mm thick axial slices with 1 mm × 1 mm in plane resolution). Stimulation sites were defined by marking the skull of the subjects with a small capsule that produced high-intensity signals on the MRI images.

### *3.3.5 Localisation of the angular gyrus*

The angular gyrus site was first established for each subject by using a visual search task. The search task is commonly used to localise the angular gyrus/posterior parietal cortex. To avoid repetition the task is described in detail in Chapter 4 (in particular section 4.3.5.2) and Chapter 5 where it is of most relevance. The addition task was then carried out while rTMS was delivered at the site that showed

disruptive effects for the visual search task (see figure 3-2). The location of the angular gyrus site was confirmed by MRI scan using the method of frameless stereotaxy (Paus, 1999). A Polaris (Northern Digital, Ontario, Canada) infra-red tracking device was used to measure the position of the subject's head and Brainsight software (Rogue Research, Montreal, Canada) was used to co-register the subject's head with the subject's MRI scan. In all subjects the coil was placed between the posterior superior temporal sulcus and the intraparietal sulcus.

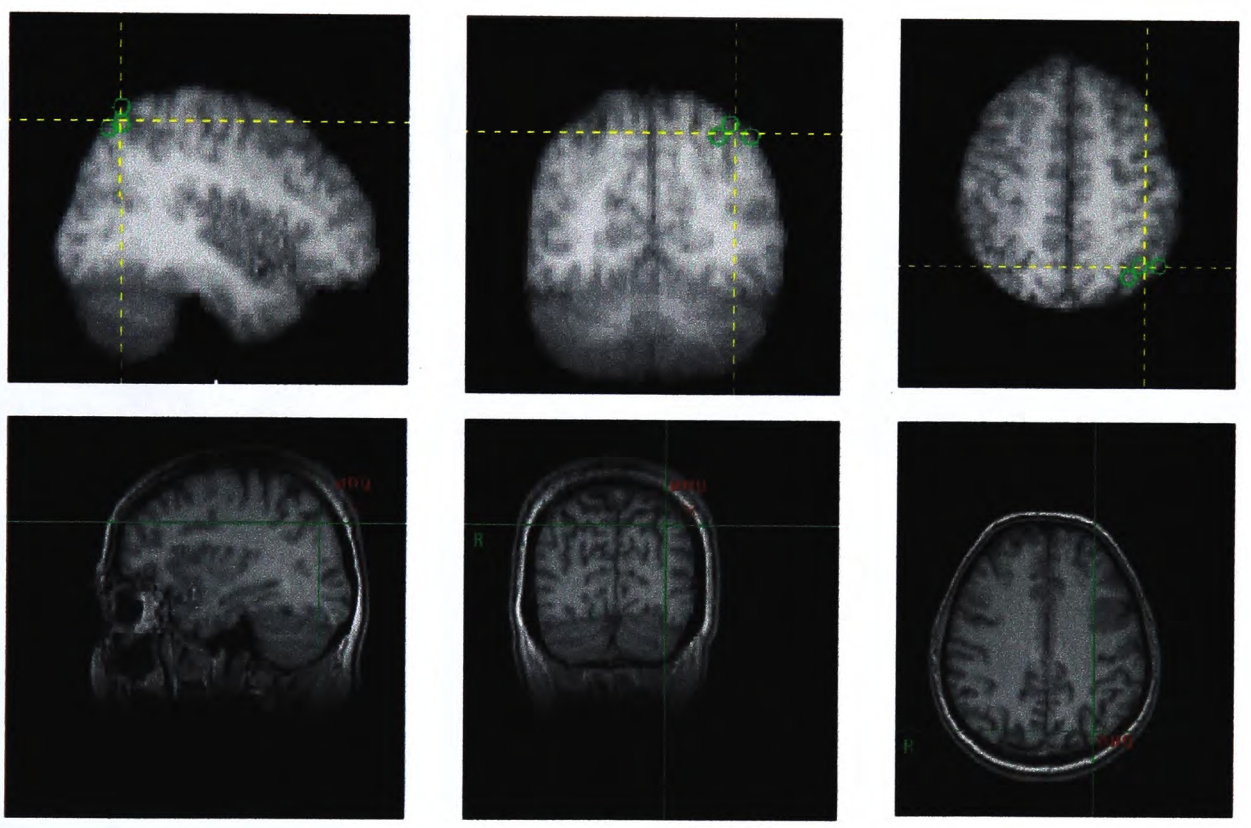


**Figure 3-2:** TMS sites over left angular gyrus/posterior IPS. The top row of pictures shows sagittal, coronal and axial views of an average MRI scan derived from three subjects after transformation to a standard template (Evans et al., 1992; Talairach & Tournoux, 1988). Green circles indicate the points where TMS was directed in these three subjects. All of the target areas cluster around the posterior part of the intraparietal sulcus adjacent to the angular gyrus (mean co-ordinates indicated by yellow crosshairs: x = -40 , y = -61 , z = 54). The bottom row of pictures shows approximately sagittal, coronal, and axial views of a single subject's MRI scan prior to registration into Talairach space. The MRI scan was co-registered with visible landmarks on the subject's head so that the position of the TMS coil could be measured with respect to the subject's brain during the experiment. Red crosses indicate the position of the TMS coil at the angular gyrus site at which rTMS affected the visuo-spatial search task and the number line task.

### *3.3.6 Localisation of the supramarginal gyrus*

Instead of using the visual search task to identify the cortical site at which the rTMS was delivered, the hand area of the subjects' motor cortex was first identified for each hemisphere separately with a small 40 mm coil, using procedures described in Schluter et al. (1998) and Schluter et al. (1999). The addition task was then carried out while rTMS was delivered 3 cm posterior and 1 cm lateral from this site (see figure 3-3).

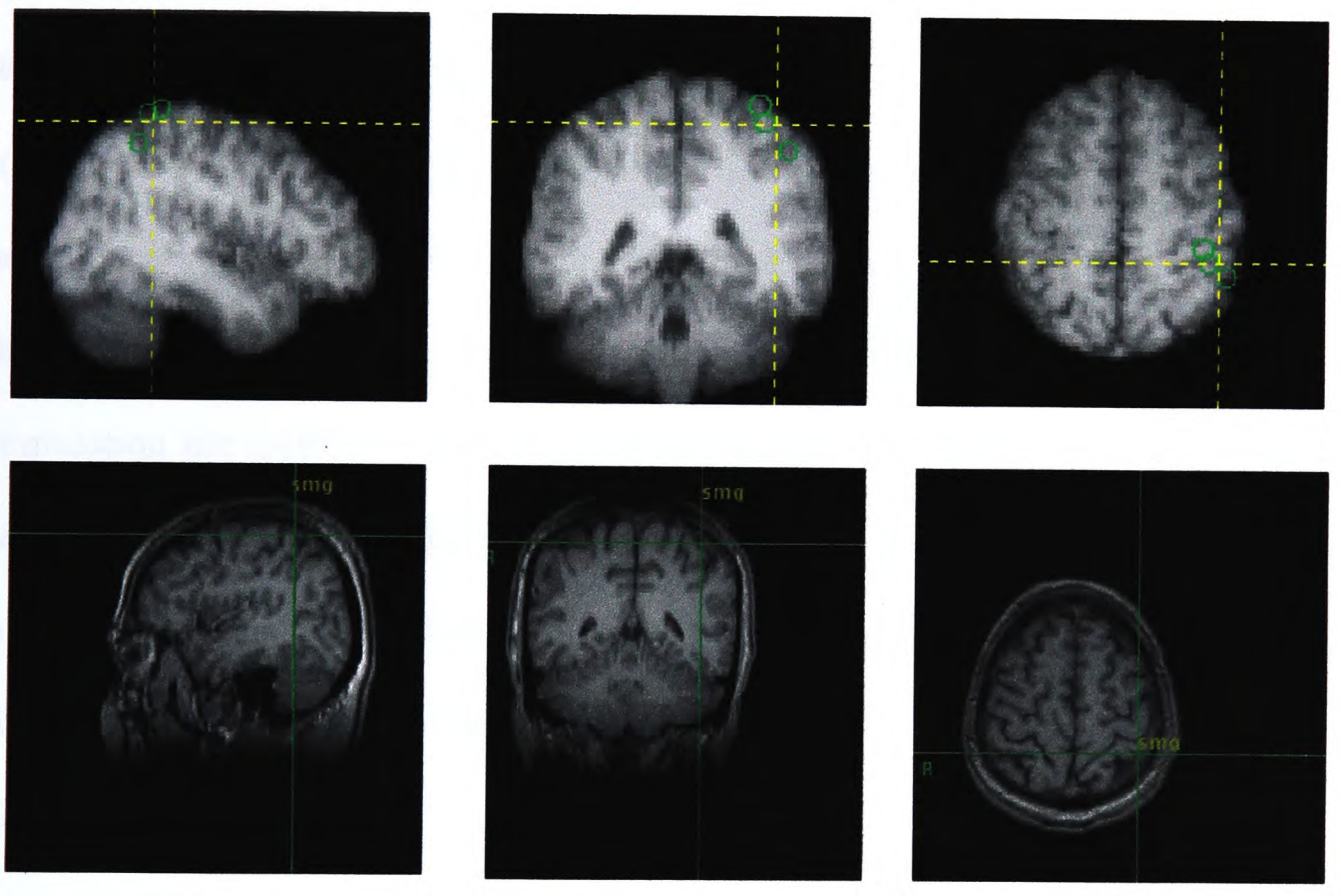



**Figure 3-3:** TMS sites over left supramarginal gyrus/anterior IPS. The figure follows the same format as figure 3-2 and represent data from the same subjects. The top row of pictures shows sagittal, coronal and axial views of an average MRI scan derived from three subjects after transformation to a standard template (Evans et al., 1992; Talairach & Tournoux, 1988). Green circles indicate the points where TMS was directed in these three subjects. Although the clustering is not as tight as in figure 3-2, it is clear that stimulation was consistently directed at the anterior part of the intraparietal sulcus where it meets the postcentral sulcus, i.e. around the supramarginal gyrus (mean co-ordinates indicated by yellow crosshairs: x = -45, y = -40, z = 58). The bottom row of pictures shows approximately sagittal, coronal, and axial views of a single subject's MRI scan prior to registration into Talairach space.

### *3.3.7 Data analysis*

SPSS version 9.0 was used to analyse median reaction times. Median reaction times were calculated rather than means, because they are less sensitive to extreme scores and therefore reflect the central tendencies of reaction times based on a small number of observations better. Reaction times from erroneous responses (7.9 % of all responses) were not included in the analysis.

The correct answer could be chosen without taking the decade digit into account. All subjects reported that they only paid attention to the last digit of the double-digit numbers and only calculated the sum of the two unit digits. Therefore, trials were analysed only according to the sum size of the unit digits (e.g. both addition tasks 22+34 and 42+24 are considered to have the same sum size, 6). A three-way ANOVA was carried out on reaction times with trial type (control-TMS), stimulation site (pIPL+S – aIPL+S) and sum size (3 to 17) as within-subject factors and with hemisphere of stimulation (left hemisphere – right hemisphere) as between-subject factor. This was followed up separately for each hemisphere by a three-way ANOVA on reaction times with trial type (control-TMS), stimulation site (pIPL+S – aIPL+S) and sum size (3 to 17) as within-subject factors.

## *3.4 Results*

### *3.4.1 Problem-size effect*

Subjects responded more slowly the larger the sum size of the two displayed numbers ($F(12,144) = 3.21$, $p < .01$). Mean median behavioural RTs increased from 393 ms for the smallest sum size (3) to 508 ms for the largest sum size (17) (see figure 3-4). The problem-size effect did not interact significantly with other factors and was not affected by TMS (sum size × trial type: $F(12,144) = 1.02$, $p = .44$; sum

size × trial type × hemisphere of stimulation: $F(12,144) = 0.94$, $p = .51$; sum size × trial type × stimulation site: $F(12,144) = 1.04$, $p = .41$; sum size × trial type × stimulation site × hemisphere of stimulation: $F(12,144) = 1.26$, $p = .25$).

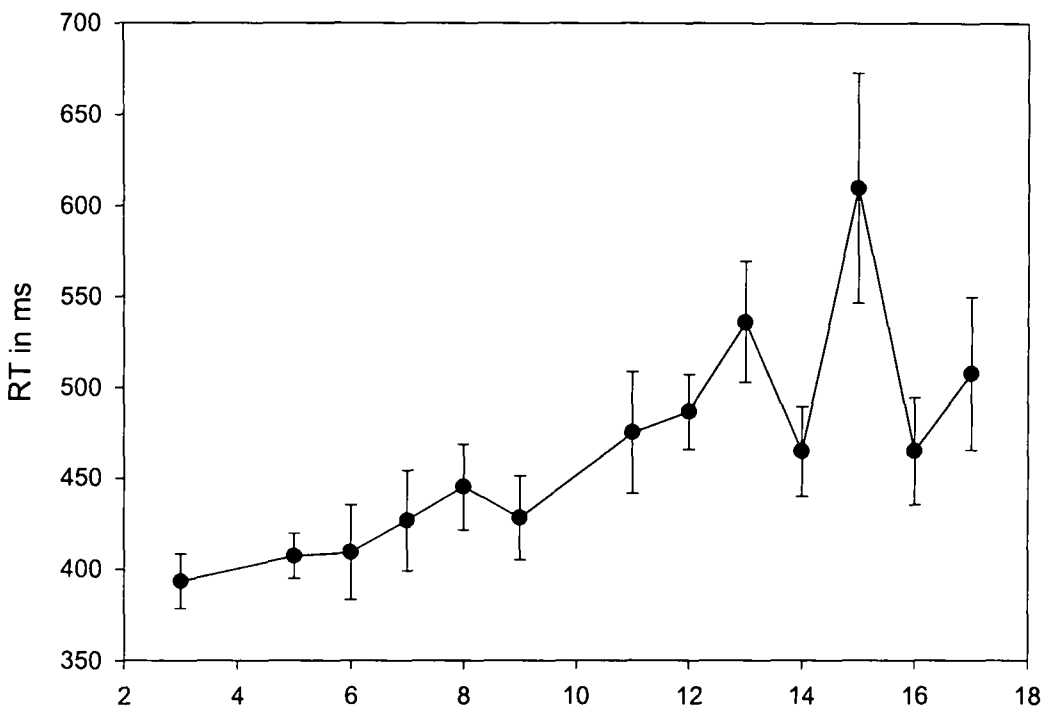



**Figure 3-4:** Behavioural problem size effect. Mean median reaction time (RT; in ms) increased with the size of the sum

### *3.4.2 Stimulation results*

*TMS over the left and right hemisphere has a different effect:* There were significant differences between the TMS effect when subjects were stimulated over the right hemisphere in comparison to when stimulation was applied over the left hemisphere ($F(1,12) = 3.70$, $p = 0.04$; one-tailed linear contrast TMS × hemisphere) (see figure 3-5 and 3-6). Therefore, each hemisphere was analysed separately.

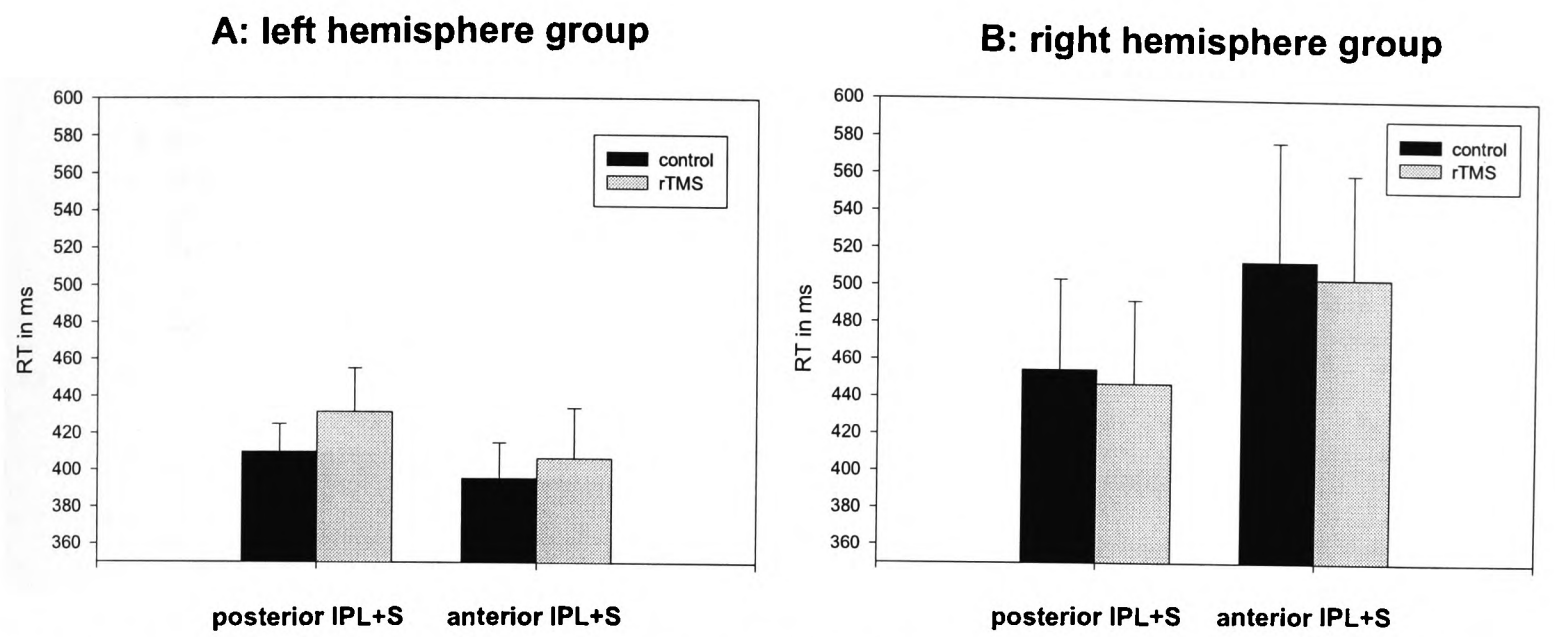



**Figure 3-5:** rTMS effect. Mean median reaction times (RT) for addition in ms; behavioural data (black boxes) and reaction time with rTMS (grey boxes) applied over one of two inferior parietal areas (angular gyrus/posterior IPS or supramarginal gyrus/anterior IPS) in either left (A) or right hemisphere (B).

*Increase in RT with rTMS over left hemisphere:* When TMS was applied over the left hemisphere mean median reaction times increased from 403 ms to 419 ms ($F(1,6) = 11.14$, $p = 0.02$). In contrast, when TMS was applied over the right hemisphere there was a slight, non-significant decrease in mean median reaction times from 484 ms to 475 ms ($F(1,6) = 0.77$, $p = 0.41$).

*TMS effects stronger over left angular gyrus/posterior IPS:* Although there was an increase in reaction times for both stimulated sites in the left parietal lobe, there was a trend towards a stronger increase when subjects were stimulated over the left angular gyrus/posterior IPS ($F(1,6) = 3.94$, $p = 0.09$; see figure 3-5a). Mean median reaction times increased by 21 ms from 410 ms to 431 ms with TMS stimulation. In contrast when stimulated over the left supramarginal gyrus/anterior IPS the mean median reaction times only increased by 10 ms (from 396 ms to 406 ms). TMS did not interact significantly with any other factors.

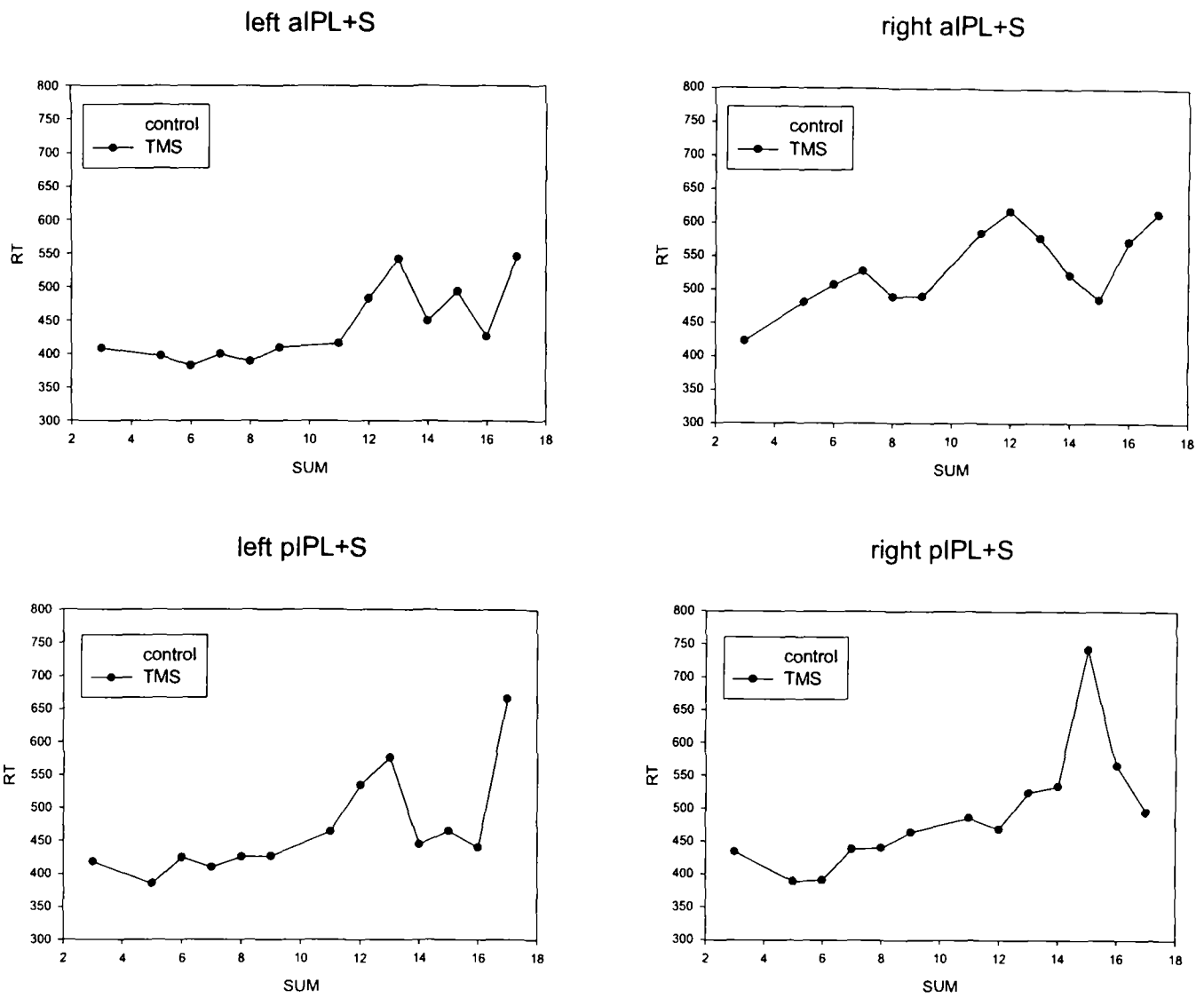



**Figure 3-6:** rTMS effect and problem-size effect. Mean median reaction times (RT) for addition in ms; behavioural data (grey lines) and reaction time with rTMS (black lines) applied over one of two inferior parietal areas (aIPL+S. see top row; pIPL+S, see bottom row) in either left or right hemisphere.

### *3.5 Discussion*

In this first experiment rTMS stimulation over left inferior parietal areas resulted in a significant increase in reaction times in a simple addition task. This effect was specific to left hemisphere stimulation. There was no increase in reaction times for TMS stimulation over right hemisphere. On the addition trials without transcranial magnetic stimulation subjects showed the classical problem size effect with longer reaction times the larger the sum of the two operands.

### *3.5.1 Did the subjects really calculate?*

However, looking at the display of the addition task, one could doubt whether subjects really calculated in the experiment. Perhaps they used other strategies for selecting the correct sum out of the two displayed answers? Krueger & Hallford (1984), for example, reported that in sum verification tasks in which the addition task and the possible answers were displayed concurrently (e.g. 22 + 34 = 57 ?) subjects did not always calculate the sum and compare it to the proposed answer, but instead, very frequently, used a parity check. Only if the two operands are of different parity, will the correct sum be odd, otherwise the correct sum should be even. In principle, the subjects could have used a parity check without calculation to choose the correct answer, because the displayed possible answers were always just one unit apart and therefore of different parity. However, there are several good reasons to believe the subjects really calculated the sum and subsequently pressed the response key that corresponded to the side of the answer they computed. First, in contrast to Krueger & Hallford's experiment, subjects in our experiment could not compare the parity of the operands with the parity of the sum without remembering the two numbers, because they were not displayed at the same time. Second, subjects were explicitly instructed to calculate before the experiment. They were also encouraged implicitly to calculate by a blank screen that followed the addition task and was displayed for 300 ms. Additionally, the choice they had to make was not a simple true/false response, rather they had to choose the correct answer out of two displayed answers. Therefore, a pure parity check would not have been a more efficient strategy in this situation that normal calculation. Third, LeFevre & Kulak (1994) found, using a memory probe procedure, that the sum of a pair of digits (even without a plus sign between them) is computed by subjects even though this

calculation in their experiment was irrelevant to, and indeed, interfered with, the task. Fourth, if subjects used a rule-based parity check there should be no increase in reaction times for larger sums. The subjects, however, showed a significant problem-size effect. This is good cause to be confident therefore that in most cases the subjects really calculated or retrieved the sum and did not use parity check.

### *3.5.2 Importance of the left inferior parietal lobe for addition*

The significant effect of TMS specific to the left inferior parietal lobe provides further evidence for the importance of the left inferior parietal lobe, and the angular gyrus/posterior part of IPS in particular, for calculation. This is in line with patient studies showing that acalculia is more common after left- hemispheric lesions (Cipolotti, Butterworth, & Denes, 1991; Grafman, Passafiume, Faglioni, & Boller, 1982; Henschen, 1919; Mayer, et al., 1999). Although there is still considerable debate in the neuroimaging literature over a general dominance of the left hemisphere in mathematical tasks, the greater contribution of the left hemisphere to calculation tasks is mostly agreed upon. In several neuroimaging studies the importance of the left inferior parietal lobe and the left angular gyrus in particular for exact calculation processes has been shown (Cowell, Egan, Code, Harasty, & Watson, 2000; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Zago, et al., 2001).

These data support the conclusion that the left angular gyrus is important in mental calculation of addition tasks. However, several questions remain unanswered. First, there was also an increase in reaction times for stimulation over the left more anterior site (supramarginal gyrus/anterior IPS), although somewhat smaller than over the angular gyrus. There are at least two possible explanations for this effect. First, this anterior site could contribute itself to calculation processes. From studies

on patients, for example, it is not clear whether damage to both supramarginal gyrus and angular gyrus is necessary or whether a breakdown in just one of these systems is sufficient to produce acalculia. In most cases both areas are damaged. Second, EEG studies on the spread of activation after TMS stimulation have shown that resulting changes in electrical activity were maximal close to the point of stimulation, but that the effect spread to adjacent areas within 5 to 30 ms (Ilmoniemi, et al., 1997). It is thus impossible to exclude the possibility that the effect observed when stimulated over the left anterior IPL+S could be due to the spread of activation to areas belonging to the left angular gyrus. Nevertheless, angular gyrus and supramarginal gyrus are not directly connected (Cavada & Goldman-Rakic, 1989a; Cavada & Goldman-Rakic, 1989b; Eidelberg & Galaburda, 1984; Passingham, 1998; von Bonin & Bailey, 1947) and behavioural effects of TMS in these two areas have been distinguished before (Rushworth, Ellison, & Walsh, 2001). On the basis of the current data it is impossible to decide between these alternatives.

### *3.5.3 Dissociating different operations with TMS*

The experiment in this chapter shows a TMS effect on addition tasks. An open question is whether one would obtain different results for multiplication, subtraction and division tasks. Several patients have been reported with impairments selective to one or two operations, while their performance in other operations is spared, such as selective impairments in addition, but not in subtraction or multiplication (van Harskamp & Cipolotti, 2001; Delazer & Benke, 1997) or impaired division with intact multiplication (Cipolotti & de Lacy Costello, 1995).

These dissociations led to modifications in models of number representation. Dehaene & Cohen (1997), for example, claim that there are at least two routes used for solving calculation: rote verbal retrieval or strategical quantity manipulation.

They explain dissociations in patients by selective failure of one of these routes. More precisely, they assume that multiplication and simple addition depend on rote verbal memory while subtraction, division and complex addition (sum > 10) require semantic manipulation of numerical quantities and rely on back-up strategies. In their model therefore impairments in addition could occur through deficits in either the asemantic or semantic routes. According to their model certain patterns of operational dissociations are impossible such as a selective impairment of multiplication and subtraction with intact performance on addition. Their notion that different arithmetic types may involve dissociable number representations has also been supported by a recent functional neuroimaging study. Lee (2000) showed that the BOLD signal was higher during multiplication than subtraction at the border between the angular and supramarginal gyri of the left hemisphere, while the signal was higher during subtraction than multiplication in the IPS of both hemispheres.

Clearly, TMS is the optimal research tool to further test the hypothesis proposed in this model by selectively disrupting the semantic and asemantic routes in multiplication and subtraction tasks.

### *3.5.4 Problem-size effect*

Several models used memory retrieval to account for the problem-size effect observed in calculation tasks. Campbell & Graham (1985) proposed that the order according to which problems were learnt during childhood might explain the greater difficulty of larger problems. Ashcraft et al. proposed that larger problems may just be less often practised as suggested by their lower frequency of presentation in textbooks (Ashcraft, 1995; Hamann, 1985). LeFevre et al. (LeFevre, Bisanz, Daley, Buffone, et al., 1996; LeFevre, Sadesky, & Bisanz, 1996) suggested that the multiplicity of strategies exhibited by subjects contributes significantly to the effect.

They showed that direct retrieval of answers is not the only strategy used and they claimed that a large part of the problem-size effect could be attributed to averaging across retrieval and non-retrieval trials on large problems.

Dehaene, Bossini, & Giraux (1993) highlighted the importance of number magnitude in general and the role it might play in problem-size effects in particular. Magnitude might be represented on a compressed psychophysical scale in such a manner that magnitudes of large numbers are less discriminable (Dehaene, 1989; Dehaene, 1992; Gallistel & Gelman, 1992). Because of this lower discriminability, large operands and large answers take longer to process and/or produce more errors than small operands or answers

Recently Butterworth, Zorzi, Girelli, & Jonckheere (2001) developed a model for the retrieval of single-digit addition facts, the so called COMP model, that points towards number magnitude as the underlying factor causing problem-size effects in addition. In this model they propose that simple addition information is stored in long-term memory in only one form, in a maximum operand + minimum operand format (i.e. both addition tasks 2+7 and 7+2 will be solved by accessing the memory representation for 7+2). Therefore the first step in solving an addition task would be the comparison of the two operands in order to decide which of the two is the larger, possibly change the order accordingly and then to look up the corresponding fact. It is well known that the time it takes to decide which of two displayed numbers is larger is longer the closer the two numbers are numerically to each other (Moyer & Landauer, 1967). This numerical distance effect will be investigated in detail in subsequent experiments.

### *3.6 Conclusion*

Recently Isaacs et al. (2001) reported a study on voxel-based morphometry that led to the identification of a reduction in grey matter in the left intraparietal sulcus in prematurely-born children with dyscalculia in comparison to equally premature children without dyscalculia. This is in line with adult patient data and suggests that mathematical difficulties in children and adults might be due to cortical changes in a similiar left inferior parietal region. In this experiment I have shown the important contribution of this same region for solving addition tasks.

Additionally, TMS was used successfully in the experimental situation to obtain results in a normal sample that show parallels to patterns observed in a population of patients. This is to our knowledge the first study in which deficits seen in acalculic patients have been produced in normal adults by rTMS stimulation.

These results justified the use of TMS as a neuroimaging tool for investigating the neural basis of mathematics. In the next chapter TMS will be used to interrupt a more basic numerical process that is seldom disrupted in patients: the judgement of number magnitude.

# 4. The Mental Number Line and the angular gyrus

*The contribution of the inferior parietal lobes in a number comparison task*

## 4.1 Summary

To investigate the hemispheric organisation of a language-independent spatial representation of number magnitude in the human brain, I applied focal repetitive Transcranial Magnetic Stimulation (rTMS) to the right or left angular gyrus (ANG) while subjects performed a number comparison task with numbers between 31 and 99. Repetitive TMS over the angular gyrus disrupted performance of a visuospatial search task and rTMS at the same site disrupted organisation of the putative "number line". In some cases the pattern of disruption caused by angular gyrus rTMS suggested that this area normally mediates a spatial representation of number. The effect of angular gyrus rTMS on the number line task was specific. rTMS had no disruptive effect when delivered over another parietal region, the supramarginal gyrus (SMG), in either the left or right hemisphere.

## 4.2 Introduction

Our lives are influenced by numbers at every turn. Numbers mark events such as the beginning of every day on our alarm clocks, the amount of sugar in our morning coffee, the bus we take to work, the room we work in and the money we get for working. Numbers also mark the beginning, duration and end of our lives.

"Numerals are always pictured by me in a straight line from left to right." (page 254) said one of Galton's subjects (Galton, 1880). As early as 1880 Galton found evidence for a spatial representation of numbers akin to a mental number line. He asked subjects to describe how they think of numbers and many described overt visuospatial representations of numbers sometimes even with specific colours or

characters associated with certain numbers. In most of these descriptions numbers were represented on a line – a mental number line.

A language independent spatial representation of number magnitude (Dehaene & Cohen, 1995; Seron et al., 1992) is only one type of number representation. There is evidence for a second representational format of numbers in human brains: for exact arithmetical knowledge we mainly use language-based representations (Dehaene, Spelke, Pinel, et al., 1999).

Over a hundred years after Galton's observation, the idea of a language-independent spatial representation of numbers in the human brain is still useful (Butterworth, 1999; Dehaene, Bossini, & Giraux, 1993; Seron, Pesenti, Noel, et al., 1992). This spatial representation may rely on visuospatial cerebral networks (Dehaene, Spelke, Pinel, et al., 1999). As the parietal cortex plays a crucial role in these patchworks (Andersen, Snyder, Bradley, & Xing, 1997; Colby & Goldberg, 1999; Corbetta, Kincade, Ollinger, et al., 2000; Corbetta & Shulman, 1999; Gitelman, et al., 1999; Nobre, et al., 1997) it is reasonable to propose the parietal cortex as a candidate area that may contribute to the representation of the number line. Within the human parietal cortex it is clear that the posterior inferior regions, the angular gyrus and the adjacent intraparietal and superior temporal sulci which bound the angular gyrus, are most closely involved in visuospatial attention (Corbetta, Kincade, Ollinger, et al., 2000; Corbetta & Shulman, 1999; Gitelman, et al., 1999; Nobre, et al., 1997; Rushworth, Ellison, & Walsh, 2001; Rushworth, Paus, & Sipila, 2001; Rushwort, Krams & Passingham, 2001). The angular gyrus might therefore be expected to play a role in mediating the spatial representation of numbers.

Recent neuropsychological and neuroimaging studies strongly suggest that the left parietal cortex is important for the representation or estimation of number (Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Pesenti, Thioux, Seron, & De Volder, 2000; Rickard, et al., 2000; Stanescu-Cosson, et al., 2000; Zago, et al., 2001). Lesions in the posterior regions of the left hemisphere can cause acalculia; in many cases it is clear that the critical focus of the lesion is within the parietal cortex and the angular gyrus is often damaged (Cipolotti, Butterworth, & Denes, 1991; Grafman, Passafiume, Faglioni, & Boller, 1982; Hecaen, Angelergues, & Houllier, 1961; Henschen, 1919; Henschen, 1920; Jackson & Warrington, 1986; Mayer, et al., 1999; Warrington, 1982). Lesions in this region can also lead to a loss of number meaning (Delazer & Benke, 1997) or number magnitude (Delazer & Butterworth, 1997).

Although the percentage of subjects who are able to describe their number lines as colourfully and elegantly as Galton's subjects might be low (Seron, Pesenti, Noel, et al., 1992), one phenomenon is found consistently: the symbolic distance effect (SDE). Number magnitude is often studied by using comparison judgment tasks in which individuals have to decide which of two numbers displayed is the larger. Moyer & Landauer (1967) found a symbolic distance effect (SDE) in which the larger the difference in numerical value between two numbers the shorter was the time needed to decide which of the numbers is larger (Banks, Fujii, & Kayra-Stuart, 1976; Buckley & Gillman, 1974; Garner, Podgorny, & Frasca, 1982). Dehaene, Bossini & Giraux (1993) showed that individuals are faster to respond to small numbers with the left hand and to large numbers with the right hand and called this effect the spatial-numerical association of response codes or SNARC effect. These

findings again strongly suggest that number magnitude is represented as a number line with an orientation from left to right.

Recently, several neuroimaging studies used explicit number comparison tasks in order to investigate which brain areas are involved in number magnitude processing. Dehaene (1996) reported right hemisphere activation in an ERP study for numbers smaller than ten. Neuroimaging studies employing number comparison tasks have consistently found activation in the inferior parietal lobes (Chochon, Cohen, van de Moortele, & Dehaene, 1999; LeClec'H, et al., 2000; Pesenti, Thioux, Seron, & De Volder, 2000; Pinel, et al., 1999). When it comes to hemispheric side of activation and activation of sub-areas in the inferior parietal lobes their results are inconsistent. These differences could be because different investigators used different absolute number sizes, different reference numbers and different control conditions. But precise location and hemispheric side of activation could also depend on distance from the reference number. Pinel et al. (1999) reported left intraparietal sulcus activation for numbers close to the reference number (5) and right intraparietal sulcus activation for numbers far from the reference number. Only two fMRI studies used numbers larger than ten in a number comparison task (LeClec'H, et al., 2000; Rickard, et al., 2000). Rickard et al. (2000) used number detection as a control task. They report reliable bilateral angular gyrus activation in some of their subjects while LeClec'H et al. (2000) using a body part comparison task as a control found bilateral supramarginal activation and right intraparietal sulcus activation.

I used another neuroimaging method, repetitive transcranial magnetic stimulation (rTMS), to investigate the importance of parietal cortex for number representation and whether numerical representation takes a spatial form. The

application of TMS over a brain area results in the activation of its neurons and its normal functioning is transiently disrupted (Cracco, Cracco, Maccabee, & Amassian, 1999; Edgley, Eyre, Lemon, & Miller, 1997; Pascual-Leone, Walsh, & Rothwell, 2000; Walsh & Cowey, 1998; Walsh & Rushworth, 1999). If the stimulated area is essential for the cognitive task then performance is impaired and slower. If the area is not essential then TMS either has no effect or even facilitates task performance (Marzi, et al., 1998; Oliveri, et al., 1999; Walsh, Ellison, Battelli, & Cowey, 1998). Such facilitation may have two possible origins. First, TMS is associated with a sound and tactile sensation and these tend to speed performance due to an intersensory facilitation effect (Hershenon, 1962; Marzi, et al., 1998). It is also possible, however, that the TMS induced disruption of one cortical circuit may disinhibit competing cortical circuits (Oliveri, et al., 1999; Walsh, Ellison, Battelli, & Cowey, 1998). The more easily interpreted disruptive effects of TMS are the focus of this investigation.

Subjects were asked to indicate whether double-digit numbers (31-99) presented on a screen are smaller or bigger than a reference number (65) by pressing one of two possible keys. On some of the trials rTMS was administered over left or right angular gyrus and the adjacent part of the posterior IPS (experiment 1). The angular gyrus site was first identified by testing the effect of rTMS on a visual search task. Neuroimaging studies as well as studies on patients have suggested that this part of the parietal cortex is concerned with the performance of such visual search tasks (Ashbridge, Cowey, & Wade, 1999; Corbetta & Shulman, 1999; Donner, et al., 2000; Friedman-Hill, Robertson, & Treisman, 1995). Walsh et al. have previously shown that rTMS at this parietal region, but not others, disrupts

visual search tasks (Ashbridge, Walsh, & Cowey, 1997; Walsh & Cowey, 1998; Walsh & Rushworth, 1999).

Two control procedures were used. Because rTMS is associated with tactile and auditory sensations it is important to check that any effect of rTMS is specific to a particular underlying cortical region and not just the consequence of its distracting sound and feel. In experiment 2, rTMS was administered over a control site; an adjacent, but distinct region of parietal cortex (left or right supramarginal gyrus and adjacent part of the anterior IPS).

The supramarginal gyrus (SMG) was chosen as the control site for two reasons. First, to use a different site within the parietal lobe. Second, the supramarginal gyrus is more anterior, i.e. nearer to the motor cortex than the angular gyrus. If the rTMS effects were simply due to interference in basic motor cortical function, perhaps by a spread of TMS induced excitation, then stimulation at this control site, and not the angular gyrus, would be expected to have the more disruptive effect. Moreover the supramarginal gyrus is closely associated with motor attention (Deiber, Ibanez, Sadato, & Hallett, 1996; Rushworth, Ellison, & Walsh, 2001; Rushworth, Krams, & Passingham, 2001; Rushworth, Paus, & Sipila, 2001) and the control of limb movements. If the interference effects of rTMS were simply due to disruption of the responses required by the task then, again, the deficit would be greater when rTMS was applied over the SMG control site than over the ANG site.

In brief, ANG rTMS disrupted performance in the number line task but rTMS over the SMG control site caused no deficit. I therefore carried out a third experiment as an additional control procedure to again ensure that the effect of ANG rTMS was driven by the spatial characteristics of the number stimuli and their

mental representation in space rather than just the responses required in the task. In this final experiment subjects were required to use a reversed-response version of the number line task.

## *4.3 Materials and Methods*

### *4.3.1 Stimuli and apparatus*

Subjects were seated in a lighted room at a distance of approximately 50 cm from a computer screen. The experiment was controlled by a PC running the SuperLab software version 1.04. Stimuli were presented centrally on a 17-in. colour monitor and appeared as black against a grey background. The stimuli consisted of a set of 68 double-digit numbers, each presented individually on the screen. Numbers were displayed in Times New Roman font (type size = 18 points) and when viewed from the distance of 50 cm subtended 1° of visual angle. Subjects wore rubber bathing caps on which the relevant co-ordinates of the International 10/20 EEG system (AEEGS, 1991) were marked.

To generate the magnetic pulses a Magstim stimulator, Model Super Rapid (The Magstim Company Limited, Whitland, UK) was used with a 70 mm figure of eight coil. The maximal magnetic field strength at the coil surface was 1.8 Tesla. Precise timing of onset of both the visual and the magnetic stimulus was verified using an oscilloscope.

### *4.3.2 Procedure*

In each block, target numbers ranged from 31 to 99 (see figure 4-1b). Each number was displayed once in each block, with the exception of the numbers 33, 38, 45, 59, 64, 66, 71, 86, 93 or 97 which occurred twice. The number 65 was never presented. The order of the numbers appearing on the screen was pseudo-random within each

block. Subjects were required to indicate with one of two possible key presses whether the number on the screen was greater or less than 65. In experiments 1 and 2 the index finger of the right hand was used to indicate 'greater than' response and the index finger of the left hand was used to indicate the 'less than' response. Stimuli remained on the screen until subjects made a response. The intertrial interval was one second. During each session subjects performed 4 blocks of 78 trials, preceded by an initial training block of 10 non-TMS trials (a total of 322 trials). In experiment 3 the index finger of the left hand was used to indicate 'greater than' response and the index finger of the right hand was used to indicate the 'less than' response. In a pilot study subjects made significantly more errors with this reversed response mode. Subjects in experiment 3 were therefore asked to complete 166 practice trials in which they trained the reversed response mode before the experiment began.

On 10 trials in each experimental block rTMS was applied over the subject's scalp for 500 ms at 10 Hz. The rTMS stimulation started before onset of the visual stimulus. The rTMS trials occurred pseudo-randomly with the constraint that the number on the screen was 33, 38, 45, 59, 64, 66, 71, 86, 93 or 97. During the whole experiment the coil was held in a constant position with reference to the subject's head.

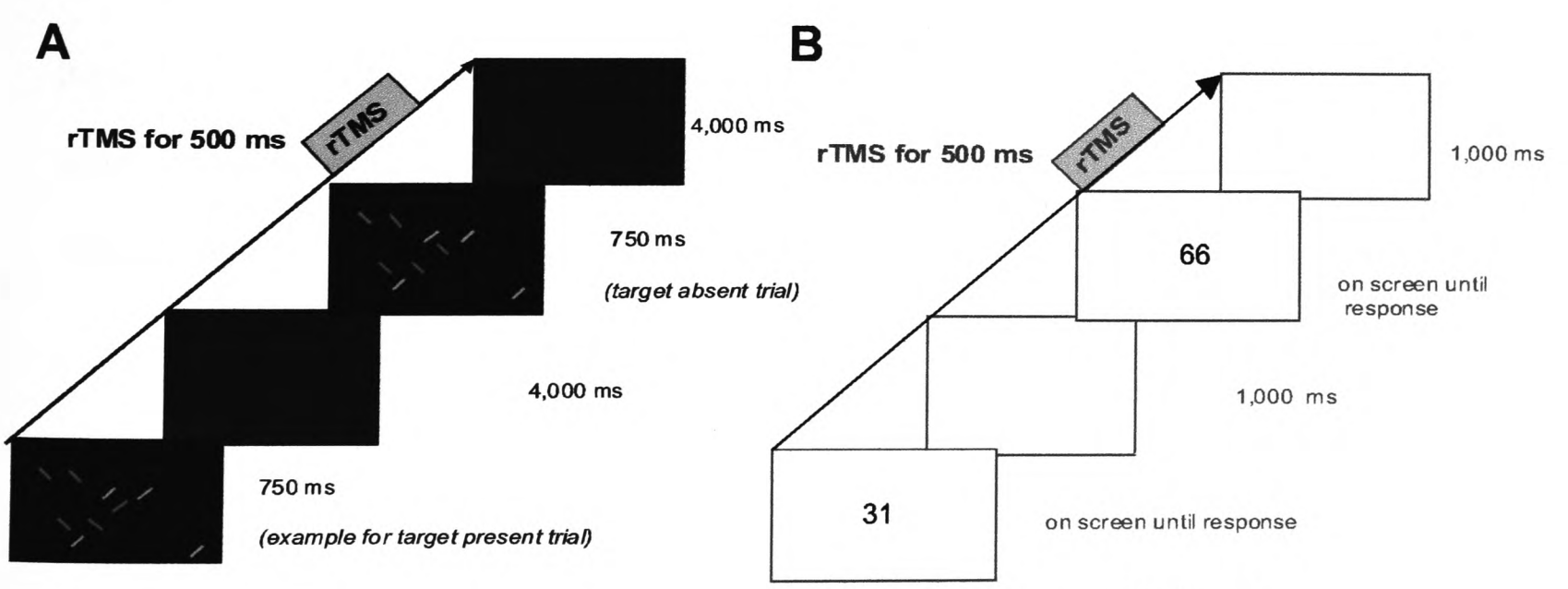



**Figure 4-1:** *a) Visual search task.* Subjects were presented with green and red forward and backward slashes and were asked to indicate with one of two possible key presses whether the target (a red forward slash) was present (lower screen) or absent (upper screen). Stimuli remained on the screen for 750 ms. The intertrial interval was four seconds. On some trials rTMS was applied. *b) Number comparison task.* Subjects were presented with numbers between 31 and 99 and were asked to indicate with one of two possible key presses whether the number on the screen was greater or less than 65. Stimuli remained on the screen until subjects made a response. The intertrial interval was one second. On some trials rTMS was applied.

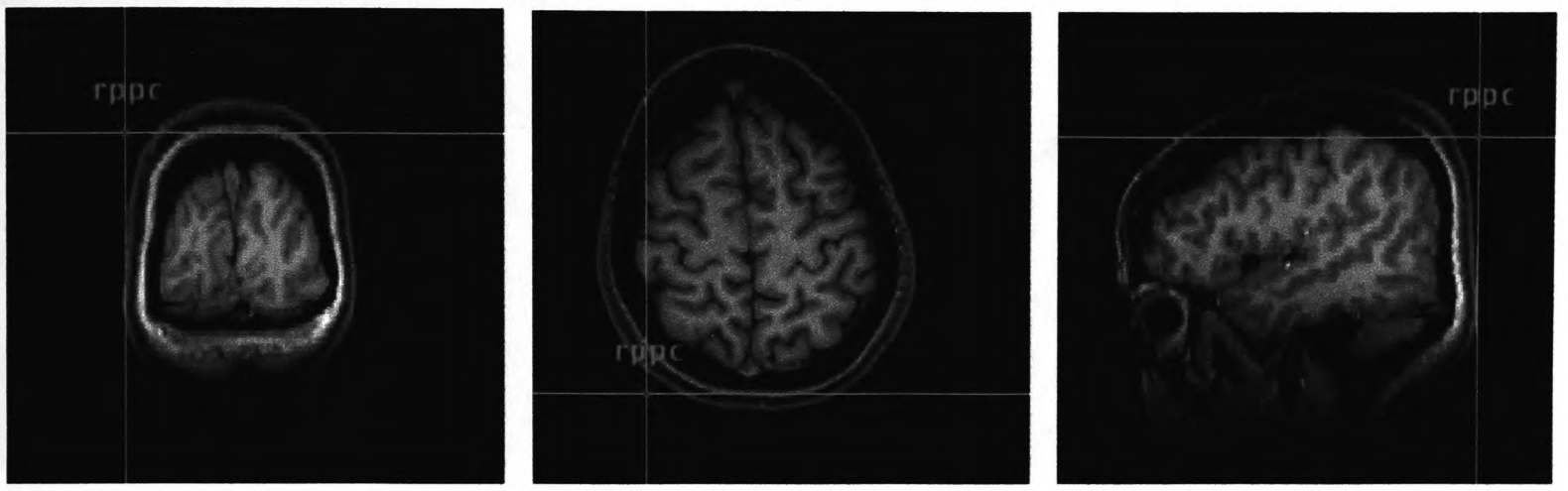
The magnetic stimulus intensity used was between 50% and 80% of the maximum stimulator output. The intensity of the magnetic stimulation was set separately for each individual at 5% above motor threshold. Motor threshold was defined as the minimum percentage of the stimulator output required to evoke a visually detectable twitch in a tense muscle of the subject's hand contralateral to the stimulated motor cortex (Pridmore et al., 1998). Frequency, intensity and duration of rTMS were in accordance with the safety guidelines established by Wassermann (1998).

All subjects were checked for TMS exclusion criteria (Wassermann, 1998) and gave their written informed consent before participating. The procedure was approved by the Ethics Committee of the University of Oxford, Department of Experimental Psychology. Subjects were at least in university education, had normal or corrected to normal visual acuity and were free of any neurological condition. They were reimbursed for travel expenses and time taken to participate in the study.

### *4.3.3 Magnetic resonance imaging (MRI)*

Images of individual subjects' brain anatomy were determined with high-resolution T1-weighted anatomical scans on a 3 Tesla Varian INOVA MRI system (1.5 mm thick axial slices with 1 mm × 1 mm in plane resolution). Stimulation sites were defined by marking the skull of the subjects with a small capsule that produced high-intensity signals on the MRI images (see figure 4-2 and 4-3).

## Angular Gyrus/Posterior IPS



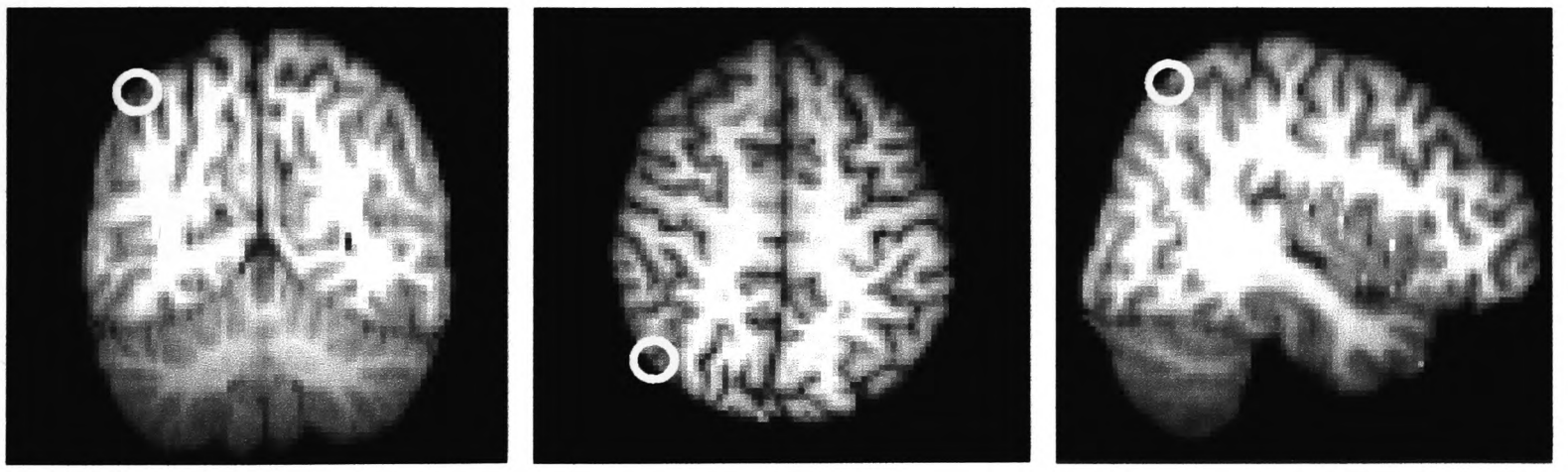



**Figure 4-2:** *TMS sites over angular gyrus/posterior IPS.* The top row of images shows approximately coronal, axial, and sagittal views of a single subject's MRI scan. The MRI scan was co-registered with visible landmarks on the subject's head so that the position of the TMS coil could be measured with respect to the subject's brain during the experiment. The cross hairs indicate the position of the TMS coil at the angular gyrus site at which rTMS affected the visuospatial search task and the number line task. The bottom row of images shows coronal, axial, and sagittal views of the same subject's MRI scan after transformation to a standard template (Talairach & Tournoux, 1988; Evans et al., 1992). The circle marks the centre of the stimulated brain area under the centre of the TMS coil in the angular gyrus just lateral to the intraparietal sulcus ($x = 42$, $y = -58$, $z = 52$).

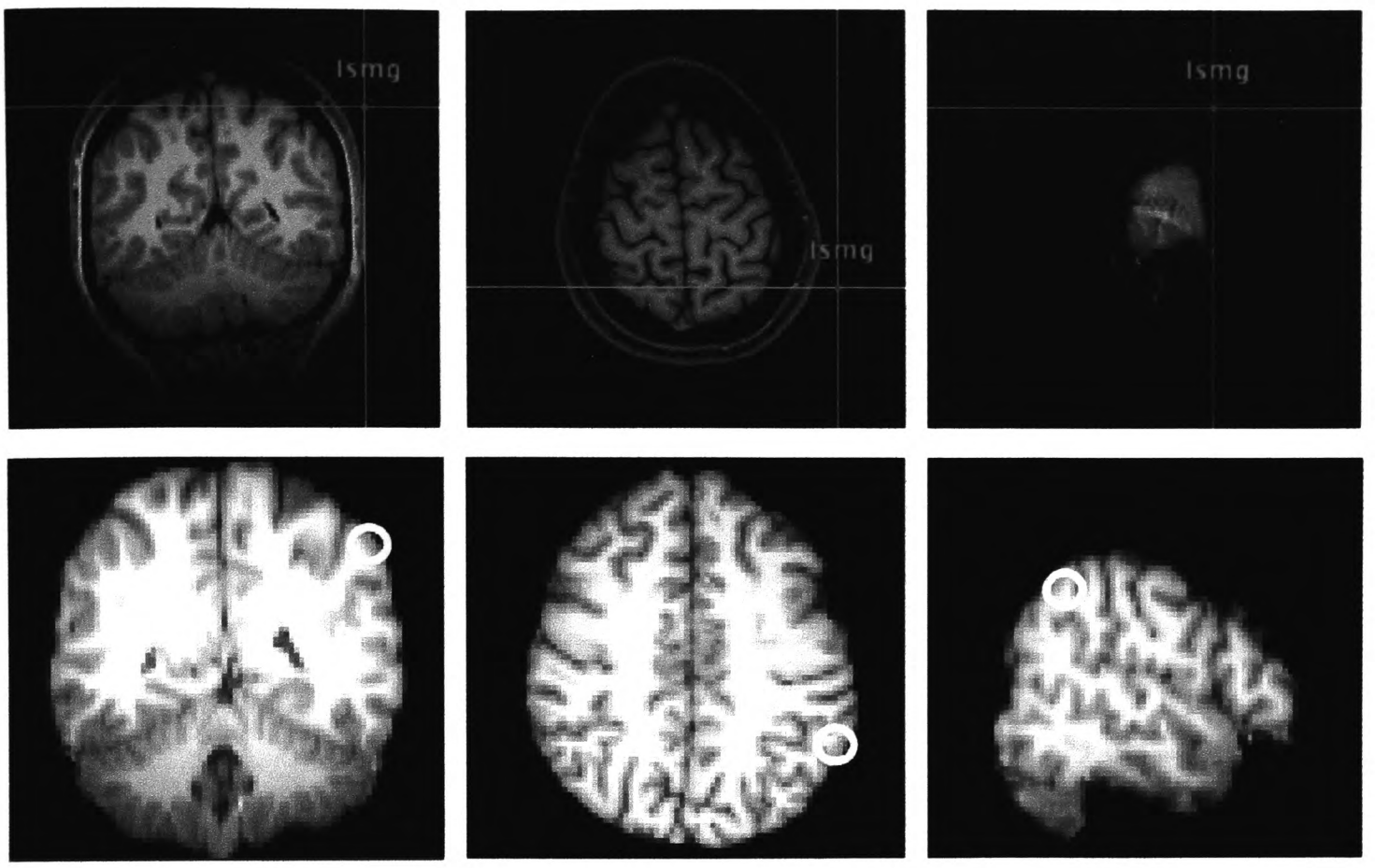



**Figure 4-3:** *TMS sites over supramarginal gyrus/anterior IPS.* The figure follows the same format as figure 4-2 and represents data from the same subject. The top row of images shows approximately coronal, axial, and sagittal views of the position of the TMS coil with respect to the subject's supramarginal gyrus. The bottom row of images shows coronal, axial, and sagittal views of the registered brain. The circle marks the centre of the stimulated brain area under the centre of the TMS coil in the supramarginal gyrus just posterior to the post-central sulcus and the intraparietal sulcus (x = -52, y = -46, z = 44).

### *4.3.4 Data analysis*

The statistical package SPSS (version 9.0) was used to analyse the data according to the following procedure: first, the behavioural data were analysed in order to see if the classical distance effect occurred. An analysis of variance (ANOVA) was performed on mean reaction times with target-standard distance (1 - 34) and size of target number (smaller than 65 – larger than 65) as within subject conditions. Secondly, reaction times were compared for trials with and without rTMS. Only

reaction times to the numbers 33, 38, 45, 59, 64, 66, 71, 86, 93 or 97 were analysed. An analysis of variance (ANOVA) was performed on reaction times with trial type (control trial – trial with rTMS), side of TMS stimulation (left hemisphere - right hemisphere), target-standard distance (1 - 32) and size of target number (smaller than 65 – larger than 65) as within-subject factors. For ease of exposition, only rTMS effects and their interactions with other variables will be reported.

In figures 4-5, 4-6 and 4-7 smoothed data are shown. For data smoothing a centered moving average procedure with span = 3 (SPSS version 9.0) was used. The statistical analyses of data were conducted prior to smoothing.

### *4.3.5 Experiment 1 (angular gyrus - ANG)*

#### *4.3.5.1 Participants*

Nine right-handed volunteers were tested twice on different days. Three subjects were female, six male. Their ages varied from 20 to 38 years with a mean age of 25.7.

#### *4.3.5.2 Visual search task & Localisation*

Ashbridge, Walsh & Cowey (1997) had previously shown that TMS of a posterior parietal site beneath a scalp position approximately 9 cm anterior and 6 cm lateral to the inion disrupts performance of visual search. The parietal site at which the rTMS was delivered was therefore identified by first asking subjects to perform a visual search task (see figure 4-1a) with red backward and green forward slashes. A target stimulus was defined by a conjunction of colour and orientation (a red forward slash). The number of distractors was always 8. Stimuli remained on the screen for 750 ms unless subjects responded earlier. The intertrial interval was 4 s long. Before stimulation sessions subjects performed 30 trials to familiarise themselves with the task. They then performed blocks of 10 trials, starting with a behavioural block

followed by a block with rTMS stimulation over P4 (AEEGS, 1991). A 3 cm × 3 cm grid with nine points was used for stimulation and P4 was the centre of this grid. If there was no increase in RT greater than 100 ms on target present trials, subjects were asked to complete another behavioural block followed by a block with rTMS stimulation over a different site (from P4 the coil was first moved more medial and then, on following trials, clockwise). This procedure was repeated until a RT increase with rTMS of at least 100 ms across a block of 10 trials was found. For two subjects no significant increase in RT could be found. They were excluded from the study before proceeding to the number line test used in the second stage of the experiment.

The site at which rTMS disrupted visual search was first established for each subject and the number classification task was then carried out while rTMS was delivered at the same site (see figure 4-2).

The location of the angular gyrus site was confirmed by MRI scan using the frameless stereotaxy method (Paus, 1999). A Polaris (Northern Digital, Ontario, Canada) infra-red tracking device was used to measure the position of the subject's head and Brainsight software (Rogue Research, Montreal, Canada) was used to co-register the subject's head with the subject's MRI scan. In all subjects the coil was placed near the posterior superior temporal sulcus in the angular gyrus.

*4.3.5.3 Data analysis*

For the visual search task a three-way ANOVA was conducted on mean RTs with trial type (behavioural-TMS), hemispheric side (left-right) and target type (target present – target absent) as within-subject factors. For the number classification task reaction times from erroneous responses (6.8 % of all responses) and reaction times longer than 1500 ms were excluded from the analysis.

### *4.3.6 Experiment 2 (control site: supramarginal gyrus)*

#### *4.3.6.1 Participants*

Six right-handed volunteers were tested individually. Two subjects were female, four male. Their age varied from 19 to 31 years with a mean age of 22.7.

#### *4.3.6.2 Localisation*

Instead of using the visual search task to identify the cortical site at which the rTMS was delivered, the hand area of the subjects' motor cortex for each hemisphere was first identified separately with a small 40 mm coil, using procedures described in Schluter et al. (1999) and Schluter et al. (1998). The number classification task was then carried out while rTMS was delivered 3 cm posterior and 1cm lateral from this site (see figure 4-3).

#### *4.3.6.3 Data analysis*

Reaction times from erroneous responses (6.5% of all responses) as well as reaction times longer than 1500 ms were not included in the analysis.

### *4.3.7 Experiment 3 (ANG - reversed-response)*

#### *4.3.7.1 Participants*

Seven right-handed volunteers were tested. One subject was female, six male. Their ages varied from 19 to 40 years with a mean age of 25.9.

#### *4.3.7.2 Localisation*

The site at which rTMS disrupted visual search was first established for each subject as described in detail for experiment 1. The number classification task was then carried out while rTMS was delivered at the same site (see figure 4-2).

#### *4.3.7.3 Procedure*

The number classification task followed the same procedure as described above with two exceptions. Firstly, subjects were instructed to classify numbers by pressing the

left button with the left index finger for numbers larger than 65 and by pressing the right button with the right index finger for numbers smaller than 65 (reversed response). In general, subjects find this a much more difficult and counter-intuitive task to perform (Dehaene, Dupoux, & Mehler, 1990). This has been taken as evidence for the existence of a number line with a left to right orientation in many western subjects. Secondly, because in a pilot study subjects made significantly more errors with this reversed response mode, subjects were asked to complete 166 practice trials in which they trained the reversed response mode before the experiment began.

*4.3.7.4 Data analysis*

For the visual search task a three-way ANOVA was conducted on mean RTs with trial type (behavioural-TMS), hemispheric side (left-right) and target type (target present – target absent) as within-subject factors. For the number classification task reaction times from erroneous responses (6.5 % of all responses) as well as reaction times longer than 1500 ms were not included into the analysis.

## 4.4 Results

### *4.4.1 Experiment 1: Angular Gyrus*

*4.4.1.1 Visual search results*

In the visual search task subjects responded slower to all trial types when TMS was applied (see figure 4-4). Mean RTs increased on trials where the target was present from 727 ms to 956 ms when rTMS was applied over left ANG and from 678 ms to 980 ms when rTMS was applied over right ANG. TMS significantly slowed down responses to all trial types ($F(1,8) = 39.21$, $p < .001$), but had a stronger influence on trials where the target was present ($F(1,8) = 8.176$, $p = 0.021$).

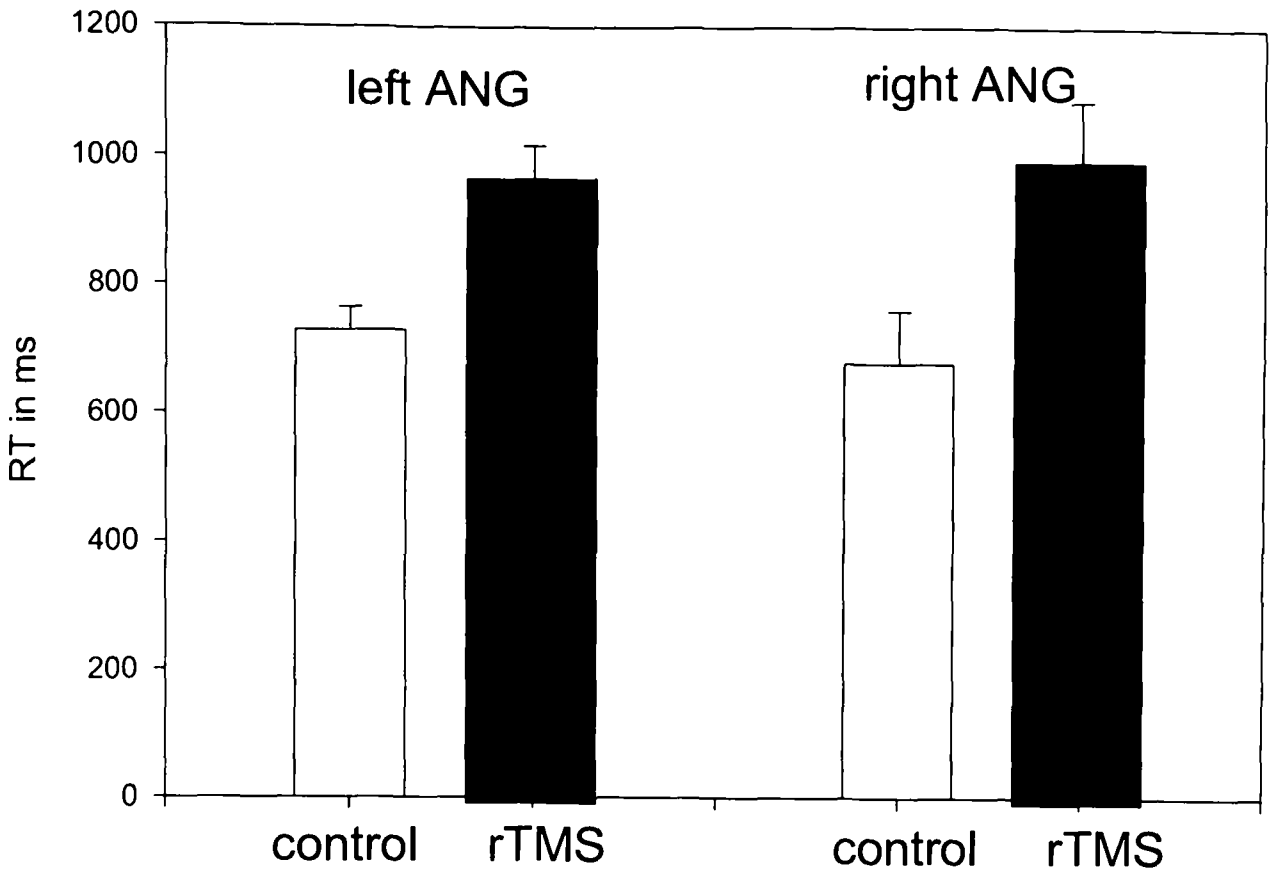



**Figure 4-4:** *Results for the visual search task:* mean reaction time (RT) in ms for target present trials in conjunction visual search task; behavioural data (open boxes) and reaction time with rTMS (black boxes) applied over left or right angular gyrus/posterior IPS.

*4.4.1.2 Number task: behavioural results*

First the behavioural data were analysed in order to see if the classical distance effect occurred. Subjects responded more slowly the closer the displayed number was to 65. With larger distances between standard and target number RTs decreased significantly ($F(33,264) = 10.53$, $p < .001$) (see figure 4-5, grey line).

*4.4.1.3 Number task: stimulation results*

In general TMS slowed down performance. The mean reaction time on trials increased by 43 ms from 569 ms on non-TMS trials to 612 ms when TMS was applied. An analysis of variance (ANOVA) was performed on reaction times with trial type (control trial – trial with rTMS), side of TMS stimulation (left hemisphere - right hemisphere), target-standard distance (1 - 32) and size of target number (smaller than 65 – larger than 65) as within-subject factors. There was a marginally

significant main effect of TMS ($F(1,8) = 4.49$, $p = .07$). There was also a three way interaction between trial type, size of target number and side of TMS stimulation ($F(1,8) = 12.96$, $p = .007$) indicating a greater disruption with TMS over left but not right angular gyrus for numbers greater than 65. A four way interaction between trial type, size of target number, side of TMS stimulation and target-standard distance was found ($F(4,5) = 10.315$, $p = .01$). This four way interaction may reflect that the stronger effect of left angular gyrus TMS for numbers greater than 65 is even larger for numbers closer to the standard (see figure 4-5a). All remaining interactions with TMS were non-significant. In order to follow up the significant interactions an ANOVA was conducted for each hemisphere separately with trial type (control-TMS), target-standard distance (1 - 32) and size of target number (smaller than 65 – larger than 65) as within-subject factors.

When the results for rTMS stimulation over left ANG were considered separately, subjects responded more slowly than without TMS. Their mean RT increased by 53 ms (from 571 ms to 624 ms) (see figure 4-5a). This TMS-induced increase was greater for numbers larger than 65 and it was especially greater for numbers larger than 65 that were close to the reference number. The effect of TMS was thus manifest as a two way interaction of both this factor (standard-target distance) and the factor of number size ($F(1,8) = 13.36$, $p = .006$) and also as a three way interaction of TMS, number size, and distance from the reference number ($F(4,5) = 6.43$, $p = .03$). The results for rTMS stimulation over right ANG separately showed that subjects responded more slowly than without TMS.

There was a clear trend towards an increase in RT ($F(1,8) = 4.97$, $p = .06$) (see figure 4-5b). In clear contrast to stimulation over left ANG there was no difference in RT increases for numbers larger or smaller than 65.

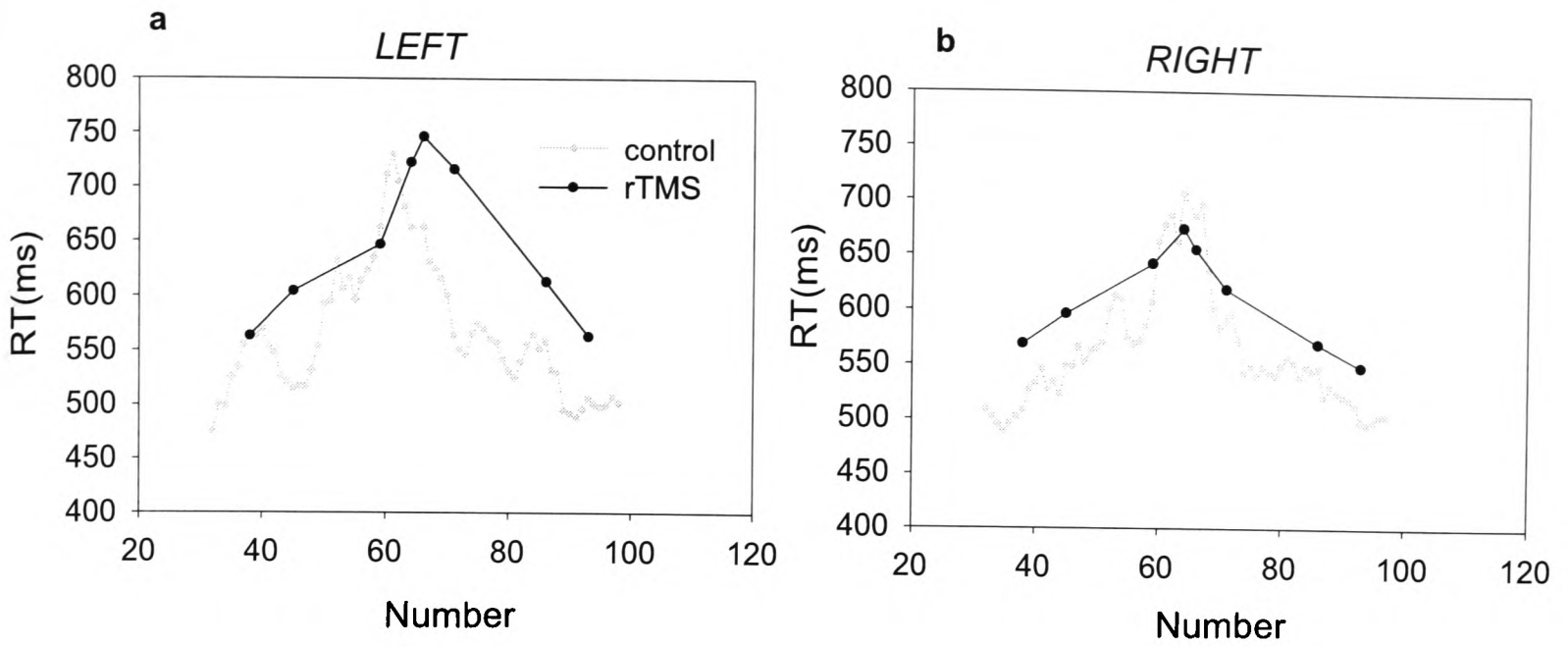



**Figure 4-5:** *Results for experiment 1 - stimulation over ANG/pIPS:* mean reaction time (RT) in ms in two digit number comparison with standard 65; behavioural data (grey line) and reaction time with rTMS (black line) applied over either left (a) or right (b) angular gyrus/posterior IPS.

### *4.4.2 Experiment 2: Control site (supramarginal gyrus)*

#### *4.4.2.1 Number task: behavioural results*

Again, subjects responded more slowly the closer the displayed number was to 65, showing a significant SDE ($F(33,165) = 6.68$, $p < .001$).

#### *4.4.2.2 Number task: stimulation results*

Unlike the case of the angular gyrus, the application of TMS over the SMG/aIPS of either the left or right hemisphere had no effect on task performance. When TMS was applied the mean reaction time decreased slightly but not significantly from 561 ms on non-TMS trials to 557 ms. Hemispheric side of TMS stimulation had no direct effect nor did size of target number. There were no significant interactions.

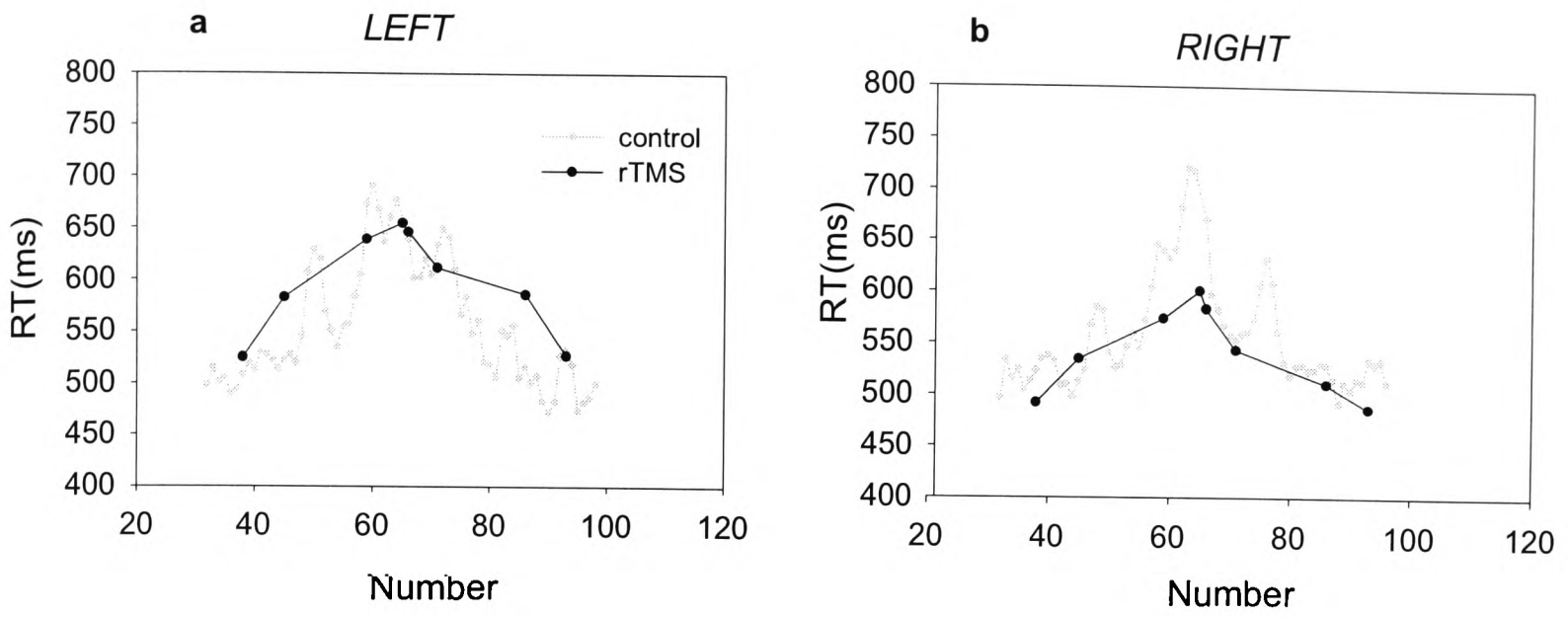



**Figure 4-6:** *Results for experiment 2 - stimulation over SMG/aIPS:* mean reaction time (RT) in ms in two digit number comparison with standard 65; behavioural data (grey line) and reaction time with rTMS (black line) applied over either left (a) or right (b) supramarginal gyrus/anterior IPS.

When the results for rTMS stimulation over left SMG were considered separately, using the same analysis as in experiment 1, subjects responded more slowly than without TMS. Their mean RT increased by 22 ms (see figure 4-6a). When the results for rTMS stimulation over right SMG were considered separately, subjects responded faster than without TMS. Their mean RTs decreased by 31 ms (see figure 4-6b). Neither of these RT changes reached or approached significance. There was no effect specific to numbers larger than 65 nor any other significant interactions involving the factor of TMS.

### *4.4.3 Experiment 3: Control task - ANG* – reversed-response

#### *4.4.3.1 Visual search results*

In the visual search task subjects responded again slower to all trial types when TMS was applied. Mean RTs increased on trials where the target was present from 647 ms to 811 ms when rTMS was applied over left ANG and from 660 ms to 784 ms when

rTMS was applied over right ANG. TMS significantly slowed down responses to all trial types ($F(1,6) = 31.25$, $p = .001$).

*4.4.3.2 Number task: behavioural results*

First the behavioural data were analysed in order to see if the classical distance effect could be observed. Again, subjects responded more slowly the closer the displayed number was to 65. With larger distances between standard and target number RTs decreased significantly ($F(33,198) = 7.54$, $p < .001$) (see figure 4-7, grey line). In general, subjects responded faster than in experiment 1 and 2.

*4.4.3.3 Number task: stimulation results*

The mean reaction time increased by 26 ms from 484 ms on non-TMS trials to 510 ms when TMS was applied. TMS significantly disrupted performance ($F(1,6) = 6.06$, $p = .05$).

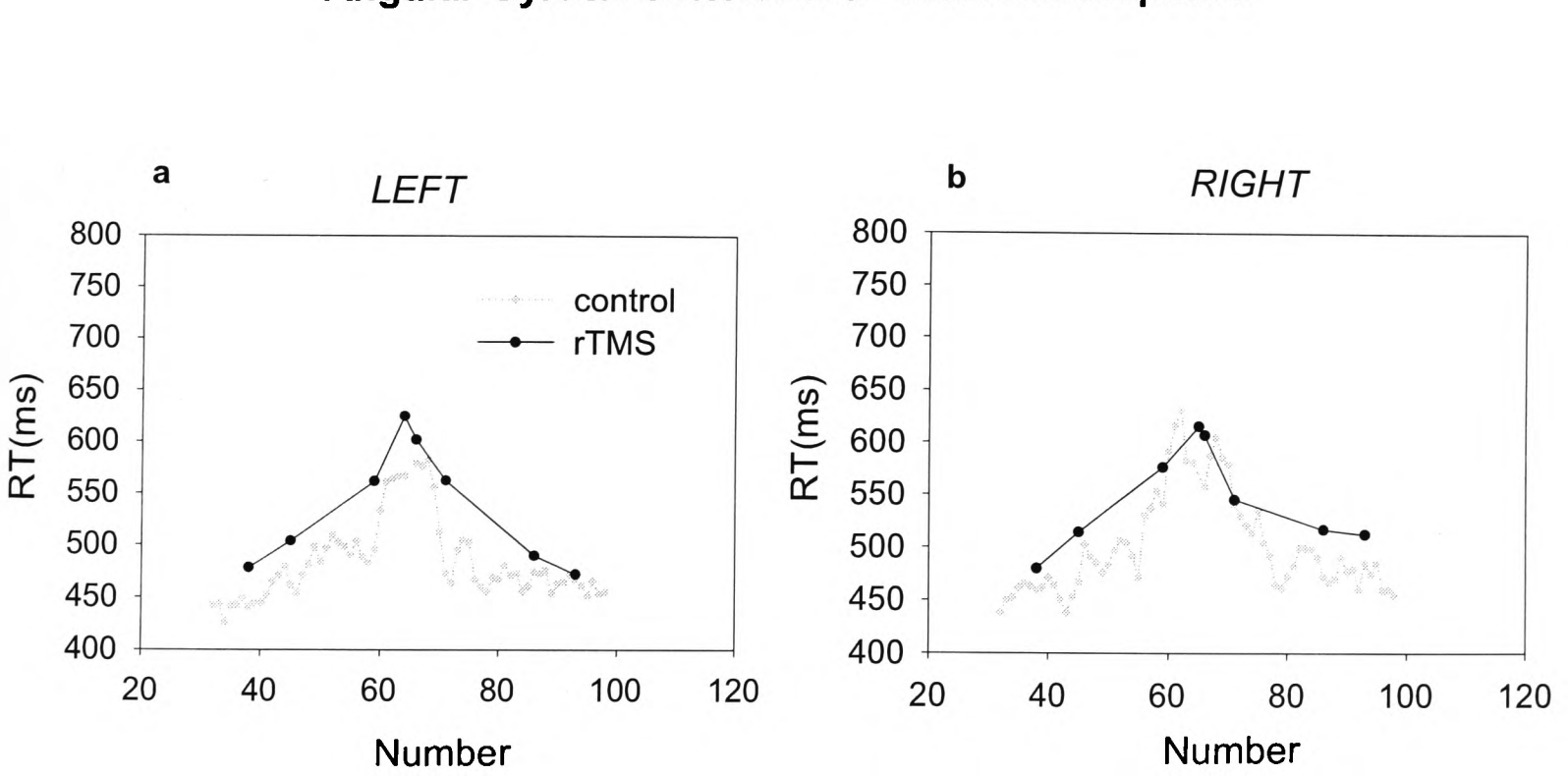



**Figure 4-7:** *Results for experiment 3 - stimulation over ANG/pIPS, reversed response:* mean reaction time (RT) in ms in two digit number comparison with standard 65; behavioural data (grey line) and reaction time with rTMS (black line) applied over either left (a) or right (b) angular gyrus/pIPS. In contrast to figure 4-5 and figure 4-6 numbers were correctly classified by pressing the left button with the left index finger for numbers larger than 65 and by pressing the right button with the right index finger for numbers smaller than 65.

When the results for rTMS stimulation over left ANG were considered separately, using the same analysis as in experiment 1, subjects responded more slowly than without TMS. Their mean RT increased by 23 ms (from 480 ms to 503 ms) (see figure 4-7a). This increase was significant ($F(1,6) = 6.92$, $p = .04$). There were no significant interactions.

When the results for rTMS stimulation over right ANG were considered separately, subjects responded more slowly than without TMS. Their mean RT increased by 28 ms (from 489 ms to 517 ms) (see figure 4-7b). There was a trend towards an increase in RT ($F(1,6) = 3.83$, $p = .10$). None of the interactions involving TMS approached significance.

### *4.5 Discussion*

As expected, the behavioural data provide a replication of the robust symbolic distance effect (Banks, Fujii, & Kayra-Stuart, 1976; Buckley & Gillman, 1974; Garner, Podgorny, & Frasca, 1982). Classification RTs for numbers close to the reference number took longer than classification RTs for numbers much smaller or greater than the reference number.

Left and right angular gyrus rTMS led to impaired and slower performance on the number comparison task when judging numbers from 31 to 99 (the effect of right pIPL+S rTMS reached a marginal significance of $p = 0.06$). The increase in RT is not due to a non-specific effect of rTMS but is specific to the angular gyrus/posterior IPS. Stimulation at the same angular gyrus/posterior IPS sites, in the same subjects, immediately prior to the number line experiment was shown to interfere with performance of a visuospatial search task. When rTMS was applied over a more anterior site, the supramarginal gyrus and adjacent anterior parts of the

IPS, subjects' performance on the number comparison task did not change significantly (experiment 2).

The results are therefore consistent with neuropsychological and neuroimaging studies that have emphasised the role of the parietal cortices in mathematical cognition and the representation of number (Cipolotti, Butterworth, & Denes, 1991; Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000; Grafman, Passafiume, Faglioni, & Boller, 1982; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Henschen, 1919; Henschen, 1920; Mayer, et al., 1999; Pesenti, Thioux, Seron, & De-Volder, 2000; Rickard, et al., 2000; Stanescu-Cosson, et al., 2000; Warrington, James, & Maciejewski, 1986; Zago, et al., 2001). It has not been clear from patient studies which regions within the parietal lobe are essential for maintaining and manipulating even basic aspects of numerical representations, such as number magnitude; even small lesions involve damage to the white matter and may result in the disconnexion of more than one parietal area (Mayer, et al., 1999). The precise areas of activation recorded in neuroimaging investigations of number magnitude vary with the control task against which comparisons are made. It is possible that while several areas may be activated by number tasks only a few sub-areas are essential for the representation of number magnitude per se. The present rTMS results confirm the importance of the angular gyrus and adjacent posterior IPS in spatially based number magnitude representations (Rickard et al., 2000).

### *4.5.1 Why angular gyrus and not supramarginal gyrus?*

The pre-emininent role of the angular gyrus and adjacent posterior IPS, as opposed to the supramarginal gyrus and adjacent anterior IPS, in the present experiment and in the experiment of Rickard et al. (2000) might partly be a function of the type of number stimuli used. Large number stimuli, between 31 and 99, were used and there

is some evidence that the precise region of the parietal cortex that is critical in a number task varies (Stanescu-Cosson et al., 2000); tasks involving large numbers tend to involve the more posterior angular gyrus/IPS (Rickard et al., 2000) while tasks involving mainly small numbers (less than twenty) may involve the more anterior supramarginal gyrus/IPS (LeClec'H et al., 2000). This hypothesis will be followed up in the next chapter. It is not clear if damage to both or just one of these systems is sufficient to produce acalculia. It may be the case that smaller numbers, that are often learned early in life, depend on a distinct code that may emphasise verbal memory for rote counting or hand-based counting strategies (Butterworth, 1999). The supramarginal gyrus has been implicated in both motor attention (Rushworth, Ellison, & Walsh, 2001; Rushworth, Krams, & Passingham, 2001; Rushworth, Paus, & Sipila, 2001) and verbal memory (Paulesu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992). It seems plausible that a spatial representation of magnitude would be of particular importance when such verbal and manual over-learned coding strategies are not available; the angular gyrus might be most essential on such occasions.

### *4.5.2 Evidence for the spatial nature of the representation of number*

Number forms as described by Galton (1880) are the most obvious examples of representations of numbers in mental space. There is no doubt that adults who do not possess these number forms nevertheless show automatic associations between number size and spatial response codes. Dehaene et al. (1993; 1990) showed that western subjects in a parity judgement task are faster to respond to smaller number with their left than right hand and to larger numbers with their right than left hand (SNARC-effect). It has been argued that the nature of the mapping of numbers to space could be culturally acquired. Indeed, Dehaene et al. (1993) showed a reversed

SNARC-effect in immigrant Iranian subjects who have lived for a long time in a left-to-right writing system. This suggests that the nature of numerical representation in mental space might be influenced by various cultural factors including direction of reading. In line with these findings, Bächtold et al. (1998) showed that mapping of numbers to spatial response codes can be manipulated by providing different spatial templates. In their study, responses to the digits one to five were faster with the left hand when the reference template was a ruler with a range from one to ten, while responses to the same digits were faster with the right hand when the reference was a clock face with a range from one to twelve. In addition, Fischer (in press) showed that a spatial task can be influence by number magnitude. In a bisection task on lines that were flanked by digits subjects showed a reliable bias towards the digit representing the larger magnitude, although they could have completely ignored the digits during bisecting the lines.

These findings suggest, that although the precise nature of the numerical representation in mental space is unclear and might be culturally determined, most western subjects show a initial association between number size and spatial response codes which can be best described by a one-dimensional line in mental space (Shepard, Kilpatrick & Cunnigham, 1975). In this representation of numbers in mental space smaller numbers are initially associated with locations on the left side of extrapersonal space and left-hand responses while larger numbers are associated with locations on the right side of extrapersonal space and right-hand responses. What remains to be explained is why an association between number and spatial concepts is found at all. There is no such deep connection to spatial concepts in the case of other domians such as colour, or shapes. A natural mapping between numbers and space might simply arise because nearby and presumably similar neural

structures in the inferior parietal lobule/IPS are involved in the representation of both domains.

Two observations then provide tentative support that particularly the left angular gyrus might be involved in mapping numbers onto space. First, rTMS at the same angular gyrus site at which rTMS impaired performance in number comparison also disrupted performance of a visuospatial search task. Although rTMS has a lower spatial resolution than some techniques, it is clear from combined rTMS and neuroimaging studies that only a limited area of cortex is activated by rTMS (Paus, et al., 1998). The critical areas responsible for visuospatial search and number line judgements may be distinct but they are likely to be in close proximity within the angular gyrus and/or adjacent posterior IPS (Naccache & Dehaene, 2001).

The second observation is that in experiment one, the TMS effect over left angular gyrus was quite different from the effect of magnetic stimulation over the right angular gyrus. TMS over right angular gyrus led to an equal increase of reaction times for numbers smaller or larger than the reference number. TMS over left angular gyrus, however, affected the distance effect. Magnetic stimulation specifically impaired number comparison when the number was larger than the reference number and close to the reference number. One way to account for these findings is to assume that within the left angular gyrus there is an association between numbers and mental space in which numbers smaller than 65 are located on the left side of the mental number space while numbers larger than 65 are located on the right side of the mental number space. It has been shown that parietal lesions do not only impair attention to the contralateral side of real space but also of mental space (Kerkhoff, 2001). In experiment 1 then it could be argued that stimulation over left angular gyrus disrupted particularly the right side of the mental number space

leading to an impairment for numbers larger 65. If both angular gyri were involved in mapping numbers onto space we would have expected a stronger TMS effect over the right hemisphere for numbers smaller than 65. There was, however, no such effect for right hemiphere stimulation. In experiment 1, there is only evidence for a spatial representation of numbers within the left angular gyrus.

### *4.5.3 TMS effect can not be explained by disruption of motor responses*

The effect of left angular gyrus rTMS is not simply due to a direct disruption of motor responses. In experiment 3, rTMS over the left angular gyrus still slowed down subjects' classification of numbers larger than the reference even though a reversed response version of the number line task was used and they were therefore using their left hands to make these responses. The reversed response task required subjects to classify numbers as being smaller or larger than the reference number by making right and left hand responses respectively – the opposite response pattern to that required in the first experiment. Western subjects accustomed to left-to-right scripts find the reversed response task more difficult than the more intuitive task used in experiment one (Dehaene et al., 1990), but with some practise they can learn to perform the task. This is indeed what we observed in experiment 3. At first subjects had great difficulty with the reversed response task and made many errors. This suggests that there is an initial spatial-numerical association of response codes (left for smaller, right for larger). Subjects then received an training of 166 trials before the experiment. This training was not used in experiment 1 and 2. After the training session subjects could clearly perform the task well; the error rate in experiment 3 was not higher than the error rates in experiments 1 and 2, and reaction times were faster. It can be argued that the additional training before experiment 3 led to more automatised and hence faster performance than in experiment 1 and 2.

The more over-learned performance in experiment 3 may account for the additional effect of TMS on the left side of the putative number line which is consistent with a stimulus-response mapping interpretation; it is known that performance on number line tasks reflects not just the mental representation of the numbers on a spatial line but the translation from the co-ordinates of that spatial number representation to the co-ordinates for action (Bächtold, Baumüller, & Brugger, 1998). Thus a simple response account cannot explain the rTMS induced RT deficits obtained in both experiments 1 and 3 since in experiment 3 the response hand (left) was ipsilateral to the site of TMS stimulation.

The results from experiment 2 also suggest that the effect of angular gyrus/pIPS rTMS on the number line task was not due to the task's response requirements. This conclusion can be drawn from considering the results for the left supramarginal gyrus in experiment 2. No lateralized effect on number line responses was observed after supramarginal gyrus rTMS despite two factors: this region is closer to the motor cortex, so any spread of effect to the motor cortex would have been greater; this region is more directly involved in motor response preparation (Deiber, Ibanez, Sadato, & Hallett, 1996; Rushworth, Ellison, & Walsh, 2001; Rushworth, Krams, & Passingham, 2001; Rushworth, Paus, & Sipila, 2001).

The results reported in this chapter confirm the importance of both left and right angular gyri in number representation and concur with reports of bilateral activation of the posterior parietal cortex found in neuroimaging studies when subjects were performing an approximate arithmetical task which consisted of number comparison (Dehaene, Spelke, Pinel, et al., 1999; Pinel, et al., 1999; Rickard, et al., 2000). Although there was an increase in RT when rTMS was applied over either of the angular gyri the increase was larger for stimulation over

left angular gyrus in both experiments one and three. This is in accordance with results from lesion studies which show that acalculia is more commonly associated with left than right hemisphere damage (Cipolotti, Butterworth, & Denes, 1991; Delazer & Benke, 1997; Delazer & Butterworth, 1997; Grafman, Passafiume, Faglioni, & Boller, 1982; Hécaen, Angelergues, & Houllier, 1961). The role of the right angular gyrus in number magnitude representation therefore remains to be determined more clearly in future experiments.

### *4.5.4 Are the effects specific to number?*

It is reasonable to ask whether the effects on number representation are simply due to non-specific spatial effects entailed by using visual search as an assay to define the functional location of the angular gyrus. There are several reasons why this is not the case. First of all, the important deficit in number processing was greatest with left angular gyrus stimulation (experiments 1 and 3), whereas visual search deficits are usually larger after right angular gyrus TMS stimulation (Ashbridge et al., 1997; Walsh et al., 1998; Walsh et al., 1999). This is consistent with the well-known predominance of the right hemisphere in visuospatial attention (Corbetta & Shulman, 1999; De Renzi, 1982; Mesulam, 1981; Nobre, et al., 1997) and the left hemisphere's well-known predominance in numerical processing (Boller & Grafman, 1983; Butterworth, 1999; Dehaene, 1999). If the effects were due to non-specific visuospatial processing the number line deficit would have been greater with TMS over this right hemisphere angular gyrus site. Second, in this study the numbers were all presented centrally and it has been shown in another study that right angular gyrus TMS does not impair detection of targets when their upcoming location is known (Ellison, 2000). Thus the two spatial processes involved in visual search and number representation can be dissociated.

### *4.5.5 Unit-decade compatibility effects in number comparison*

Although we have only analysed the distance effect found in the behavioural data of experiments 1 - 3, visual inspection of figures 4-5, 4-6 and 4-7 shows clear effects of unit-decade compatibility. This effect was first described by Nuerk et al. (2001). In a two-digit number comparison task a given number comparison is called unit-decade compatible, if both comparisons for the tens and units lead to the same decision (e.g. for 24_36, both $2 < 4$ and $4 < 6$). A task is unit-decade-incompatible if the two comparisons for the tens and the units lead to different results (e.g. for 58_73, $5 < 7$ but $8 > 3$). If units and tens do not play a role in number magnitude representation, compatibility should not have an effect when overall distance is controlled, albeit Nuerk et al. (2001) could show a clear compatibility effect, that is also visible in our behavioural results of double-digit number comparison. Nuerk et al. therefore argued that a single number line for single- and double-digit numbers could not account for this compatibility effect. They suggest that the magnitude of double-digit numbers might not only be represented as semantic magnitude on a number line, but might additionally be represented in different bins for tens and units. Their model of number comparison can be seen as a hybrid of McCloskey's place value model and Dehaene's analogues number line (see 1.6.2).

## *4.6 Conclusion*

In this chapter I described a set of experiments that showed the importance of the angular gyrus in representing number magnitude for large numbers from 31 to 99. The evidence provides support for the contention that there is a spatial representation of these numbers akin to a mental number line within the left angular gyrus.

# 5. Number comparison of single digits

*The contribution of the supramarginal gyrus depends on number size*

## 5.1 Summary

To investigate the basis of magnitude representation of single-digit numbers in the human brain focal repetitive Transcranial Magnetic Stimulation was applied over right or left angular or supramarginal gyrus while subjects performed a number comparison task with numbers 1 to 9. Repetitive TMS over angular gyrus again disrupted performance of a visuospatial search task, but, contrary to the last experiment, did not impair performance of the number comparison task. This time, rTMS had a disruptive effect when delivered over the supramarginal gyrus (SMG), in either the left or right hemisphere.

## 5.2 Introduction

The last chapter showed that an area in the inferior parietal lobe, the angular gyrus, is involved in representing numbers larger than 30 and smaller than 100 in adults. In the psychological literature there is evidence that representing large numbers and representing small numbers might be based on different principles. While it takes children several years to learn to count and to master basic arithmetic (Bideaud, Meljac, & Fischer, 1992), they already have a representation for small numbers (at least for one and two) as infants. Starkey & Cooper (1980), for example, showed in a habituation experiment that 5 month-old children can tell apart two from three spots of light. Antell & Keating (1983) replicated this result in infants who were only 1-3 days old. Additionally, infants aged 6 to 8 months can detect numerical correspondences between sets of visible objects and sequences of sound present at

same time (Starkey, Spelke, & Gelman, 1990). Infants at that age can also tell apart two from three and three from four moving items on a video screen (Van-Loosbroek & Smitsman, 1990) and enumerate physical actions produced by a puppet jumping in a sequence (Wynn, 1996). Although there is still considerable debate as to whether there is an innate capacity for numbers and perhaps even for simple arithmetic (Dehaene, Dehaene-Lambertz, & Cohen, 1998), it seems to be agreed by most that infants as young as 5 months of age are sensitive to some numerical relationships between small numbers.

There is recent evidence that this early capacity is not restricted to humans, but is also present in animals. Tomasello & Call (1997) state that primates, birds and rats can not only estimate quantities, but can also identify specific places in a series and be trained to perform an act a specific number of times. Furthermore, monkeys and apes can judge small quantities accurately.

The upper limit of their ability varies between different studies and species. Matsuzawa (1985) trained a chimp to use Arabic numerals to identify the number of items in an array; the animal could not identify more than 6 items. Brannon & Terrace (1998) trained a rhesus monkey to discriminate between 1 and up to 4 objects, they reported that subsequently the monkey could, without any further training, discriminate between 1 to 9 objects. Sulkowski & Hauser (2001) showed that rhesus monkeys can "calculate" the outcome of subtraction operations of food items remarkably well for 3 items or less. Rhesus monkeys also succeeded in numerical comparisons of pieces of apples for 1 versus 2, 2 versus 3, 3 versus 4, but failed at 4 versus 5 and 3 versus 8 (Hauser, Carey, & Hauser, 2000). So far no study has reported animals who are able to make exact judgement of numerosities over 10.

In general, the animal data seem to suggest that numerosities one to three, perhaps up to four, seem to come almost naturally to many animals. This is reflected in young infants who seem to show roughly the same boundary (Fischer, 1992). Interestingly, one to four is also the number of items that can usually be "subitized". The word subitizing was coined by Kaufman (1949) for the ability to enumerate a group of objects without counting, typically quickly, accurately and with high confidence. The upper limit of the number of items that can be subitized lies between four and seven objects, depending on characteristics of the objects and the display (Buckley & Gillman, 1974; Simon & Vaishnavi, 1996) and can vary widely between subjects (Jensen, Reese, & Reese, 1950). Several attempts have been made to explain subitizing: fast counting (Gallistel & Gelman, 1991); pattern recognition (Mandler & Shebo, 1982); limited capacity preattentive visual processing: the FINST model (Trick & Pylyshyn, 1993) and subitizing as precise estimation (van Oeffelen & Vos, 1982). So far, however, none has successfully accounted for all the empirical data. To date it is still unclear whether subitizing is a separate process from counting (potentially with separate brain areas supporting it; Sathian et al., 1998) or whether both can be explained by one single underlying process. The latter view, put forward for example by Balakrishnan & Ashby (1992), suggests that the characteristic increase in the slope of reaction times between subitizing and counting can be explained by a non-specific increase in complexity. A recent PET-study also provides evidence that at the neural level subitizing and counting are not dissociable and might rather be two different levels along a continuum of complexity (Piazza, Mechelli, Butterworth, & Price, 2002), i.e. the difference may be quantitative rather than qualitative.

However, if one accepts subitizing as a descriptive term without automatically assuming a different underlying process, it can be used as a probe to shed some light on processing of smaller numbers. In some patients with acalculia simple arithmetic with small numbers maybe preserved together with subitizing (Cipolotti & van Harskamp, 2001). However, some severe cases report abolition of all number sense. Cipolotti, Butterworth, & Denes (1991), for example, report a patient (CG) with Gerstmann's syndrome who, after a cerebral vascular accident leading to damage in the left fronto-parietal region, was totally unable to deal with numbers above four. She was unable to recognise or produce spoken number words above four, to recognise numerals above four or to judge which of two numbers above four is greater whether presented as words or as dot patterns. In contrast, her performance was perfect for numbers below four (apart from zero). Interestingly, this patient was also unable to subitize.

While patients with a left hemisphere lesion often lose the ability to perform exact arithmetic tasks, many can still perform approximation (Dehaene, 1992; Dehaene & Cohen, 1991). Recently, Spelke (2001) has put forward a model of numerical development in children that incorporates small number representations and an approximate number sense. She suggests that there are two innate core numerical representations which humans share with animals. One system is specialised for representing and tracking objects and it is this system that is used for counting and comparing small sets of objects. This system is limited by the size of the set and only works for small numbers. The second system she proposes is an approximate system that is active when comparing larger sets and making approximate judgements. This system is not limited by number size but rather by set size ratio. This model is supported by neuroimaging studies showing activations of

different brain regions for exact arithmetic and approximate arithmetic (Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999) and by patients showing dissociations between exact arithmetic and approximate number sense (Dehaene, 1992; Dehaene & Cohen, 1991; Warrington, 1982).

Spelke (2001) claims that in animals and young children these two systems (exact small numbers for representing/tracking objects and approximation) are unrelated. According to Spelke, neither of these two systems is enough for children to master counting which they understand at around 4 years of age.

Spelke further suggests that the language system (in particular via number words) provides the missing link between the small exact system and large approximate system and also argues that language is necessary for combining the two systems. This is a strong claim, not completely supported by the literature, because there is evidence that human subjects can attain high levels of mathematical competence in the absence of very developed language skills (Donlan, 1998; Hermelin & O'Connor, 1990; Rossor, Warrington, & Cipolotti, 1995). So far there has been little attempt to identify other processes that could mediate between these two proposed brain systems.

To sum up, in accordance with Spelke's theory there is evidence from neuroimaging (Dehaene et al., 1999) and patient studies (Dehaene, 1992; Dehaene & Cohen, 1991) that different brain areas underly exact calculation and approximation. Additionally, psychological research suggests differences between representing small numbers and representing large numbers. So far, however, no study has reported activations in different brain areas for the representation of small versus large numbers. Pinel et al. (1999, 2001) carried out two fMRI studies looking at brain areas active during a number comparison task. In the first study they used

small numbers (1-9) and a small reference number (5), while for the second study they used numbers between 30 and 99 and a larger reference number (65). In both studies they found activations in the inferior parietal lobule. Interestingly, in both studies they also found that loci of activation varied with the distance to the reference number. This will be discussed in more detail in the chapter 7. They did not, however, report differences in the brain regions activated in the two studies investigating the neural representation of small and larger numbers.

I therefore decided to investigate the contribution of the inferior parietal lobes to the representation of small numbers with rTMS by using the same number comparison task as in the previous experiment but with small numbers (range from 1 to 9) and with 5 as the reference number. Repetitive TMS was applied separately over left and right angular gyri and left and right supramarginal gyri. In line with neuroimaging and patient studies, it was expected that magnetic stimulation over the angular gyri would interfere with performance in a single-digit number comparison task, thus showing the importance of the angular gyrus in representing numbers irrespective of size.

## *5.3 Materials and Methods*

### *5.3.1 Stimuli and apparatus*

Subjects were seated in a lighted room at a distance of approximately 50 cm from a computer screen. The experiment was controlled by a PC running the SuperLab software version 1.04. Stimuli were presented centrally on a 17-in. colour monitor and appeared as black against a grey background. The stimuli consisted of a set of 8 single digit numbers (1, 2, 3, 4, 6, 7, 8, 9), each presented individually on the screen. Numbers were displayed using the font Times New Roman (type size = 18 points) and when viewed from the distance of 50 cm subtended 1° of visual angle. Subjects

wore rubber bathing caps on which the relevant co-ordinates of the International 10/20 EEG system (AEEGS, 1991) were marked.

For generating the magnetic pulses a Magstim stimulator, Model Super Rapid (The Magstim Company Limited, Whitland, UK) with a 70 mm figure of eight coil, was used. The maximal magnetic field strength at the coil surface was 1.8 Tesla. Precise timing of onset of both the visual and the magnetic stimulus was verified using an oscilloscope.

### *5.3.2 Participants*

Eight right-handed volunteers were tested. One subjects was female, seven male. Their ages varied from 19 to 24 years with a mean age of 21.6.

### *5.3.3 Procedure*

Subjects were tested during a single session. Target numbers ranged from 1 to 9 (see figure 5-1). Each number was displayed nine times in each block. The number 5 was never presented. The order of the numbers appearing on the screen was pseudo-random within each block. Subjects were required to indicate with one of two possible key presses whether the number on the screen was greater or less than 5.

The index finger of the right hand was used to indicate the 'greater than' response and the index finger of the left hand was used to indicate the 'less than' response. Stimuli remained on the screen until subjects made a response. The intertrial interval was one second. During each part of the session subjects performed 4 blocks of 72 trials, preceded by an initial training block of 10 non-TMS trials. On 8 trials in each experimental block rTMS was applied over the subject's scalp for 500 ms at 10 Hz. The rTMS stimulation started before the onset of the visual stimulus and occurred pseudo-randomly. During the whole experiment the

coil was held in a constant position with reference to the subject's head. In each of the four parts of the session magnetic stimulation was applied over a different brain area: left angular gyrus, right angular gyrus, left supramarginal gyrus or right supramarginal gyrus. The order of stimulation sites varied between subjects and was controlled.

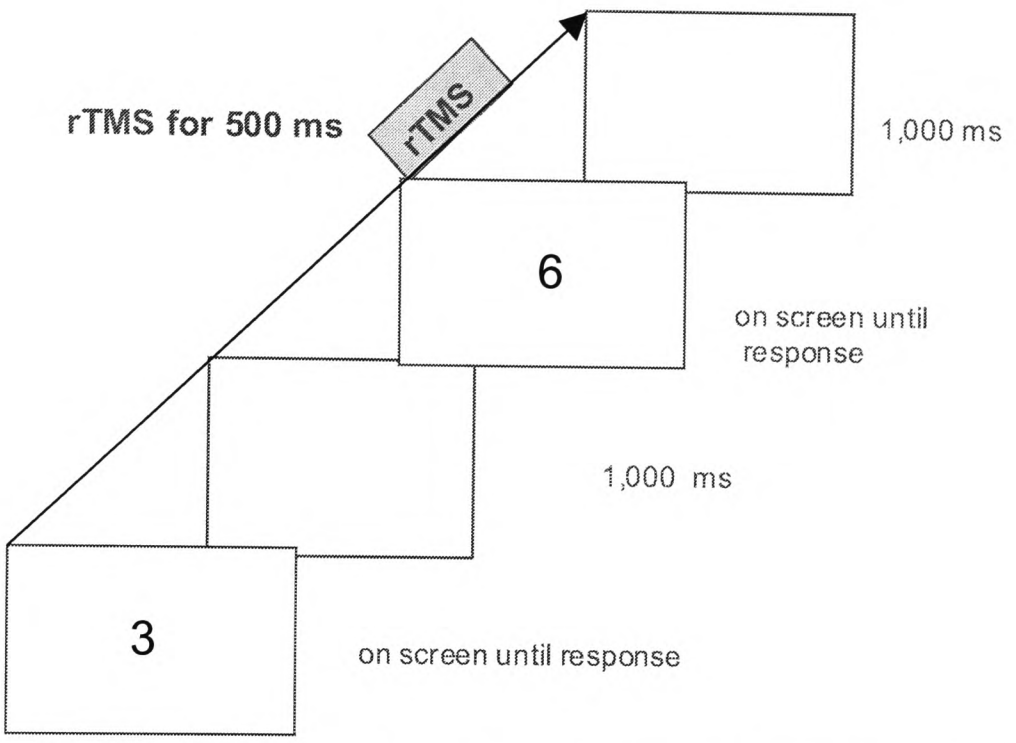



**Figure 5-1:** Number comparison task. Subjects were presented with numbers between 1 and 9 and were asked to indicate with one of two possible key presses whether the number on the screen was greater or less than 5. Stimuli remained on the screen until subjects made a response. The intertrial interval was one second. On some trials rTMS was applied.

Magnetic stimulus intensity between 45% and 70% of the maximum stimulator output was used. The intensity of the magnetic stimulation was set separately for each individual at 5% above their motor threshold. Motor threshold was defined as the minimum percentage of stimulator output that can evoke a visually detectable twitch in a tensed muscle of the subject's hand contralateral to the stimulated motor cortex. Frequency, intensity and duration of rTMS were in accordance with the safety guidelines established by Wassermann (1998).

All subjects were checked for TMS exclusion criteria (Wassermann, 1998) and gave written informed consent before participating. The procedure was approved

by the Ethics Committee of the University of Oxford, Department of Experimental Psychology. Subjects were educated at least to university level, had normal or corrected to normal visual acuity and were free of any neurological condition. They were reimbursed for travel expenses and time taken to participate in the study.

### *5.3.4 Magnetic resonance imaging (MRI)*

Images of individual subjects' brain anatomy were determined with high-resolution T1-weighted anatomical scans on a 3 Tesla Varian INOVA MRI system (1.5 mm thick axial slices with 1 mm × 1 mm in plane resolution).

### *5.3.5 Localisation*

Functional and anatomical methods as described in detail in sections 3.3.5 and 3.3.6 were used to localise stimulation sites.

#### *5.3.5.1 Functional localisation*

The angular gyrus site was identified for each subject in each hemisphere separately by first establishing the site at which rTMS disrupted visual search. The number classification task was then carried out while rTMS was delivered at the same site (see figures 5-2).

In contrast, for stimulation over supramarginal gyrus the number classification task was carried out while rTMS was delivered 3 cm posterior and 1 cm lateral from hand area of the subjects' motor cortex (see figure 5-3).

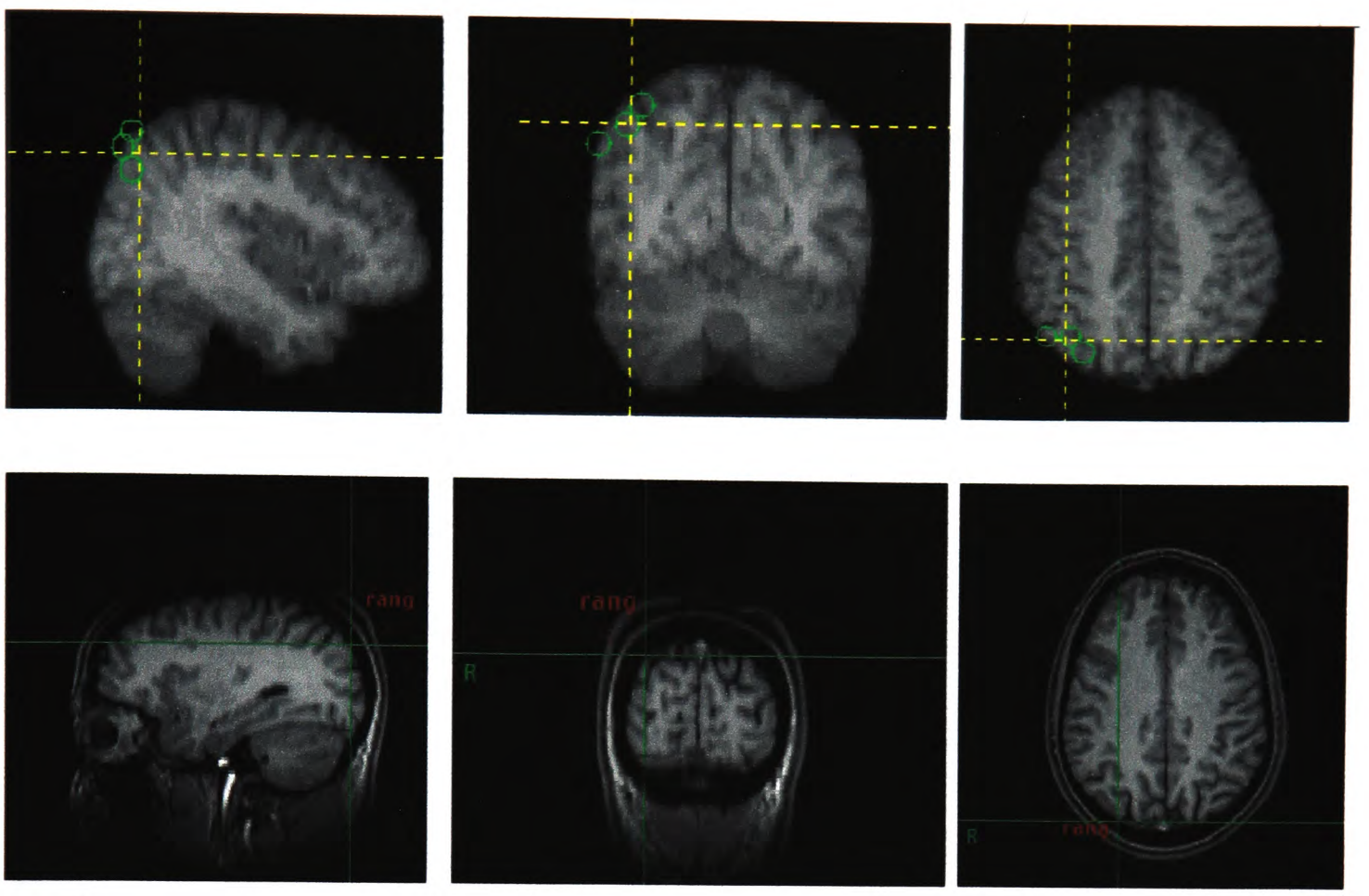



**Figure 5-2:** TMS sites over right angular gyrus/posterior IPS. The top row of images shows sagittal, coronal and axial views of an average MRI scan derived from three subjects after transformation to a standard template (Evans et al., 1992; Talairach & Tournoux, 1988). Green circles indicate the points where TMS was directed in these three subjects. All of the target areas cluster in or just lateral to the posterior part of the intraparietal sulcus adjacent to the angular gyrus (mean co-ordinates indicated by yellow crosshairs: x = 42 , y = -67 , z = 45). The bottom row of images shows approximately sagittal, coronal, and axial views of a single subject's MRI scan prior to registration into Talairach space. The MRI scan was co-registered with visible landmarks on the subject's head so that the position of the TMS coil could be measured with respect to the subject's brain during the experiment. Red crosses indicate the position of the TMS coil at the angular gyrus site at which rTMS affected the visuo-spatial search task and the number line task.

### *5.3.5.2 Anatomical localisation*

The location of these two sites was confirmed by MRI using frameless stereotaxy. A Polaris (Northern Digital, Ontario, Canada) infra-red tracking device was used to measure the position of the subject's head and Brainsight software (Rogue Research, Montreal, Canada) was used to co-register the subject's head with the subject's MRI scan. In all subjects, for stimulation over the angular gyrus the coil was placed near

the posterior superior temporal sulcus in the angular gyrus lateral to the posterior IPS. For stimulation over supramarginal gyrus the coil was placed more anteriorly, over the anterior part of the intraparietal sulcus where it meets the postcentral sulcus.

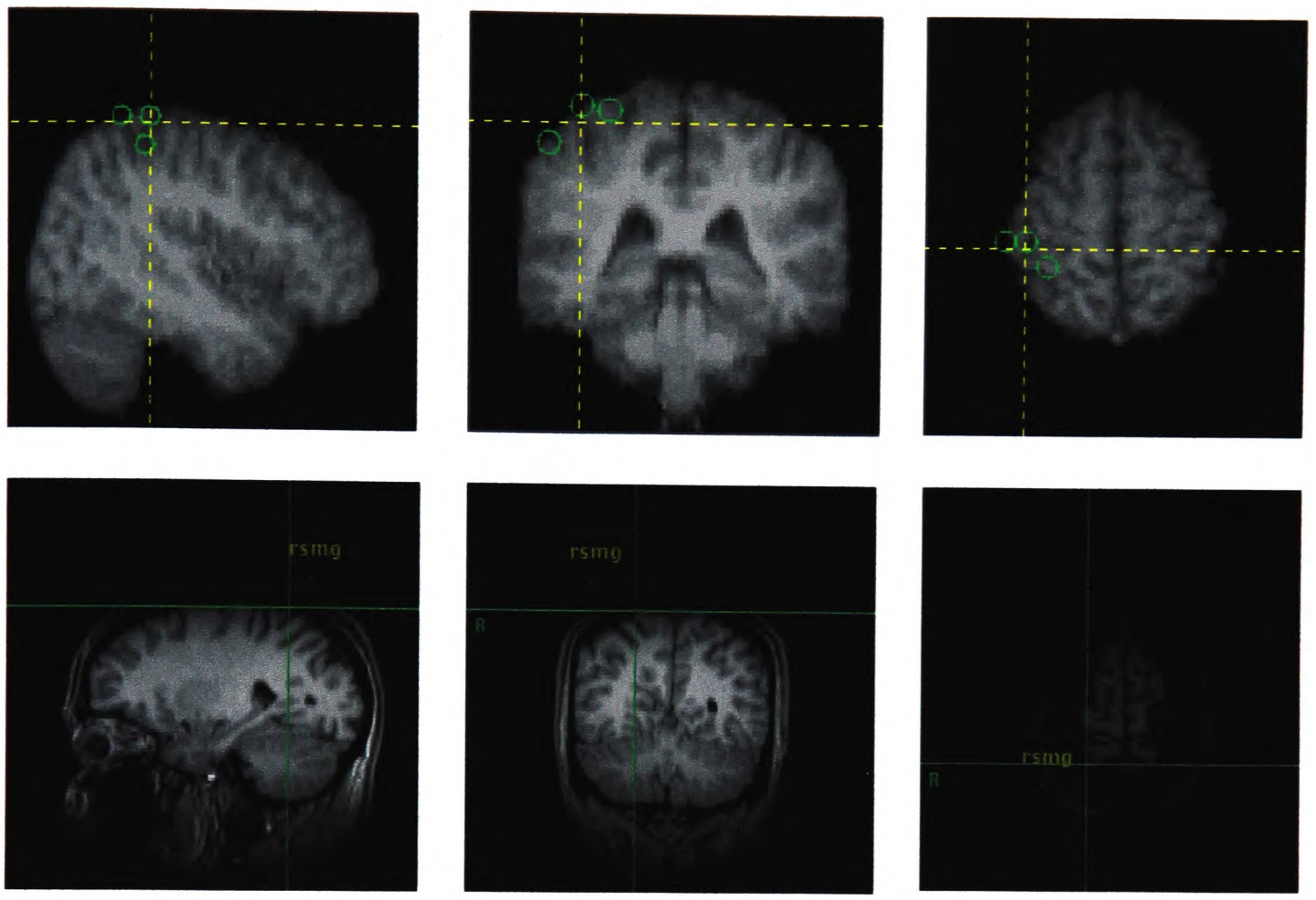



**Figure 5-3:** TMS sites over right supramarginal gyrus/anterior IPS. The figure follows the same format as figure 5-2 and represent data from the same subjects. The top row of images shows sagittal, coronal and axial views of an average MRI scan derived from three subjects after transformation to a standard template (Evans et al., 1992; Talairach & Tournoux, 1988). Green circles indicate the points where TMS was directed in these three subjects. Stimulation was consistently directed at the anterior part of the intraparietal sulcus where it meets the postcentral sulcus. The group average (mean co-ordinates indicated by yellow crosshairs: x = 43, y = -35, z = 61) falls on the IPS. However, in some cases stimulation sites were close to the postcentral gyrus (for example the most medial site in the coronal section). The bottom row of images shows approximately sagittal, coronal, and axial views of a single subject's MRI scan prior to registration into Talairach space.

### *5.3.6 Data analysis*

The statistical package SPSS version 9.0 was used. For the visual search task a three-way ANOVA was conducted on mean RTs with trial type (control-TMS), hemispheric side (left-right) and target type (target present – target absent) as within-subject factors.

Data from the number task were analysed according to the following procedure: first, the behavioural data were analysed in order to see if the classical distance effect could be observed. An analysis of variance (ANOVA) was performed on mean reaction times with target-standard distance (1 - 4), size of target number (smaller than 5 – larger than 5) and session (left ANG, right ANG, left SMG, right SMG) as within subject conditions. In a second analysis, reaction times were then compared for trials with and without rTMS. An analysis of variance (ANOVA) was performed on reaction times with trial type (control trial – trial with rTMS), hemispheric side of TMS stimulation (left hemisphere - right hemisphere), site of TMS stimulation (supramarginal gyrus – angular gyrus), target-standard distance (1 - 4) and size of target number (smaller than 5 – larger than 5) as the within-subject factors. For ease of exposition, only rTMS effects and their interactions with other variables will be reported. For the number classification task, reaction times for erroneous responses (5.8 % of all responses) were not included in the analysis.

## *5.4 Results*

### *5.4.1 Visual search results*

In the visual search task subjects responded more slowly to all trial types when TMS was applied (see figure 5-4). Mean RTs increased on trials where the target was present from 648 ms to 825 ms when rTMS was applied over left ANG and from 616 ms to 848 ms when rTMS was applied over right ANG. TMS significantly

slowed down responses to all trial types ($F(1,7) = 19.52$, $p = .003$), but had a stronger influence on trials where the target was present ($F(1,7) = 10.63$, $p = .02$).

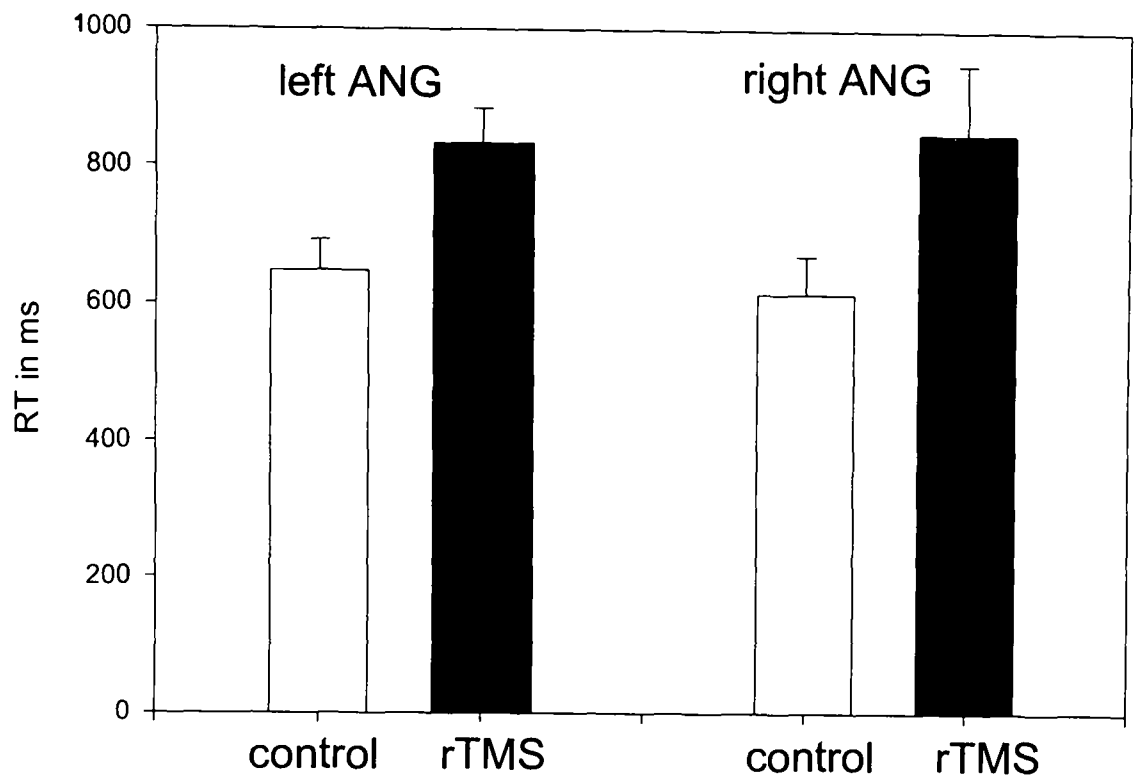



**Figure 5-4:** Results for the visual search task: mean reaction time (RT) in ms for target present trials in conjunction visual search task; behavioural data (open bars) and reaction time with rTMS (black bars) applied over left or right angular gyrus and adjacent posterior IPS.

### *5.4.2 Number task: behavioural results*

*Symbolic distance effect:* First, the behavioural data were analysed in order to see if the classical distance effect could be observed. The closer the displayed number was to 5, the more slowly the subjects responded. With larger distances between standard and target number, RTs decreased significantly ($F(3,5) = 15.91$, $p = 0.005$) (see figure 5-5, black line).

### *5.4.3 Number task: stimulation results*

*Symbolic distance effect:* In general, there was still a significant distance effect (main effect of distance: $F(3,5) = 9.10$ , $p = 0.02$). There was, however, a significant

difference between the distance effect observed for the behavioural trials and the distance effect for TMS trials ($F(3,5) = 5.70$, $p = .045$, interaction TMS × distance).

*General increase in RT with rTMS:* In general TMS slowed down performance. The mean reaction time on trials increased by 30 ms from 411 ms on non-TMS trials to 442 ms when TMS was applied. There was a main effect of TMS that approached significance ($F(1,7) = 4.75$, $p = .066$).

*Significant general increase with rTMS over SMG:* rTMS stimulation over SMG had a significantly greater effect than stimulation over ANG ($F(1,7) = 11.92$, $p=.011$, interaction effect site × TMS). When rTMS was applied over SMG subjects' mean RT increased by 45 ms (from 422 ms to 467 ms) in comparison to only 15 ms increase when rTMS was applied over ANG (from 402 ms to 417 ms).

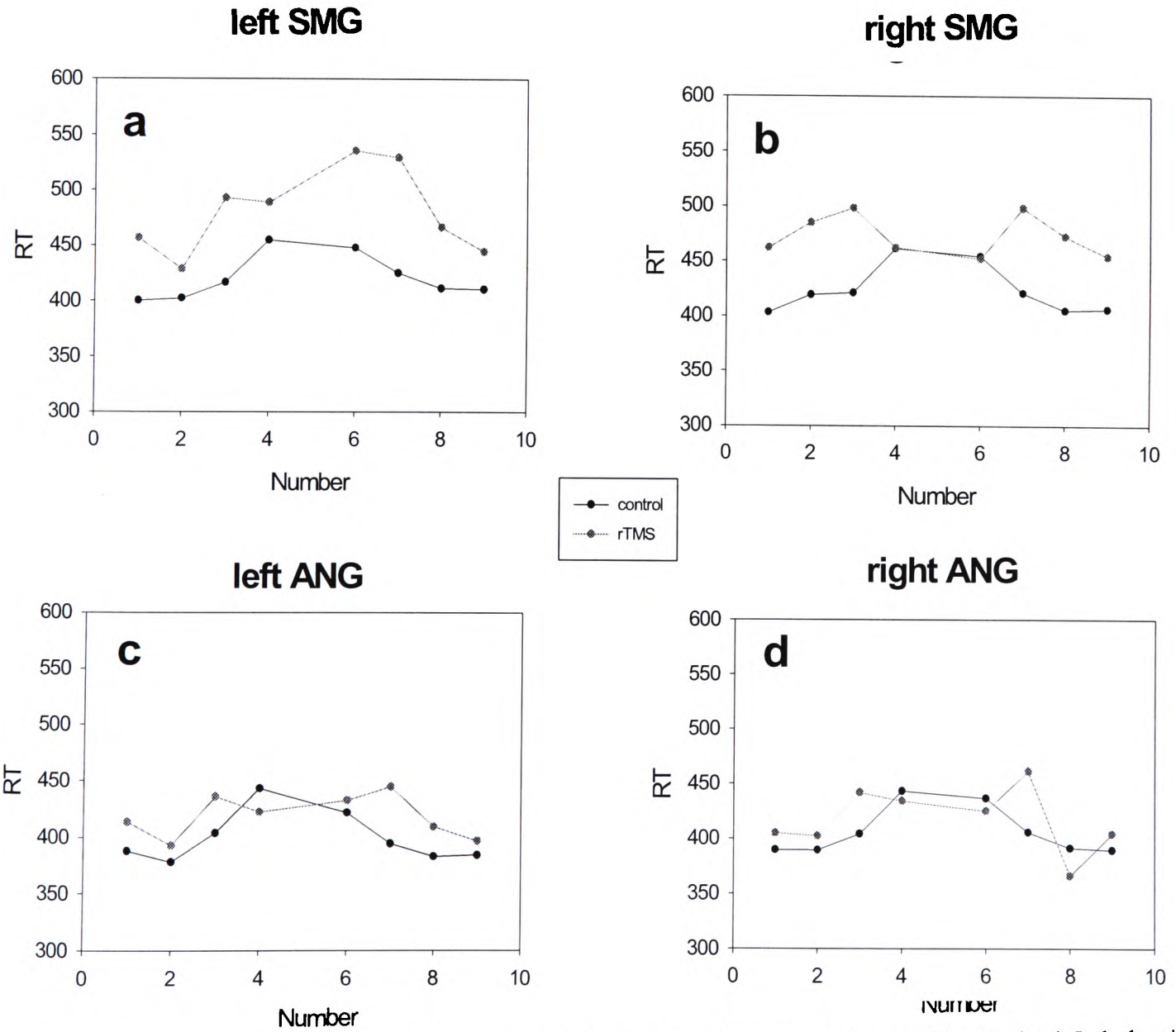



**Figure 5-5:** Mean reaction time (RT) in ms in single digit number comparison with standard 5; behavioural data (black line) and reaction time with rTMS (grey line) applied over either left (a) or right (b) supramarginal gyrus and adjacent anterior IPS, left (c) or right (d) angular gyrus and adjacent posterior IPS.

*The rTMS effect is modified by distance from reference number and size of target number:* The TMS-induced increase was greater for numbers larger than 5 ($F(1,7) = 55.87$, $p < .001$, interaction effect TMS × size) and was also modified by distance from the reference number ($F(3,5) = 5.70$, $p = .045$, interaction TMS × distance). All remaining interactions with TMS were non-significant. In order to follow up those significant interactions an ANOVA was conducted for each site separately with trial type (control - TMS), side of TMS stimulation (left hemisphere - right hemisphere), target-standard distance (1 - 4) and size of target number (smaller than 5 – larger than 5) as within-subject factors.

In this separate analysis for stimulation over SMG, there was again a significant main TMS effect ($F(1,7) = 7.84$ , $p = .027$), but no significant interactions with TMS. This is in clear contrast to the results of the ANOVA for stimulation over ANG, where there was no main effect of TMS ($F(1,7) = 1.18$, $p = .313$). However, there was a significant four-way interaction between the effect of TMS, hemispheric site of TMS, distance from the reference number and size of target number ($F(3,5)= 12.60$, $p = .009$) suggesting that the effect of rTMS over ANG is strongly modified by distance from reference number, size of target number and hemisphere.

## *5.5 Discussion*

In this rTMS experiment, as in the experiment reported in chapter 4, there was again a significant increase in reaction times in a number comparison task when subjects were stimulated over inferior parietal cortex. This confirms the important contribution of that region to the representation of numbers in line with neuroimaging and patient data.

### *5.5.1 More evidence for the spatial nature of the angular gyrus representation of number*

As in the previous experiment (chapter 4) with larger numbers (31-99), stimulation over the angular gyri resulted in an increase in reaction times for number comparison. This again shows the importance of the angular gyri for number representation. But in contrast to the previous experiment the TMS effect over the angular gyrus was only present as a significant four-way interaction effect. This suggests that the TMS effect over the angular gyrus in this experiment is strongly dependent on the distance from the reference number and on whether the displayed number is larger or smaller than the reference number (5). It is also modified by hemispheric side of stimulation. A similar pattern of results was reported by Pinel et al. (1999). Using fMRI they found that a left inferior parietal area, close to the parieto-occito-temporal boundary, was significantly more active for numbers close to 5 than for number far from 5, while a right intra-parietal area was significantly more active for far than for close numbers.

The results for stimulation over angular gyrus may be interpreted as evidence that the angular gyri also contribute to the representation of small numbers. This contribution, however, seems to be a rather complex one, certainly not as clear as in the case of larger numbers (chapter 4). It is dependent on the distance from the reference number and whether the number is larger or smaller than the reference number and which hemisphere is stimulated. When stimulating over the angular gyri the representation of small numbers seems not to be affected equally. The importance of such factors might be taken to suggest that spatial processes necessary for number comparisons have been disrupted.

### *5.5.2 Effect of rTMS over supramarginal gyrus*

The more compelling result in this experiment is the clear effect rTMS has on reaction times when stimulating over the supramarginal gyri. This is in clear contrast to the previous experiment where TMS stimulation over supramarginal gyrus showed no significant effect on reaction times. Additionally, in the current experiment the TMS effect over supramarginal gyri is significantly stronger than the TMS effect over angular gyri. This is an almost complete reversal of the findings of the previous experiment. While in the previous experiment (using numbers 31-99) stimulation over both supramarginal gyri did not lead to any significant changes in reaction times, in the current experiment (using numbers 1-10) stimulation over the very same regions lead to a significant increase in reaction times. At the same time there was no significant overall TMS effect in this experiment when stimulating over angular gyri. It is thus clear that the supramarginal gyrus is of greater importance for the representation of small numbers. Traditionally, the angular gyrus has been more closely associated with acalculia than the supramarginal gyrus, but as early as 1919 Henschen pointed out a potential role of the supramarginal gyrus in number representation. Also, in several recent imaging studies the supramarginal gyrus, along with the angular gyrus and the intraparietal sulcus, was activated during numerical tasks (Cowell, Egan, Code, Harasty, & Watson, 2000; Menon, Rivera, White, Glover, & Reiss, 2000; Rueckert, et al., 1996; Zago, et al., 2001). LeClec'H, et al. (2000) investigated the representation of numerals and body parts in a comparison task using fMRI. They reported several regions of greater activation for numerals versus body parts including left and (at a lower significance level) right supramarginal gyrus.

### *5.5.3 A role of the supramarginal gyrus in representing small numbers?*

LeClec'H et al. (2000) interpreted the activity they found in the left supramarginal gyrus as activity not related to using a semantic representation of quantity, but to subjects relying on a phonological re-coding strategy when doing the task. This interpretation is partly justified, because the supramarginal region in the left hemisphere has been related to verbal memory (Paulesu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992). It can be argued that the experiments with double-digit numbers described in chapter 4 and the experiment discussed in this chapter differ in memory load. For single-digits each digit was seen nine times per block and therefore the comparison with the reference number was made nine times in each of the four blocks. In contrast during number comparison of double-digit numbers, most numbers were only presented once. Therefore the comparison with the reference number was just made once in this condition. Could it be that for a large proportion of the single-digit but not the double-digit trials the subjects were simply remembering the judgement previously made and that therefore the disruptive effect of magnetic stimulation over the supramarginal gyrus was partly due to an impairment in working memory caused by TMS? Although it cannot be argued that the differences in the frequency of presentation of each number between single-digit and double-digit number comparison did not lead to different strategies for some of the subject and/or on some of the trials, it seems unlikely that the disruptive effect of TMS over left and right SMG is entirely due to an impairment of working memory for two reasons.

First, in chapter 7 an fMRI study on number comparison will be presented that is very similar in design to the experiments described in chapter 4 and in this chapter. There were blocks, in which subjects had to compare double-digit numbers

to a reference number (65), and blocks, in which they had to compare single-digit numbers to a reference number (5). Again, there is a difference in frequency of presentation of each number between the single- and double-digit blocks with each single-digit number being presented thirteen times and each double-digit number being presented maximally twice. If subjects in this experiment were using a memory-based strategy for single-digit stimuli that they were not using for double-digit stimuli, we should see corresponding differences in activation patterns. However, no significant activation outside the visual cortex was found for the contrast double-digit versus single-digit blocks (see 7.4.2.2) .

Second, only the left supramarginal region has been related to verbal memory (Paulesu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992). This cannot explain the clear rTMS effect that we described in this chapter for single-digit stimuli when stimulating over the right supramarginal gyrus. While not denying some role of working memory and phonological processing in the representation of numbers, it is important to consider other arguments. The supramarginal gyrus has not only been implicated in verbal memory (Paulesu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992), but also in motor attention (Paulesu, Frith, & Frackowiak, 1993; Rushworth, Ellison, & Walsh, 2001; Rushworth, Krams, & Passingham, 2001; Rushworth, Paus, & Sipila, 2001; Zatorre, Evans, Meyer, & Gjedde, 1992). I will argue that it may be this motor attention function which might be essential for finger-counting that relates the supramarginal gyrus to numbers.

### *5.5.4 Small numbers, movements and the supramarginal gyrus*

In a recent recording study in monkeys Sawamura, Shima, & Tanji (2002) found a relationship between a region representing body movements and the numerical

elements of a task. They recorded neuronal activity of cells in the superior parietal lobule. This area is thought to be primarily involved in constructing the body schema, by integrating somato-sensory inputs of several sub-modalities with visual information about the posture and movement of the body (Graziano, Cooke, & Taylor, 2000; Iriki, Tanaka, & Iwamura, 1996; Ramachandran & Hirstein, 1998). Sawamura, Shima & Tanji (2002) trained monkeys to select and perform a movement (A) five times, then switch to a second movement (B) for five repetitions and return back to movement A in a cyclical fashion. They showed that the cellular activity in the superior parietal lobule reflected the number of self-movement executions. Most of the number selective cells were found in a region in the anterior bank of the intraparietal sulcus that extended mediolaterally.

There are several reason for suggesting that small numbers might also be somehow related to motorical activity in humans. During counting there is often an obvious association between body movements and numbers. Dantzig (1962) claimed that whenever a counting technique exists at all, finger-counting has been found either to procede it or to accompany it. There are still tribes who use body parts and names of body parts to count. The Yupno people in Papua New Guinea for example have no special words for numbers, but use body-parts and body-part names to count (Wassman & Dasen, 1994). It is thought that even modern European number words were derived from body-part names (Menninger, 1969). Can it just be coincidence that the Latin word for finger is digitus and that the ten numerals used in writing numbers (0,1,2,3,4,5,6,7,8,9) are often called digits? Most modern languages including English also have base ten number systems - that is they have separate number names only for the first ten numbers corresponding to the ten fingers used for counting. Finger-counting must naturally have given rise to finger arithmetic.

Counting and calculating with fingers comes very naturally and children do it even when discouraged by teachers (Butterworth, 1999). Children often learn to count by using their fingers and an important step in learning the principles of counting is actually pointing to the objects they count (Gelman & Gallistel, 1978), because this one-to-one correspondence between fingers and objects directly enables quantification. In every day life we often count on our fingers to quantify small numbers (for example when counting the weekdays until a certain event). Brissiaud (1992) argued that the usage of fingers is a genuine analogue mode of quantification, not a mere by-product of counting.

The use of fingers in counting seems to have some prognostic value as well. The presence of finger agnosia in childhood (in developmental Gerstmann's syndrome: Benson & Geschwind, 1970), for example, often predicts dyscalculia (Butterworth, 1999). Furthermore, Fayol, Barrouillet, & Marinthe (1998) showed a significant relationship in children between performance in neurological-motorical tests and performance in arithmetical tests a year later. They tested 177 children in nursery school with neuropsychological tests aimed at evaluating the somato-sensory integrity of the sensory cortex. The children's performance in the neuro-psychological tests measured at 5 years of age predicted a significant proportion of the variance in the arithmetic tests administered to the same children at the age of 6 years. So there is clear evidence of an association between counting, finger use and ability to deal with numbers.

Butterworth (1999) gives this as one reason why the representation of numbers is to be found in the parietal lobes: it is where fingers and hand shapes are represented. I agree with this suggestion and argue that when children first learn to count it is clearly advantageous for them to use their fingers and that it is by this

finger usage that the representation of small numbers (i.e. finger countable numbers) becomes related to finger movements. This early behavioural association between motorical movements and number representation might be reflected in the brain by using areas that are related to attention to movements, such as the supramarginal gyrus, for the neuronal representation of small numbers.

It seems plausible that a spatial representation of magnitude would be more appropriate for larger numbers for which manual coding strategies are inefficient or impossible. The angular gyrus might then be more essential in these situations.

### *5.6 Conclusion*

In this chapter I described a set of experiments that demonstrated the importance of the supramarginal gyrus in representing number magnitude for small numbers from 1 to 9. Furthermore, there was again some evidence for a spatial representation of these numbers, akin to a mental number line, within the angular gyrus.

# 6. 'Numbers are steps on a ladder, it's like climbing up a ladder'

*A single case description of a person with a vivid mental number line*

## 6.1 Summary

In this chapter an overview of the literature on explicit visuospatial representation of numbers, called number forms, is given and the number form of one subject (HS) is described in detail. HS's number form is subdivided into several parts. He described it like a motorway going up a long hill and in some parts it looked to him like the route his family drove to his grandmother's house when he was a child. HS said that his number form was activated automatically each time he was confronted with a number and that he used his number form in every aspect in life.

Explicit number forms like the number form of HS may only be special cases of a more general association between space and numbers that might be present in most subjects. Behavioural evidence suggests that one spatial representation of numbers in normal subjects is as a 'number line'.

## 6.2 Introduction

Although Hayes (1973) pointed out the importance of visual imagery for professional mathematicians and for prodigious calculators, the role of visualisation in mathematics, especially in arithmetic remains controversial (Giaquinto, 1993). Nevertheless, an interest in imagery for mathematics and numbers was present even in the very early days of psychology. Mary Calkins (1892), who must have been one of the first female Psychology Professors, reported subjects who associated specific colours with certain numerals, letters, words or music and called this phenomenon pseudo-chromesthesia. Nowadays, this phenomenon is called synaesthesia (Baron-

Cohen & Harrison, 1997). One of her subjects described her association in the following way: "4 is honest, but mathematically angular and ungraceful, 3 I cannot trust though it is fairly good-looking in personal appearance. 1 is dark in complexion. 9 is dark, a gentleman, tall and graceful, but politic under his suavity" (page 454).

The first to study the association of numbers with certain characteristics such as colours, personalities or certain mental forms was Galton. He published an article in Nature in 1880 entitled "Visualised Numerals". This article generated such interest that a follow-up article by him on the same topic appeared in Nature within the same year by which time he had received nearly 80 drawings of what he called numerical forms. In the first article Galton cites 21 examples of numerical forms, later to be called number forms (e.g. in Calkins, 1892).

A man from Cambridge (number 17) described his number forms in Galton's article as follows: "Numerals are always pictured by me in a straight line from left to right. They are black, on a ground varying in illumination, which is bright up to 10, then getting very shady from 10 to 20; 20 to 40, bright; 40 to 60, moderate; 60 to 80, shady. Shadiest are from 10 to 20, 60 to 80 or 90, 100 to 2000. The millions are in a vague, bright distance to the right." (page 254-255). Figure 6-1 shows a drawing of another number line taken and re-coloured from Galton's original article.

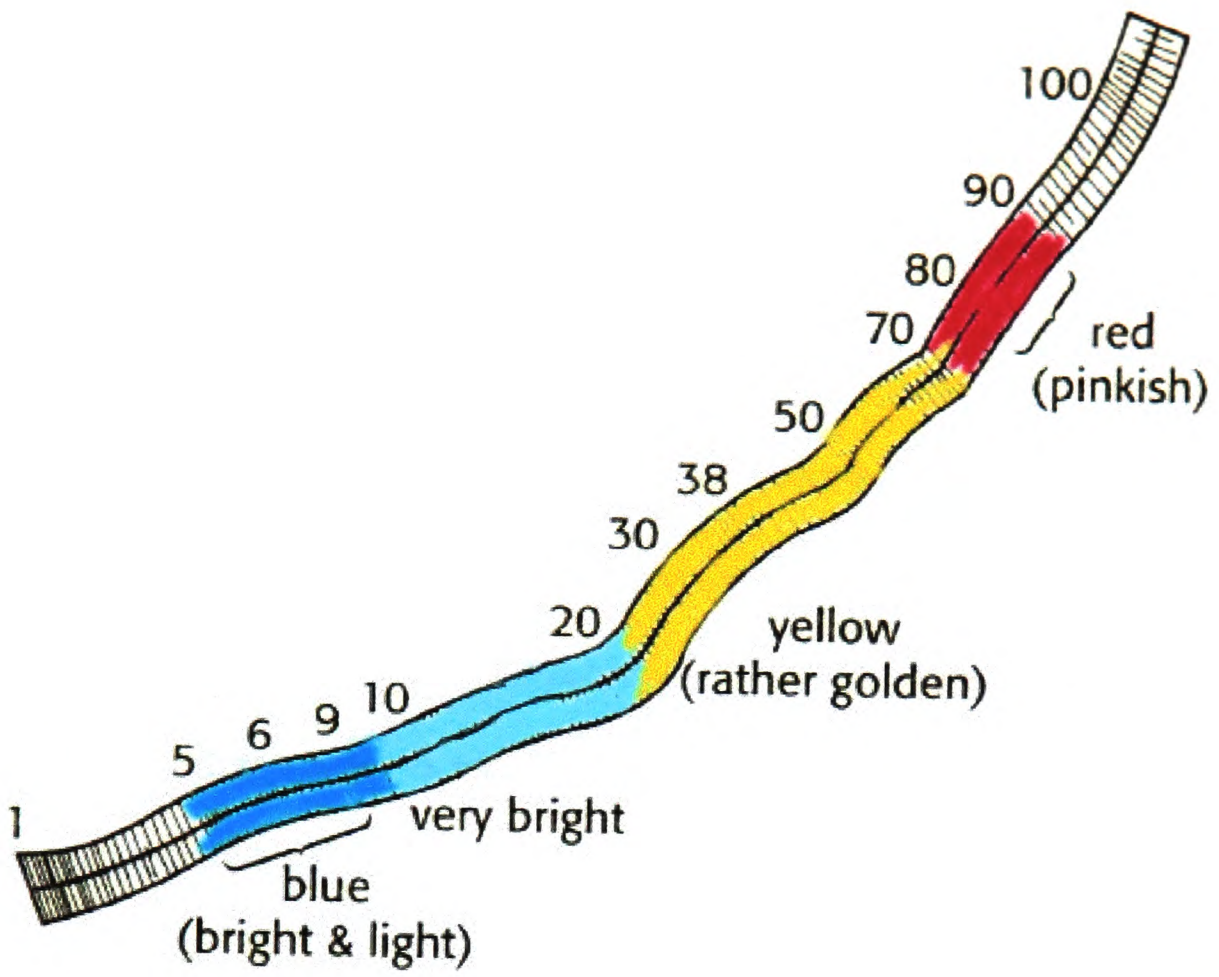



**Figure 6-1:** A number form with changes in brightness an colour (taken and re-coloured from Galton, 1880)

Obviously, all number line descriptions are based on introspection; those reported by Galton are thought to originate mainly from Galton's friends and acquaintances (Morton, 1936).

### *6.2.1 Definition of number forms*

Galton's publication inspired several researchers to further investigate the frequency and shape of number forms (Calkins, 1892; Morton, 1936; Oswald, 1960). Most of the number forms described go from left to right. Although the majority of these researchers seem to agree that the defining characteristic of number forms is a stable, visual, ordered arrangement of numbers in space, there are several features in the definition of number forms that are not agreed upon.

While Morton (1936) for example stated that the whole of the number form must be visible at any one time, Oswald (1960) believed that this is never the case. He observed that at each point in time only a particular number is seen with a sense of position with only a vague awareness of adjacent numbers.

### *6.2.2 Conditions under which the number forms are experienced*

Galton described the appearance of number forms as automatic whenever a series of numerals is thought of (page 494). But subsequent research seems to indicate that the appearance of these images is not inevitable; whether or not the image appears might depend upon the particular task. For example, all those in Oswald's study (1960) who possessed number forms were asked to multiply 8 by 8; subsequently all but four denied that they had seen 64 in its position on the form though they could do so if they tried. Oswald suggests that number forms only become activated when certain numbers are thought of as a series. There have been cases, however, reporting that their number forms appear any time they think of a number (Calkins, 1892; Galton, 1880a; Galton, 1880b). Oswald (1960) additionally argues that not only the number forms, but also the conditions under which subjects experience number forms can be quite different between individuals. Therefore, the conditions under which number forms are experienced might be almost as diverse as the individual number forms.

### *6.2.3 Frequency of number forms*

Several researchers have tried to quantify the frequency of number forms in the general population. Galton (1880b) states that based on his data about one out of 30 males (ca. 3.3 %) and one out of 15 females (ca. 6.6 %) assign numerals a definite place in their mental field of view. Galton therefore claimed a higher frequency of

number line representations in women; a statement supported by Seron, Pesenti, Noel, Deloche, & Cornet (1992). Oswald (1960), however, found no significant sex differences in frequency of number forms in a sample of 200 subjects.

Calkins (1892) reported a statistical study of pseudo-chromesthesia and of mental forms. She consulted 525 subjects, 35 of which reported pseudo-chromesthesia (ca. 7%) and 50 (ca. 9.5%) described number forms. In a second study with 203 participants Calkins found 61 subjects with number forms (ca. 30 %). Morton (1936) found 20 possessors of number forms in 867 schoolchildren aged 12-14; i.e. one possessor of number forms in 43 (ca 2.3%). This result is in contrast to the results of Galton who stated that young people see forms more commonly than adults (Galton, 1880b). However, both Galton (1880) and Morton (1936) agree that number forms in children are much more rudimentary, less developed and less definite than those of adults.

In order to address the question of frequency of number forms systematically Seron et al. (1992) gave a short questionnaire to 194 psychology students at a Belgian university. Twenty-seven of these students reported number forms [21 females (13.7%) and 6 males (14.6%)]. They also reported another inquiry on 217 students from a variety of departments in which 42 reported having a number form. In this study a higher rate of number forms was observed among females (ca. 26%) as compared to males (ca. 14%).

In conclusion, no reliable figure for the frequency of number forms in the general population can be given. The frequency most likely lies somewhere between the highest reported rate (30%, Calkins, 1892) and the lowest reported rate (2.3 % in children; Morton, 1936). It remains unclear whether the incidence rate is higher in females as compared to males.

### *6.2.4 Origins of number forms*

Why do certain people develop these representations and how did they arise? Galton (1880) believed that number forms arose in childhood as "mnemonics", as memory aids which assisted the memorisation of numbers. Oswald (1960) sees them as aids to the comprehension of abstract concepts, particularly for concepts of sequence. Calkins (1892) reports a classification of the points at which number-forms bend and showed that three quarters of these turns are at numbers which are prominent in early arithmetical exercises and in ordinary usage.

Almost all colour associations and forms seem to date back to childhood (Seron, Pesenti, Noel, Deloche, & Cornet, 1992). Calkins (1892) observes that the forms are chiefly those of ordinary objects, always frequent and sometimes prominent in the child's environment. She also stated that nearly all of her subjects with number forms are good visualisers, suggesting a relationship between the ability to visualise and possessing a number form. Seron et al. (1992), however, showed that the imagery scores of subjects with number forms were only slightly higher than those of subjects without number forms. Interestingly, they found that verbal scores of subjects with number forms were significantly lower than those of subjects without number forms.

Galton (1880) and Calkins (1892) believed that there was a strong inherited tendency to possess number forms, but this claim has yet to be supported by data.

### *6.2.5 Usefulness of number forms*

Galton (1880) was not able to come to a definite conclusion as to whether number forms are useful to their possessors or not; nevertheless he was inclined to believe that they are developed because they are useful. Calkins (1892) asked subjects with

number forms whether they found their number forms useful and roughly one-half of those with number forms answered affirmatively.

Morton (1936) tested 717 pupils for ability in mechanical arithmetic and showed that those children who had number forms (n = 17) tended to show superior ability in mechanical arithmetic. Thirteen of the seventeen children with number forms (76.4%) were in the upper quartile of all those who were given the arithmetic test. This seems to indicate that children who have number forms are generally good at mechanical arithmetic. So far, however, Morton's study has been the only one investigating a relationship between number forms and arithmetical ability and although he tested 717 pupils, his group of pupils with number forms (17) is certainly too small to draw any general conclusions.

### *6.2.6 Summary*

In general, number forms feel very natural to people possessing them. In Calkins (1892) for example one man wrote: "I cannot realise how any one can dispense with something of the kind. It seems to me that without this form, numbers would have no meaning and a person would be entirely lost in considering them." (page 450). It is however unclear, how frequent these number forms are and whether there are sex differences. Furthermore, number forms differ widely in structure and usage between individuals. Some subjects do not report using their number form at all, while others use them for most simple, every day numerical tasks. Calkins (1892), for example, cites a person using his number form for basic calculation: "When I add numbers, I invariably think of my form, e.g. if I add 5 to 27. I feel as if I passed on a step. When I multiply, I feel as if I jumped as it were from one place to another, e.g. 6 × 9 is a long jump compared with 3 × 6." (page 450). Most number form possessors believe that their number form developed during childhood. There is

some evidence that children with number lines might be better in mechanical arithmetic. Further research will have to clarify whether having a number form is related to mathematical and verbal abilities and/or ability of visual imagination.

## *6.3 Case study*

In the following the number form of a person, the conditions under which this form appears and usage of the form will be illustrated in detail.

### *6.3.1 Methods*

#### *6.3.1.1 Participant*

I met the participant HS first in high school around 1991 when we both took classes in mathematics A-levels. It was then that he first told me about his number form, but only later, for the first time in 2000, did I question him in detail on his number form. HS is male, German and was 26 years old when the first interview was conducted. At that time he studied Technical Mechanics at a German university.

#### *6.3.1.2 Procedure*

The first interview was carried out in December 2000. This interview was very brief and took place in an informal setting. I asked HS to draw his number representation as accurately as possible (see figure 6-2) and noted the comments he made while drawing (see appendix A). Unfortunately, this interview was conducted in German and I did not use a tape recorder. At the end of that interview I did not tell HS that I was planning a second, more detailed interview about half a year later to see how far his number representation was reliable and stable over time. On 5 July 2001 I met HS again and conducted the second interview. This time I asked him to describe his number form in detail in English and recorded the interview (transcripts of the

interview are to be found in the appendix B). The interview took approximately 75 minutes.

### *6.3.2 Results*

It became clear that HS used his number form also as a historical line with marks for certain historical events (such as the end of Second World War). Furthermore he described that around his number line he could see a year spiral on which he records personal events in past, present and future. He stated he used this spiral as a calendar and for planning events. In the following description I will focus on the number form itself. Readers interested in HS's year and historical forms will find sketches of them in the appendix C, and a description of them in the transcript of the second interview (appendix B).

#### *6.3.2.1 Number form description*

Figure 6-2 shows the number line drawn by HS in December 2000. He emphasised several times that it was difficult for him to draw the number form precisely on a sheet of paper, because he saw it in three dimensions, but he was, nevertheless, asked to draw it in two dimensions.

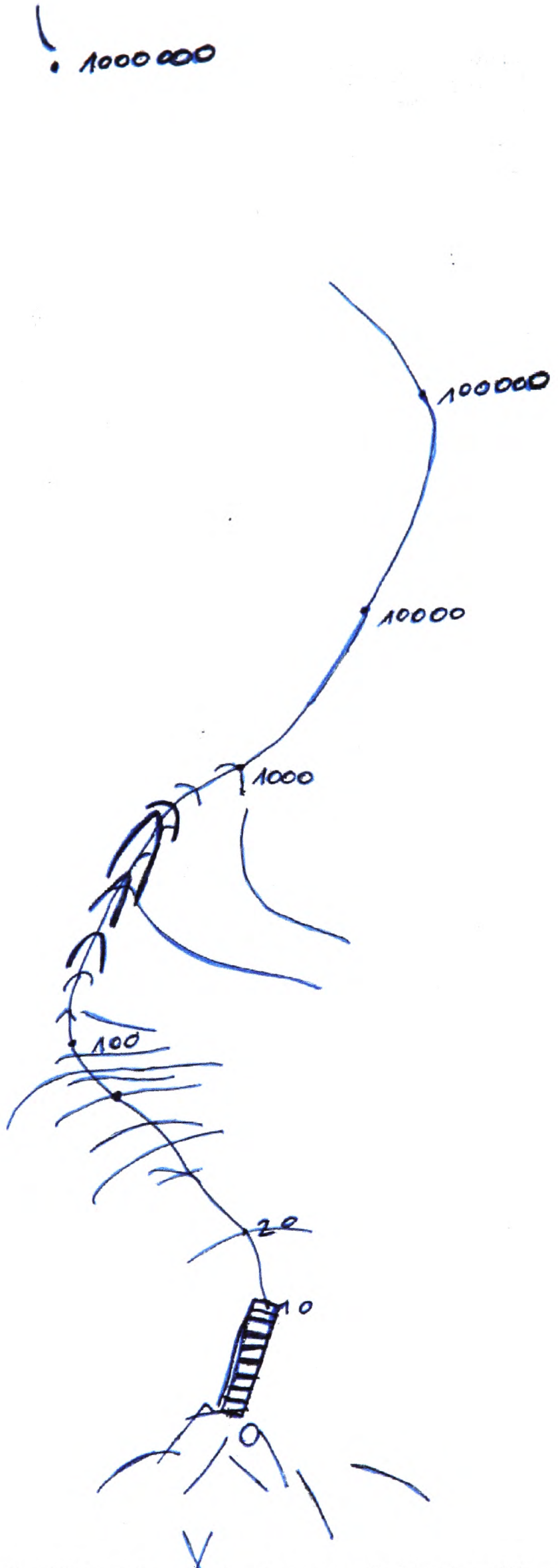



**Figure 6-2:** The drawing HS produced when he was asked to draw his number form in two dimensions in December 2000

More than six month later HS described his number line as follows:

> *"It's subdivided into two parts: negative and positive numbers. ... I'm normally staying at the origin at zero and looking forward into the positive direction .... When I am looking backwards on a negative number, it's like a waterfall just going down and ... not a discrete ... way in its own. It's more ... a blurred waterfall, no discrete line anymore and the positive numbers ... are discrete lines ... subdivided into ... several parts ... from 0 to10, from 10 to 20, from 20 to 100, then to 1000, then to 10 000, then to 100 000 and then to one million, then to one billion and then it's ... blurred it's not a discrete line anymore."*

He went on to describe it:

> *"It's like a ...like ... a motorway going up a very long hill. .... From 1 to 10 it's like ... standing in a flat plane, from 10 to 20 the ... motorway itself is a bit skipped to the left ... from 100 to 1000 ... it's falling straight down and it is very shadowed. Afterwards it gets clearer again ... From 0 to 10 it is a straight line, then it makes a left turn to 20 and then another left turn to 100 then a right turn to 1000."*

The description of his number form fits very well with the drawing HS made six month earlier (see figure 6-1). The number form therefore seems to be reliable and to remain stable over time. Interestingly, although he wrote numbers next to the number form drawing, he insisted that he didn't see actual written numbers on his number form:

> *"All these discrete lines there is no real number at all .... I don't see the numbers itself. ... I just know that I am at 35. .... I have to give this point in space. I have ... to give it a number that everyone understands ... For me it's not necessary. "*

*6.3.2.2 Origin of the number form*

Asked where he thinks his number form originates from he answered:

> *"It in some parts looks like the way ... my parents and I drove when I when I was young to my grandma. That's a ... a way from about 15 km – it's like 10 miles, 9 miles and ... that fits pretty good to some regions of it and also the dark part between 100 and 1000 seems to be the part in the in the woods."*

When I asked him where his first memory of it goes back to, he answered:

*"I'd say that I always calculated like this .... Of course... the higher numbers ... were made up later, but I can remember that I already calculated like this maybe in the third class." (age: 9-10 years)*

His number form also incorporates negative numbers, but he could not remember when they got incorporated into his number form, but he was certain that they were not there in the beginning.

*6.3.2.3 Conditions under which he sees the number forms*

HS said that every time he is confronted with a number he sees his number form. When I asked him whether he is not always using it though, he replied that every time he calculated he used it.

*6.3.2.4 Usage of the number form*

HS claimed to use his number form "in every aspect in life". Besides using it to remember historical and personal events and for planning future events, he seemed to use it mainly in relation to numbers. He described how he used it for picturing natural numbers:

*"The natural numbers ... are steps on a ladder ... and it's like ... climbing up a ladder."*

He stated he used his number form for addition and subtraction:

*"It's like going up the ladder and climbing down again."*

as well as for multiplication:

*"multiplication? Is like you have a ...let me describe it like this you have ..., for example, ... five times seven .... Let's ... fold ... a paper five times, and then I don't really have to think about it anymore, it's just ... pops up and it's like ... you know if you have a folded ladder and then it's just bubu bubudoop and it folds up and then I know that I am at 35."*

He admitted that he did not use his number line for more complicated calculations:

*"I'm not actually able to do something like let's say 17 times 35 minus 275, ... but it works out pretty well in the range between zero and 100."*

HS gave an interesting reason why it seemed to be more difficult for him to use his number form for calculations over 100. The

> *"dark part between 100 and 1000 seems to be the part ... in the woods" and his number line "from 100 to 1000 ... it's falling straight down and it is very shadowed. So it's pretty hard for me to calculate in this region from 100 to 1000."*

Furthermore, he seemed to use it when comparing incomes or converting currencies:

> *"For example in Germany ... a roll costs let's say 50 Pfennig and in Italy it costs 500 Lire .... So it's like spreading up the numbers from one to ten to one to ... 10 000 and then I know the relation between the different values ... of currencies. ... That's how I do it so I use it in every day life and for me I know that it's ... good to earn let's say 50 000 Euro per year and ... it's like making a mark ... on my line and then I know ... okay this one is higher and ... lower. ... I do put a mark on my line if someone tells me how much he earns per year."*

### 6.4 Discussion

HS presents another case of a person with a vivid visuospatial representation of numbers. Although accounts like this seem highly unusual to the majority of people who do not posses this type of representation, there have been many documented cases of individual number forms in the literature (Calkins, 1892; Galton, 1880a; Galton, 1880b; Morton, 1936; Seron, Pesenti, Noel, Deloche, & Cornet, 1992). Although each number form is individual, they seem to share certain characteristics. In general, smaller numbers seem to be represented lower and/or more to the left than larger numbers. Most forms seem to have emerged during childhood and the number forms and their usage seem to be relatively stable over time once the possessors have reached adulthood.

There is, however, at least one report of an impairment of a number line due to brain damage. Spalding & Zangwill (1950) report a disturbance of a number form after brain injury. They saw a 24 year-old patient who suffered a left-sided occipito-parietal brain injury resulting in severe dyscalculia, disorders in visual memory and some impairment of topographical sense. The patient was slow and often wrong in oral and written double-digit calculation. He indicated that his previously well-

developed number form had lost its former distinctiveness and he could no longer use it for calculation. Spalding & Zangwill (1950) report that the most severe brain damage seems to be just below the angular gyrus on the left hemisphere. Spalding & Zangwill (1950) conclude that the greater part of "the arithmetical disability is to be ascribed to impairment of the visual-spatial number form." (page 29).

Oswald (1960) criticises this conclusion. He, however, agrees with Spalding & Zangwill (1950) that a visuospatial number representation or its usage can be disturbed by a brain lesion in a region close to or in the left inferior parietal lobe. He writes that "in regard to visual asymbolia, that though the latter may be frequently accompanied by other disorders, such as acalculia, visual agnosia, spatial disorientation, dysphasia, and hemianopia, these arise not because visual asymbolia and the other disorders are different manifestations of a single, more fundamental disorder, but because the anatomical basis of many functions is likely to be damaged by a lesion in the angular and supramarginal gyrus." (page 87).

Although the percentage of subjects who possess such explicit number lines as Spalding's & Zangwill's patient, HS, or Galton's subjects might be low, there is evidence for spatial coding of numbers in normal subjects. Hunter (1964) wrote that among 250 people who claimed to have no number form no fewer than 210 reported "a feeling that numbers somehow recede from them: some reported that numbers had a vague upward movement and others that they seemed to recede in a straight line or at an angle." (page 194). Pear (1922) argued that many people who have no number form nevertheless possess some of the rudimentary imagery from which they are built up. Morton (1936) also found indications that although they have no number forms, many children have the foundations for it (e.g. for many children the

numbers seem to progress to the right, the smaller numbers appear to be nearer, the line of numbers bends or turns at ten, twelve etc.).

Gattis (2001) claimed that for a long time psychologists recognised the possibility of a connection between the way that children think about space and their understanding of mathematics, but they have usually done so in a negative way (here she cites Piaget and Binet for example).

Dehaene, Bossini, & Giraux (1993) first described an effect that provides further behavioural evidence for spatially oriented number lines in normal subjects. Their subjects, when asked to classify a single digit as being odd or even by one of two button presses were faster to answer with a left hand button press for smaller numbers and replied more quickly with a right hand button press for larger numbers. Dehaene et al. (1993) termed this effect the SNARC effect; SNARC stands for spatial numerical association of response codes. The SNARC effect depends on relative number magnitude and is weaker or absent with letters or verbal numerals (Dehaene et al., 1993). Berch, Foley, Hill, & Ryan (1999) showed that the SNARC effect emerges in parallel with numerical skill acquisition. Interestingly, the SNARC effect seems to be linked to the direction of writing. Dehaene et al. (1993) showed that it faded or was even reversed in right-to-left writing Iranian subjects. Furthermore, the left-right oriented number line seems to be more like a default representation in Western subjects that can be altered if a different reference frame is introduced. Bächtold, Baumüller, & Brugger (1998) showed that responses to the digits one to five were faster with the left hand when the reference was a ruler with a range from one to ten, while responses to the same digits were faster with the right hand when the reference was a clock face with a range from one to twelve.

Recently, however, Fischer (in press) reported further experiments that led to the conclusion that the left-right oriented number line seems to be the dominant default representation in Western subjects. First, subjects asked to bisect long digit strings with a pencil showed an effect on spatial accuracy as predicted by the SNARC effect (i.e. small digits induced a left-bias in the bisection task whereas larger digits induced a right-bias). A control experiment with consonant vowel discrimination did not show the SNARC effect.

In a second experiment subjects were asked to bisect lines that were flanked by different digits (such as 1_____2, 8_____8, 2_____1, etc.). Despite the mainly small difference in magnitude, lines flanked by different digits induced reliable bisection biases toward the digit representing the larger magnitude (Fischer, in press). Both experiments further support the hypothesis of an automatic association between numerical magnitude information and spatial response codes.

More research on HS and his number form would certainly be useful. For example, does he show normal behavioural effects such as the distance, problem-size and SNARC effect? The location of numbers on his number form (figure 6-2) is very clearly not like on a classical mental number line (see also figure 6-1) with increasing number size from left to right. In his representation smaller numbers are located at the bottom of his line and the number size increases the higher up he moves on his line. An investigation of his spatial numerical associations of various response codes would be very interesting. Does he still show a classical SNARC effect with faster responses with his left hand to smaller numbers and his right hand to larger numbers? Also, if his number form has an influence on his spatial numerical associations of response codes, he should be faster to respond to larger numbers with a top button than with a bottom button press. Let's suppose he showed

a vertical and a horizontal SNARC effect, then it would be very interesting to investigate in how far these two effects interact. For instance, one could think about an experiment that enables us to compare his response times for smaller versus larger numbers when the response codes could be top left, bottom left, top right or bottom right.

If HS showed a vertical SNARC effect an obvious question would be whether this effect can be altered by showing a representational scheme in which numbers are associated with locations that are incongruent with his number form such as a clock face. Would he be able to ignore his number form completely or would it interfere with the representational scheme? The latter would be predicted if his number form really were as automatic as he claimed.

Originally, we planned to investigate the neural basis of HS's number form. The first question is, can his number form be altered by applying TMS to his left angular gyrus, as might be predicted by the work of Spalding & Zangwill (1950). And if it does, in which way is it altered? Are the alterations replicable and what happens when magnetic stimulation is applied over right angular gyrus? Also, does TMS alter any SNARC effects he might show?

Furthermore, HS was supposed to be one of the subjects in the fMRI study described in chapter 7. In addition to the analysis reported there, we planned to compare HS's brain activation pattern during numerical tasks to those of subjects without number forms. It would have been very interesting to see whether there were any significant differences and if there were any, in which regions they would be. I certainly expected HS to show stronger activation in visuospatial areas during number comparison than subjects without number forms. Unfortunately, HS did not

feel comfortable enough in the scanner or the TMS environment to carry out any tasks.

### *6.5 Conclusion*

In this chapter I reviewed the literature on explicit visuospatial number representations, called number forms. The number form of one subject (HS) was described in detail. It was argued that explicit number forms are only special cases of a more general association between space and numbers which is present in most subjects. This association can be observed in several psychological experiments, for example in experiments on the SNARC effect.

# 7. Using fMRI to investigate number comparison

## 7.1 Summary

Neuroimaging studies of number comparison have consistently found activation in the intraparietal sulcus (IPS). Recently, it has been suggested that activations in the IPS vary with the distance between the numbers being compared. In number comparison the smaller the distance between a number and the reference the longer the reaction times (RT). Activations in the right or left IPS, however, have also been related to attentional and intentional selection. It is possible therefore that activity in this region is a reflection of the more basic stimulus and response selection processes associated with changes in RT. This fMRI experiment investigated the effect of numerical distance independently from RT. Additionally activations during number comparison of single-digit and double-digit stimuli were compared. During number comparison blocks, subjects had to indicate whether digits were greater or smaller than a reference (5 or 65). In control blocks they were asked to perform a perceptual task (vertical line present/absent) either on numerical or non-numerical stimuli. Number comparison versus rest yielded a large bilateral parietal-motor patchwork. However, no areas showed more activation during number comparison than during the control tasks. Furthermore, no areas were more active during comparison of numbers separated by a small distance than comparisons of those separated by a large distance or vice versa. A left-lateralised parietal-motor patchwork varied significantly with RT. Our findings suggest that previous distance-related IPS activations might be mainly due to fundamental stimulus and response selection processes associated with RT changes and question the number-specific IPS contributions during number comparison.

## *7.2 Introduction*

In this chapter I will present a functional magnetic resonance imaging study of number comparison. The study was carried out to see whether the anatomical differences between the representation of small and large numbers in number comparison found with TMS as described in chapters 4 and 5 can be replicated by using a different technique which has a good spatial but relatively low temporal resolution, fMRI.

In addition, this fMRI experiment was intended to further clarify which parietal areas in general are engaged in processes of number comparison and, specifically, whether visuospatial parietal areas are activated during number comparison. Their activation would provide further evidence for the view that number comparison relies also on a visuospatial representation in normal subjects, perhaps similar to mental number line representations as discussed in the last chapter.

Most imaging studies on numerical processing so far have investigated simple calculation. Therefore, this section will commence with a brief overview of results and limitations of imaging studies (fMRI and Positron- Emission-Tomography [PET]) on calculation. This will be followed by an overview of imaging studies which have looked at number comparison specifically.

### *7.2.1 Imaging studies on calculation*

Table 7-1 gives an overview of activations found in imaging studies on calculation. Imaging studies of patients (e.g. Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000) as well as studies that did not include the parietal lobes (such as Burbaud, et al., 1995) are excluded. All subjects were right handed (unless handedness is explicitly mentioned in the table).

**Table 7-1:** Summary of activations in imaging studies investigating calculation

| Authors | N | Tasks | + | - | × | ÷ | ~ | Activations |
|---|---|---|---|---|---|---|---|---|
| **Roland & Friberg (1985)**<br><br>$^{133}Xe$ | 11 | 1: rest<br>2: serial subtraction of 3 from 50<br>3: jump every second word in a 9 word circular jingle<br>4: route finding | | ● | | | | Versus rest<br>2: B superior prefrontal cortex, anterior midfrontal cortex, L Broca's area, B ANG |
| **Rueckert, et al. (1996)**<br><br>fMRI (1.5 T) | 9 | 1: serial subtraction of 7 from 3 digit integer<br>2: counting forward starting with 1 | | ● | | | | 1 versus 2:<br>L prefrontal cortex, L PPC (ANG and/or SMG), B motor/premotor cortex |
| **Dehaene, Tzourio, Frak, Raynaud, & et al. (1996)**<br><br>PET | 8 | 1: rest with eyes closed<br>2: mental multiplication of Arabic digits (1-9)<br>3: number comparison | | | ● | | | Versus rest<br>2: B lateral occipital regions, L precentral gyrus, supplementary motor area, R cuneus, L fusiform and lingual gyri, B inferior parietal gyri |
| **Sakurai, Momose, Iwata, Sasaki, & Kanazawa (1996)**<br><br>PET<br>one subject was Soroban expert | 9 | 1: fixation on screen<br>2: covert reading of calculation material (+ / -)<br>3: calculation with oral response (addition/subtraction)<br>*visual and auditory presentations* | | ● | ● | | | 3 versus 1:<br>posterior superior temporal gyrus including part of Wernicke's area<br><br>3 versus 2:<br>L prefrontal area |
| **Burbaud, et al. (1999)**<br><br>fMRI (1.5 T) | 11 | 1: rest<br>2: think of number > 500<br>3: think of number > 500, subtract 13 or 17 | | ● | | | | Versus rest<br>2: L supplemetary motor area, L prefrontal and premotor cortices, Broca's area<br>3: L dorsolateral prefrontal cortex, L premotor cortex, L supplementary motor area, Broca's area, L inferior parietal cortex |
| **Chochon, Cohen, van de Moortele, & Dehaene (1999)**<br><br>fMRI (3 T) | 8 | 1: letter naming (A to I, without E)<br>2: digit naming (1 – 9, without 5)<br>3: number comparison (reference 5)<br>4: multiplication (x × 3)<br>5: subtraction (11 - x) | | ● | ● | | | Versus 1<br>2: R inferior frontal gyrus, R mesial frontal gyrus<br>4: B IPS, R postcentral gyrus/sulcus, superior part of L inferior parietal lobule<br>5: B IPS, superior part of both inferior parietal gyri, R postcentral sulcus<br>5 versus 4: R anterior intraparietal/postcentral region, B inferior frontal gyri, R dorsolateral gyrus |
| **Dehaene, Spelke, Pinel, Stanescu, & Tsivkin (1999)**<br><br>fMRI (3 T) | 7 | 1: letter matching<br>2: exact addition (addends 1-9, sums 3-17, no ties, two choice)<br>3: approximate addition (answers one and 4 units apart from correct answer) | | ● | | | ● | 3 versus 2: B IPS extending anteriorly to the depth of the postcentral sulcus and laterally into the inferior parietal lobule, R precuneus, B precentral sulci, L dorsolateral prefrontal cortex, L superior prefrontal gyrus, L cerebellum, B thalami<br>2 versus 3: L inferior frontal lobe, L cingulate gyrus, L precuneus, R parieto-occipital sulcus, B ANG, R middle temporal gyrus |
| **Burbaud, et al. (2000)**<br><br>fMRI (1.5 T)<br><br>*15 verbal strategy*<br>*14 visual strategy* | 29 | 1: rest<br>2: serial subtraction of 13 or 17 from a number (starting with a number larger than 500) | | ● | | | | Versus rest:<br>*In subjects with verbal strategy:*<br>Strong L dorsolateral frontal cortex, little inferior parietal cortex<br>*In subjects with visual strategy:*<br>B prefrontal cortex, strong L inferior parietal |
| **Cowell, Egan, Code, Harasty, & Watson (2000)** | 12 | 1: rest<br>2: number repetition (1 – 30)<br>3: calculation (addition, subtraction and division, answers 1-30) | | ● | ● | ● | | Versus rest:<br>2: L inferior frontal cortex, B posterior superior temporal gyri, B inferior sensorimotor cortex, L posterior middle |

| | | | | | |
|---|---|---|---|---|---|
| PET | | | | | temporal cortex<br>3: medial frontal/anterior cingulate gyri, medial thalamus, L dorsolateral prefrontal cortex, R anterior insula/putamen, L anterior insula, L lateral parietal cortex involving BA 7, ANG and SMG |
| **Fulbright, et al. (2000)**<br><br>fMRI (1.5 T) | 18 | 1: serial presentation of four zeros<br>2: match numbers in 3 digit number<br>3: multiplication of four single digit or low-value double digit numbers | | ● | Versus 1<br>2+3: medial superior frontal gyrus, anterior cingulate gyrus, B IPS, R superior frontal sulcus, middle, inferior and precentral frontal gyri, L basal ganglia, R lateral and left inferior occipital gyri<br>2-3: R middle frontal gyrus<br>3-2: L middle frontal gyrus |
| **Kazui, Kitagaki, & Mori (2000)**<br><br>fMRI (1.5 T) | 9 | 1: number counting control (list ordinal numbers in increasing rank from base number)<br>2: serial subtraction (100 – x, x= 16-19)<br>3: single digit multiplication (recite two rows) | | ● ● | Versus 1:<br>2: inferior parietal areas, B premotor and supplementary motor areas, posterior portion of inferior frontal gyrus, B prefrontal area<br>3: B premotor and supplementary motor area, posterior portion of inferior frontal gyrus, L inferior parietal area |
| **Lee (2000)**<br><br>fMRI (1.5 T) | 11 | 1: single digit subtraction<br>2: single digit multiplication | | ● ● | 2 > 1: border between ANG & SMG, L superior frontal gyrus<br>1 > 2: IPS, superior and inferior frontal gyri, B posterior inferior temporal gyri |
| **Menon, Rivera, White, Glover, & Reiss (2000)**<br><br>fMRI (1.5 T )<br><br>*2 rates of stimulus presentation (ISI of 3 s or 6 s)* | 16 | 1: rest (viewing blank screen)<br>2: easy calculation (two-operand addition or subtraction problems)<br>3: difficult calculation (three-operand addition/subtraction problems)<br>4: detecting zeros in a string of 5 (easy) or 7 (difficult) digits | ● | ● | 2>4: B inferior frontal gyrus, L middle frontal gyrus, L SMG, L ANG, L inferior temporal gyrus, L pre-SMA, L premotor cortex<br>3>4: B inferior frontal gyrus, B middle frontal gyrus, B ANG, B SMG, B premotor cortex, L pre-SMA, L inferior temporal gyrus, B middle cerebellum, B caudate, L ventrolateral nucleus of the thalamus<br>*main effect of rate:* L insula, basal operculum of the orbitofrontal gyrus<br>*main effect of number of operands:* B ANG and adjoining IPS, L pre-SMA |
| **Menon, et al. (2000)**<br><br>fMRI (1.5 T ) | 16 | 1: single digit calculation (4+2-I=4)<br>2: detect zero in seven single digit string (e.g. 1325074)<br>*8 perfect (100%) versus 8 imperfect (92%) performers* | ● | ● | 1>2: parietal cortex, inferior and middle frontal gyri, R mid-cerebellar hemisphere, R premotor cortex, L caudate<br>*perfect performers:* less activation and variability in L ANG |
| **Pesenti, Thioux, Seron, & De-Volder (2000)**<br><br>PET | 8 | 1: rest (eyes closed)<br>2: judgement on non-numerical characters<br>3: Arabic numeral processing<br>4: number comparison<br>5: simple addition | | ● | Relative to rest<br>3>2: R anterior insula, superior parietal lobule, junction between R ANG and SMG<br>4>3: L inferior parietal lobule (SMG), R superior parietal lobule, precentral areas<br>5>4: orbito-frontal gyrus, R anterior insula<br>5>2: L inferior and superior parietal foci, middle frontal gyrus and precentral sulcus |
| **Rickard, et al. (2000)**<br><br>fMRI (1.5 T) | 8 | 1: detect ones (4 2 1 7)<br>2: single digit multiplication verification<br>3: magnitude judgement (14-81) | | ● | 2>1, 3: B BA 44, dorsolateral prefrontal cortex, inferior and superior parietal areas, lingual and fusiform gyri<br>3>1: B inferior parietal cortex |
| **Stanescu-Cosson, et al. (2000)**<br><br>fMRI (3T) | 7 | 1: letter matching<br>2: exact addition (small 1-5, large 5-9)<br>3: approximation<br>*variation of operand size in 2* | ● | ● | 3>2: B IPS, precentral, dorsolateral and superior prefrontal regions<br>2>3: L inferior prefrontal cortex, B ANG<br>*increasing number size in 2:* increase in B IPS, L inferior and superior frontal gyri |
| **Gruber, Indefrey, Steinmetz, & Kleinschmidt** | 6 | 1: compound multiplication and division (one factor > 10)<br>2: simple multiplication and division (both factors < 10) | | ● ● | 2>5: dorsal inferior frontal gyrus, middle third of inferior frontal sulcus, IPS, posterior cingulate cortex and precuneus<br>1>5: L frontal areas, IPS |

| | | | | |
|---|---|---|---|---|
| **(2001)**<br><br>fMRI (1.5 T) | | 3: number substitution (2 digits)<br>4: letter substitution (2 consonants)<br>5: letter pseudo-multiplication and –division | | 1>2: dorsal parts of L inferior frontal gyrus, anterior inferior frontal sulcus and anterior cingulate cortex<br>2>1: medial parietal zone covering precuneus and posterior cingulate cortex |
| **Zago, et al. (2001)**<br><br>PET | 6 | 1: rest<br>2: read (01001..)<br>3: retrieve single-digit multiplication (small/medium)<br>4: compute double-digit multiplication | ● | 3>2: L anterior part of the insula, L precentral sulcus, L IPS, R superior occipital gyrus, L anterior and R posterior and medial cerebellum<br>4>2: L anterior insula, L precentral gyrus, IPS, B superior frontal sulcus, L middle frontal gyrus, L SMG extending to the precuneus, R IPS<br>4>3: L superior frontal gyrus, anterior part of R IPS, superior part of SMG extending to the postcentral sulcus, B inferior and middle occipital gyri, B fusiform gyri and R cerebellar vermis. |
| **Simon, Mangin, Cohen, Le Bihan, & Dehaene (2002)**<br><br>fMRI | 10 | 1: grasping,<br>2: pointing,<br>3: saccades<br>4: attention,<br>5: calculation (subtract a number from 11 or 15)<br>6: phoneme detection<br>7: letter naming | ● | 5>7: L superior frontal gyrus, precentral sulcus extending into dorsolateral prefrontal cortex and inferior prefrontal gyrus, R superior and inferior frontal gyri, B cingulate gyrus, L IPS from most superior part of posterior segment to postcentral sulcus, R horizontal segment of IPS, B anterior putamen, L insula, L putamen, L thalamus |

B = bilateral, L = left, R= right, LH = left handed, IPS = intraparietal sulcus, PPC = posterior parietal cortex, SMA = supplementary motor area, + = addition, - + subtraction, × = multiplication, ÷ = division, ~ = approximation

The most striking point of this overview is the variety of regions activated. This clearly shows that no single brain region holds a monopoly on calculation, as one might have been led to think from the patient literature. A large patchwork of brain areas is involved in calculation including prefrontal areas, motor/premotor areas, superior temporal gyrus, pre- and postcentral sulcus, parietal areas and occasionally cerebellar, thalamic and cingulate areas. Although a wealth of regions is activated by calculation, the areas most consistently activated across tasks are areas ANG and SMG in the inferior parietal lobule (Roland & Friberg, 1985; Rueckert et al., 1996, Dehaene et al., 1996; Burbaud et al., 1999; Chochon et al., 1999; Dehaene et al., 1999; Burbaud et al., 2000; Cowell et al., 2000; Kazui et al., 2000; Lee, 2000; Menon et al., 2000; Pesenti et al., 2001; Rickard et al., 2000; Stanescu-Cosson et al., 2000; Zago et al., 2001) and/or areas in the IPS (Dehaene et al., 1999; Fulbright et al., 2000; Lee, 2000; Menon et al., 2000a; Stanescu-Cosson et al., 2000; Gruber et al, 2001; Zago et al., 2001; Simon et al., 2002).

*7.2.1.1 Lateralisation of calculation*

The evidence for a left hemispheric dominance in calculation is slightly less clear cut than in patient studies. The reported activations in neuroimaging studies are often bilateral. However, in these cases of bilateral activation there is often evidence for larger activations in the left hemisphere (e.g. Menon et al., 2000; Pesenti et al., 2000; Zago et al., 2001; Simon et al., 2002; Cowell et al., 2000).

Reports of lateralisation specific for certain operations are inconsistent as to whether there is a left-lateralisation or whether the representation is bilateral. Chochon et al. (1999) for example described a larger activation for multiplication in the left inferior parietal lobule, while Dehaene et al. (1996) reported bilateral inferior parietal lobe activation for multiplication. For subtraction, Rueckert et al. (1996) and Burbaud et al. (1999), found left-lateralised activations in the inferior parietal lobe. Chochon et al. (1999) however described bilateral IPS activation for subtraction.

The evidence for a left-lateralisation of activations in the inferior parietal lobe and IPS seems to be somewhat clearer for addition than for subtraction, but there are also fewer studies investigating addition on its own than subtraction. Pesenti et al. (2000) and Menon et al. (2000a), for example, found larger activity in the left than right hemisphere during addition.

*7.2.1.2 Activation patterns for different operations*

Models of numerical processing such as the triple code model (Dehaene & Cohen, 1995; see also section 1.6.2.4) have claimed separate neural circuits for different operations, and these claims are at least partly supported by evidence from dissociations between operations found in patients (Cipolotti & van Harskamp, 2001; see also section 1.5.4.2). According to Dehaene & Cohen (1995)

multiplication problems are often learned by rote and solved through the retrieval of automatic verbal associations. Therefore they should rely on a left-lateralised patchwork including perisylvian language areas (Dehaene, 2000). In contrast, subtraction problems are, so they suggest, not systematically memorised and require the manipulation of the quantities represented by the operands. Mental manipulation of quantities is thought to be implemented by bilateral inferior parietal areas. The status of addition and division in the triple code model is in principle more ambiguous.

Imaging studies that compare the pattern of brain activations of different operations (mainly subtraction and multiplication) found some consistencies with the triple code model, but also various inconsistencies.

In general, it is clear that regions in the IPL/IPS are activated during subtraction and multiplication (Roland & Friberg, 1985; Dehaene et al., 1996; Burbaud et al., 1999; Cowell et al., 2000, Rickard et al., 2000, Simon et al., 2002). Chochon et al. (1999), for example, report bilateral activation in IPS and in the superior part of the left inferior parietal lobule for both multiplication and subtraction. Results from imaging studies, however, have not only shown that there are areas commonly activated during subtraction and multiplication, they also provide evidence that the neural circuits used for subtraction and multiplication differ (Chochon et al., 1999; Lee, 2000). The localisation of brain areas that are involved in multiplication but not in subtraction, however, is inconsistent. The triple code model, as discussed above, predicts the activation of a left-lateralised patchwork including perisylvian language areas during multiplication, but not during subtraction. Dehaene (1996) found activation in these languages areas during multiplication. Zago et al. (2001) and Lee (2000), however, showed that the retrieval

of multiplication facts in their studies did not rely on perisylvian language areas. Lee (2000), for example, found a larger activation for multiplication than subtraction at the border between ANG and SMG and in the left superior frontal gyrus. This is consistent with Dehaene's claim of a larger role of the left hemisphere in multiplication, but Dehaene would predict language areas to be active during multiplication.

Findings about brain areas activated during subtraction are partially compatible with the triple code model. When Chochon et al. (1999), for example, compared the activations of subtraction and multiplication, a right anterior intraparietal/postcentral region (along with both inferior frontal gyri and the right dorsolateral prefrontal gyrus) seems to be more active during subtraction than multiplication. Lee (2000) reported IPS, superior and inferior frontal gyri and both posterior inferior temporal gyri to be more active in subtraction than multiplication. In a recent study of various tasks that activate the parietal lobes, Simon et al. (2002) also found areas within the IPS that were activated for subtraction (in comparison to letter naming). This fits well with the triple code model, in which subtraction problems are thought to be implemented by inferior parietal areas, because they require mental manipulation of quantities.

However, Simon et al. (2002) could also show that one of the two neighbouring regions in the left IPS which were activated during subtraction was active during phonological processing as well. This might indicate that subtraction actually relies on the co-ordination of two different representations of numbers: a nonverbal quantity code involving bilateral intraparietal sulci (as suggested in the triple code model) and a verbal code involving classical language areas.

To my knowledge, only two studies so far have looked at brain areas activated in division tasks (Cowell et al., 2000 and Gruber et al., 2001). In both studies they used tasks in which division tasks were mixed either with subtraction and addition tasks (Cowell et al., 2000) or with multiplication (Gruber et al., 2001). It seems that no study has investigated the brain activations for division tasks alone. Division tasks in general are more complex than addition, subtraction or multiplication, because they are less routinised and can probably be solved by using a variety of strategies (Cohen & Dehaene, 2000). Future neuroimaging studies of division might help to elucidate the relation of division to the other three operations.

*7.2.1.3 Exact versus approximate calculation*

Differences in brain activations between exact calculation and approximate calculation have been reported by Dehaene's group (Dehaene et al., 1999; Stanescu-Cosson et al., 2000). Bilateral IPS, precentral, dorsolateral and superior prefrontal areas were more active during approximate addition than during exact addition, while a left inferior prefrontal region and left and right angular gyri showed more activation during exact addition thus suggesting a role of the right hemisphere in approximation. This finding is certainly interesting and concurs with some patient studies (e.g. Dehaene & Cohen, 1991). It nevertheless should be further investigated by other groups with slightly different tasks, because it can be debated whether the approximate addition task used in this fMRI study encourages approximation or other problem solving strategies (such as exact addition plus comparison).

*7.2.1.4 Open questions in imaging calculation*

In general, although these imaging studies provide clear evidence for the important role of both inferior parietal and intraparietal regions in calculation, so far two main questions about calculation remain unsolved. Imaging studies of calculation have not clearly identified the specific contribution of various subareas in the IPL in calculation nor have they succeeded in distinguishing between separate neuronal patchworks for the four operations as indicated by the patient data. In most imaging studies, results are often confounded by task variations, control material and the absence of adequate baseline conditions (Binder et al., 1997; Cipolotti & van Harskamp, 2001). For example, letter naming or matching is often used as a control task (e.g. Chochon et al., 1999; Dehaene et al., 1999). This may potentially remove number-related activations in the SMG, because the SMG might be involved in auditory verbal short term memory (Paulesu, Frith, & Frackowiak, 1993; Shallice & Vallar, 1990; Smith, Jonides, Marshuetz, & Koeppe, 1998; Vallar & Papagno, 1995). Furthermore, because of varying control tasks (such as fixation on screen, letter naming, letter matching, presentation of zeros, detection of zeros/ones, counting, number ranking and letter pseudo-calculation) it is often difficult to compare results across imaging studies.

*7.2.1.5 Individual differences in activation patterns during calculation*

Although neuroimaging studies of calculation are still in their infancy (Cipolotti & van Harskamp, 2001), there have been interesting attempts to look at individual differences in the areas activated during calculation. The first report of individual differences was made by Sakurai et al. (1996). One subject in their PET study was an expert on using a mental Abacus/Soroban [for research on Soroban and mental calculation see Hatta et al. (1989) or Stigler (1984)]. For this subject they found an

increase in cerebral blood flow during calculation in the left temporo-parietal area including the lower part of SMG. This increase was not detected in any other subject in that study. Burbaud et al. (2000) analysed their imaging data according to whether subjects used a verbal strategy (15 subjects) or a visual strategy (14 subjects) for subtraction. They found clear differences in the pattern of activation between these two groups. In subjects using a verbal strategy they report a strong activation of the left dorsolateral frontal cortex and relatively small activations in the IPL. For subjects with visual strategies however they found a strong activation of the left IPL and activation of both prefrontal cortices.

Menon et al. (2000b) contrasted brain activation in perfect performers (100%) and imperfect performers (mean accuracy of 92%) of single-digit calculation. Interestingly, they found less activation and variability in the left ANG for perfect performers. In a PET study Pesenti, et al. (2001) compared activation patterns of 6 normal subjects during calculation with that of a well-known calculation prodigy during mental arithmetic. This prodigy, Rüdiger Gamm, is an interesting case, because he was no child prodigy. Rather, when he was 20, he became interested in calendar calculations and calculating squares and cubes of two-digit numbers. He started to train himself for several hours on these tasks every day in order to prepare for a German television show ("Wetten dass"). Subsequently he became attracted by arithmetical and mathematical problems and he can clearly be described as an expert calculator (Pesenti, Seron, Samson, & Duroux, 1999). In the PET study of mental calculation both prodigy and normal subjects showed activations in the left SMG, IPS, left inferior-occipital and middle occipital gyrus and left occipito-temporal junction during calculation. But on top of these regions Rüdiger showed activations in additional regions during calculation (medial frontal

regions, parahippocampal gyri, upper part of the anterior cingulate, right occipito-temporal junction and left precentral lobule). This finding suggests that calculation expertise was not due to increased activity in brain regions that were also used by non-experts; rather, that expertise in this case involved new processes recruiting additional brain areas. These imaging studies certainly show that already the neural patchwork used for simple calculation tasks can be influenced by strategy use and number expertise.

### *7.2.2 Imaging studies on number comparison*

There are fewer imaging studies on number comparison than on calculation. Table 7-2 gives an overview of published studies of number comparison. Most of them report parietal activation during number comparison. In contrast to activations reported during calculation, left inferior parietal activation is not more likely than right inferior parietal activation, with bilateral activation of these structures being the most common activation pattern (e.g. Chochon et al., 1999; Rickard et al., 2000).

Several studies found increased activity during number comparison in the intraparietal sulcus (Chochon et al, 1999; Pinel et al, 1999; Le Clec'H et al, 2000; Pesenti et al, 2000; Fias et al., in press), in the angular gyri (Pesenti et al, 2000; Rickard et al, 2000) or supramarginal gyri (Le Clec'H et al., 2000) (see figure 7-1, table 7-2).

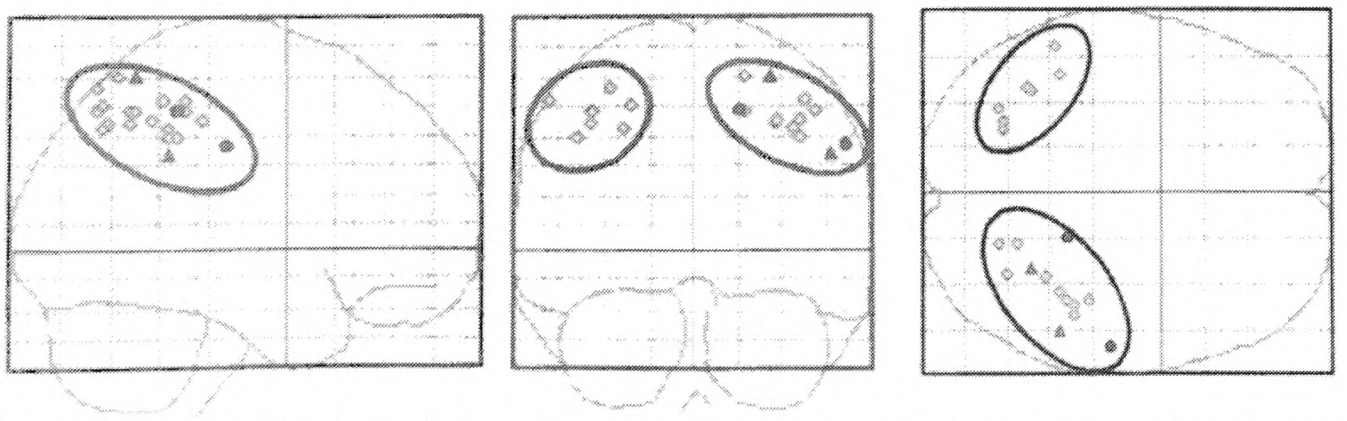


**Figure 7-1:** Glass-brain views of peak activation sites observed during number processing, compared to those observed in the parietal lobe during calculation versus letter processing (Chochon *et al.*, 1999; Dehaene *et al.*, 1999), approximate calculation relative to exact calculation (Dehaene *et al.*, 1999) and number comparison relative to the processing of meaningless symbols (Pesenti *et al.*, 2000), taken from Le Clec'H et al. (2000)

**Table 7-2:** Summary of activations in imaging studies investigating number comparison

| Authors | N | Tasks | Activations |
|---|---|---|---|
| **Dehaene, Tzourio, Frak, Raynaud, & et al. (1996)**<br><br>PET | 8 | 1: rest with eyes closed<br>2: mental multiplication of Arabic digits (1-9)<br>3: number comparison (1-9) | Versus rest:<br>3: B occipital regions, B precentral gyri and supplementary motor area, (L inferior parietal lobe close to significance)<br>3>2: R superior temporal gyrus, B middle temporal gyri, R superior frontal gyrus, R inferior frontal gyrus |
| **Chochon, Cohen, van de Moortele, & Dehaene (1999)**<br><br>fMRI (3 T) | 8 | 1: letter naming (A to I, without E)<br>2: digit naming (1 – 9, without 5)<br>3: number comparison (reference 5)<br>4: multiplication (x × 3)<br>5: subtraction (11 - x) | 3>1: R parietal lobe, R postcentral gyrus and/or sulcus, B IPS, L superior part of inferior parietal lobe, B inferior frontal gyrus, L mesial frontal gyrus, B precentral gyrus, anterior cingulate gyrus and R putamen<br>3>2: R postcentral sulcus |
| **Pinel, et al. (1999)**<br><br>fMRI (3T) | 11 | Event –related:<br>Single digit number (1, 4, 6, 9)<br>Reference number 5<br>*factors:*<br>number notation (word or Arabic)<br>distance from 5 (close/far) | Anterior cingulate, B sensorimotor areas, occipital pole, posterior parietal cortex/precuneus, inferior and dorsolateral prefrontal cortex, B thalami, B temporo-occipital junctions, B IPS, R fusiform gyrus<br>Digits> number words: R fusiform gyrus<br>Close>far: L inferior parietal area close to the parieto-occipito-temporal boundary<br>Far> close: R IPS |
| **LeClec'H, et al. (2000)**<br><br>fMRI (3T)<br>ISI: 2.5 s<br>ISI: 12 s | <br><br><br>5<br>6 | 1: number comparison (1-60), reference number 12<br>2: body part higher or lower than shoulder? (hand, head, ankle..)<br>*2 modalities: spoken or written*<br>*2 languages: English/French* | 1>2: R IPS, R inferior parietal lobule, R SMG (close to the postcentral sulcus), R precuneus, L SMG, L insula<br>2>1: L IPS, L precentral sulcus, L mesial frontal gyrus, L dorsolateral prefrontal cortex |
| **Pesenti, Thioux, Seron, & De-Volder (2000)**<br><br>PET | | 1: rest (eyes closed)<br>2: judgement on non-numerical characters<br>3: Arabic numeral processing<br>4: number comparison<br>5: simple addition | 4>2: L IPS, L superior parietal, L precentral sulcus, L inferior parietal lobule (BA 40), R superior parietal lobule<br>4>3: L IPS extending into superior parietal lobule, L inferior frontal sulcus extending into L middle frontal gyrus, L precentral sulcus and gyrus and L lingual gyrus |
| **Rickard, et al. (2000)**<br><br>FMRI (1.5T) | 8 | 1: detect ones (4 2 1 7)<br>2: single digit multiplication verification<br>3: magnitude judgement (14-81) | 3: R cuneus, B medial frontal gyrus, posterior cingulate, B ANG |
| **Pinel, Dehaene, Riviere, & LeBihan (2001)**<br><br>FMRI (3 T)<br>ISI = 2.4 s<br>ISI = 14 s | <br><br>4<br>9 | 1: number words<br>2: Arabic digits<br>reference number 65; distance:<br>close (60-64; 66-69)<br>medium (50-59; 70-79)<br>far (30-49; 80-99) | Effect of numerical distance on:<br>(smaller distance = more activation in:)<br>R IPS, B posterior imtraparietal focus, B precuneus, L middle temporal gyrus and L posterior cingulate cortex<br>Distance effect 1>2: superior parietal lobe<br>Distance effect 2>1: L PPC, B superior frontal gyri, L precentral gyrus, L cingulate, L basal ganglia, R medial frontal gyrus |
| **Nose, Itsukushima, & Masato (2002)**<br><br>FMRI | 5 | 1: perceptual comparison (8 squares)<br>2: numerical comparison (8 pairs of figures with 3-14 circles, small distance 1, large 7 or 8)<br>3: semantic comparison (8 words, varying in image size: min: strawberry – max: car) | 2>1,3:<br>R parieto-occipital junction, L middle occipital gyrus, B cuneus<br>Small distance>large distance (1,2,3):<br>L inferior frontal gyrus, L anterior insula, R lingual gyrus<br>Large distance > small distance (1,2,3):<br>L postcentral gyrus |
| **Fias, Lammertyn, Reynvoet, Dupont, & Orban (in press)**<br><br>PET | 18 | 1: compare angles<br>2: compare lines<br>3: double-digit number comparison (30-70) | Conjunction analysis (1,2,3):<br>L IPS<br>3>1,2: L more anterior IPS |

ISI= interstimulusinterval, min = minimum , max = maximum, B = bilateral, L = left, R= right, LH = left handed, IPS = intraparietal sulcus, PPC = posterior parietal cortex

Other areas which were sometimes activated during number comparison include precentral gyri (Dehaene et al., 1996; Chochon et al., 1999; Pesenti et al., 2000), postcentral gyrus/sulcus (Chochon et al., 1999; Nose et al., 2002), inferior frontal gyrus (Dehaene et al., 1996; Chochon et al, 1999; Pinel et al., 1999; Nose et al., 2002), anterior cingulate gyrus (Chochon et al., 1999; Pinel et al., 1999; Pinel et al., 2001) and occasionally the superior parietal lobule (Pesenti et al., 2000).

When number comparison is contrasted with letter naming, a right parietal patchwork seems to be more active during number comparison than letter naming (Chochon et al., 1999). This right lateralisation could be due to the subtraction of a mainly left-lateralised patchwork for letter naming. Le Clec'H et al. (2000), however, compared number comparison and a task in which subjects had to judge whether body parts (such as 'hand' or 'ankle') where higher or lower in space than their shoulder. They again described a mainly right-lateralised patchwork for number comparison. In their study the right intraparietal sulcus and the right inferior parietal lobule were more active during number comparison than during body part comparison. In general, this suggests that bilateral parietal areas underly number comparison, but typically with a stronger activation in the right hemisphere.

While most studies seem to suggest a role for intraparietal areas in number comparison, the contribution of areas in the inferior parietal lobule to number comparison varies between studies. Le Clec'H et al. (2000), for example, report higher activation of both supramarginal gyri during number comparison than during body part comparison. This is in contrast to Dehaene et al.'s (1996) results. They found a deactivation in the left supramarginal gyrus during number comparison when compared to rest with eyes closed.

*7.2.2.1 Numerical distance*

In recent studies on number comparison, numerical distance to the reference number has been investigated as a variable of interest. Pinel et al. (1999) found a left inferior parietal area close to the parieto-occipito-temporal boundary to be more active during trials in which the presented numbers were close (4,6) to the reference number (5) than during those numbers which were further away (1,9). For numbers with larger distance from the reference number the right intraparietal sulcus was more active than for numbers that were close to the reference number. In a subsequent study Pinel et al. (2001) investigated the effect of numerical distance with double-digit numbers (reference number 65). This time the smaller the distance to the reference number, the more activation they found in the right intraparietal sulcus (with an anterior focus), in left and right precuneus, in the left middle temporal gyrus and the left posterior cingulate cortex. They also found an interaction of the distance effect with presentation type (number words or Arabic digits). The effect of the distance effect was stronger for number words than Arabic digits in the superior parietal lobule. The left posterior parietal lobule, both superior frontal gyri, the left precentral gyrus, the left cingulate, left basal ganglia and the right medial frontal gyrus, however, showed a stronger effect of numerical distance when the numbers were displayed in Arabic digits than when they were shown as number words.

Pinel et al. (2001) explicitly pointed out that intraparietal activation decreased quasi-monotonically as the numerical distance increased, in parallel with the subject's response time curve. In the discussion, however, they remarked that a general concept of task difficulty did not suffice to explain their results. Their main argument is that parietal activity in their study was not modulated by notation

effects, although it took subjects on average 169 ms longer to compare verbal than Arabic numerals. It is however debatable whether differences in difficulties between tasks should be expected to yield similar brain activations as differences in difficulty within one task.

Although Pinel et al. (2001) state that activation changes in the intraparietal areas they found to be correlated with distance in their study cannot simply be explained by reaction time differences, they agree that their study does not prove that the distance effect is specific to numerical comparison. Numerical distance has clearly been shown to have an effect on which brain areas are active. Whether the brain regions underlying this distance effect are specific to number comparison, however, is still open to debate. Distance effects are not only found in number comparison, but in various tasks that require mental manipulation of visuospatial information (e.g. mental rotation; Shepard & Metzler, 1971). There is evidence that parietal neuronal activity is modulated during selection between spatially defined responses to graded visual information (Gold & Shadlen, 2001) and IPS activation has been found during various non-numerical visuospatial tasks (Carpenter et al., 1999; Richter, et al., 2000). Therefore, the intraparietal activation found during number comparison tasks could be due to a common mechanism for quantitative processing of numerical and non-numerical visuospatial stimuli.

A preliminary report by Nose et al. (2002) provides some evidence that activation found in intraparietal areas might be specific to a numerical distance effect. They found several brain areas that are more active for smaller distances than larger (and vice versa) in all their comparison tasks (perceptual, numerical and semantic), but these brain areas did not include the parietal lobes. However, a further

analysis of their neuroimaging data as to whether there are activation changes specifically related to numerical distance, has to be awaited, to judge that finding.

In contrast, Fias et al. (in press) found common parietal activation for three comparison tasks. They found an area in the left intraparietal sulcus activated during angle, line and number comparison thus showing that comparison in general rather than number comparison activates this intraparietal area. However, in the same study they reported an area in the left intraparietal sulcus which was more active during number comparison than during comparison of angles or lines. The area specifically activated by a numerical comparison task was more anterior in the IPS than the area activated by all three comparison tasks.

### *7.2.3 Outstanding questions about the neural patchwork of number comparison*

Several questions concerning the neural patchwork of number comparison remain unresolved. Firstly, often it is unclear, whether the brain regions that are activated by number comparison would also be activated by number recognition only. Chochon et al. (1999) already investigated this question. In their study only one brain region, the right postcentral sulcus, was more active during number comparison than during digit naming. Therefore, it should be properly cross-examined whether presentation of numerical stimuli in Arabic format automatically leads to activation of brain areas indicated for numerical comparison even when subjects are only asked to perform a non-numerical task on the Arabic digits.

Secondly, most studies investigating the effect of numerical distance on brain activations so far (with the exception of Pinel et al., 2001) have neglected the fact that reaction times are highly negatively correlated with numerical distance. Activations found in IPS and the inferior parietal lobe in both neurophysiology and neuroimaging have been related to the selection of motor responses, sometimes in

ways that are related to reaction time (Caminiti, et al., 1999; Deiber, Ibanez, Sadato, & Hallett, 1996; Winstein, Grafton, & Pohl, 1997). Therefore, one has to be aware of the possibility that activations, especially in parietal brain regions, described as varying with numerical distance could also just vary systematically with reaction times or task difficulty.

Thirdly, it has to be investigated further whether the effect of distance on certain brain regions as described above is specific to numerical distance or whether it is caused by a general comparison process. Nose et al. (2002) in their preliminary report identified several brain regions that vary with perceptual, semantic and numerical distance, thus suggesting an underlying general comparison process. Fias et al. (in press) as well as Pesenti et al. (2000), however, provide evidence for activations that are specific to numerical distance.

An additional question is, are there differences between comparing smaller and larger numbers as the TMS experiments discussed in previous chapters suggest? Although studies on number comparison have used several reference numbers (5, 12, 65) and various number intervals, it is impossible to attribute differences in results between these studies to changes in the size of numbers only, because control tasks and analysis methods vary greatly between studies. In a recent study Naccache & Dehaene (2001) demonstrated that different populations of intraparietal neurons encode different numbers. They found, for example, a left parietal region that showed greater activation for number 9 than number 4 (Naccache & Dehaene, 2001). They argued that this may correspond to the number size effect reported by Stanescu-Cosson et al. (2000) on exact calculation which revealed greater BOLD activations in the left IPS for numerical problems involving large numbers (from 5-9) than for those using small numbers (1-5). It has to be remarked, though, that

larger problems are commonly also associated with longer response time. Nevertheless, these studies point towards the possibility that different neuronal populations may encode different number sizes which is in line with the result from TMS experiments discussed in chapter 4 and 5. Despite these reports no fMRI or PET study of number comparison so far has manipulated the size of numbers and the distance to the reference number within the same study.

The fMRI study on number comparison that will be described in this chapter was carried out to investigate both the effect of numerical distance as well as the effect of reaction times on brain activations. Further, it was designed to detect whether there are differences in brain activation during number comparison of small versus larger numbers as predicted by TMS experiments discussed in chapters 4 and 5. Various control tasks were used to disentangle visuospatial stimuli from numerical stimuli and numerical stimulus presentation from number comparison.

## *7.3 Methods*

### *7.3.1 Subjects*

Twelve right-handed subjects (6 female, 6 male, aged 20-34, mean age 26.7) participated. Subjects gave informed consent in accordance with ethical approval from the Central Oxford Regional Ethics Committee (OxREC C02.092). After the experiment all subjects filled out a short questionnaire concerning their number representations [an English translation of Seron & Pesenti's short questionnaire of number representation (Seron et al., 1992); see appendix D]. In this questionnaire they were asked how they represent numbers when they encounter them. The choices were:

1. nothing;
2. a visual representation of numbers written in digits (8, 17);

3. a visual representation of numbers written in number words (eight, seventeen);
4. an auditory representation of numbers as they are repeated mentally;
5. other;
6. I don't know.

Subjects could choose several answers. 3 subjects chose 'nothing' as their only answer, 4 subjects reported using (2) and (4), one subject reported (1) and (4). Two subjects used only a visual representation of numbers as they are written in digits and two subjects reported using a visual representation of numbers as they are written in digits and (5) 'other'. One of these subjects uses visualising number blocks for certain tasks, the other subject wrote she used a mental number line. Both subjects were asked to fill out the extensive number representation questionnaire [an English translation of Seron et al.'s (1992) extensive questionnaire of number representation, see appendix E]. Neither of them belong to that group of subjects who have an automatic visuospatial number line representation when confronted with numbers.

### *7.3.2 Image acquisition*

A 3T Varian INOVA MRI system with a multi-slice gradient echo EPI sequence (TR = 3000 ms, TE = 30 ms, flip angle = 90°, FOV = 256 × 256, matrix = $64^2$, 24 5 mm axial slices) was used. For each subject a high-resolution T1-weighted anatomical scan was acquired.

### *7.3.3 Paradigm design*

Subjects were given full verbal and written instructions on the task before entering the scanner. Once the instructions were understood, subjects were given a practice run of all block types. The paradigm consisted of alternating 30 second blocks of 2

different tasks and rest. Both tasks required the subject to press one of two buttons with their right or left index finger as quickly and accurately as possible. Within each block, except during rest periods, yellow stimuli were presented centrally for 500 ms on a black background using the font Arial (type size = 96 points). When viewed from the distance of 3 m, single-digit stimuli subtended 1.2° of visual angle and double-digit stimuli subtended 1.9° of visual angle. The inter-stimulus interval was varied randomly between 1.4 and 1.6 seconds (mean 1.5 seconds) to minimise anticipatory responses. At the beginning of each block a visual instruction cue in red was on the screen for 3 seconds. The instruction cue was either 'rest', 'reference number: 5', 'reference number: 65' or 'vertical line ?'. Except during rest periods, each stimulus display contained a small symbolic repetition of the instruction cue (either 5 for 'reference number 5', 65 for 'reference number 65', or | for 'vertical line ?' in white font, Arial, font size = 24 point) directly above the stimulus (see figure 7-2, figure 7-4). In blocks with the instruction 'rest' a white cross appeared in the screen centre and subjects were asked to fixate that cross for the duration of the block.

When the instruction was 'reference number: 5', subjects saw single digits (1, 2, 3, 4, 6, 7, 8, 9) on the screen and had to judge whether the number on the screen was larger or smaller than the reference number 5 by pressing the left button with their left index finger for smaller and their right button with their right index finger for larger (see figure 7-2a). In blocks with instruction cue 'reference number: 65', subjects saw double-digit numbers ranging from 31 to 99 on the screen. Again they had to judge whether the number on the screen is larger or smaller than the reference number (in this case 65) by pressing the left button with their left index

finger for smaller and their right button with their right index finger for larger (see figure 7-2b).

Numbers within each of these number comparison blocks were chosen with respect to their distance from the reference number, thus generating two subtypes of blocks (distance close and distance far). For double-digit blocks the mean distance to 65 in blocks with distance-close was 7.6, while the mean distance from the reference number in blocks with distance-far was 26.5. In single-digit blocks the mean distance to reference number 5 was either 2.0 (distance-close) or 3.1 (distance-far). Subjects were not informed of these two block subtypes.

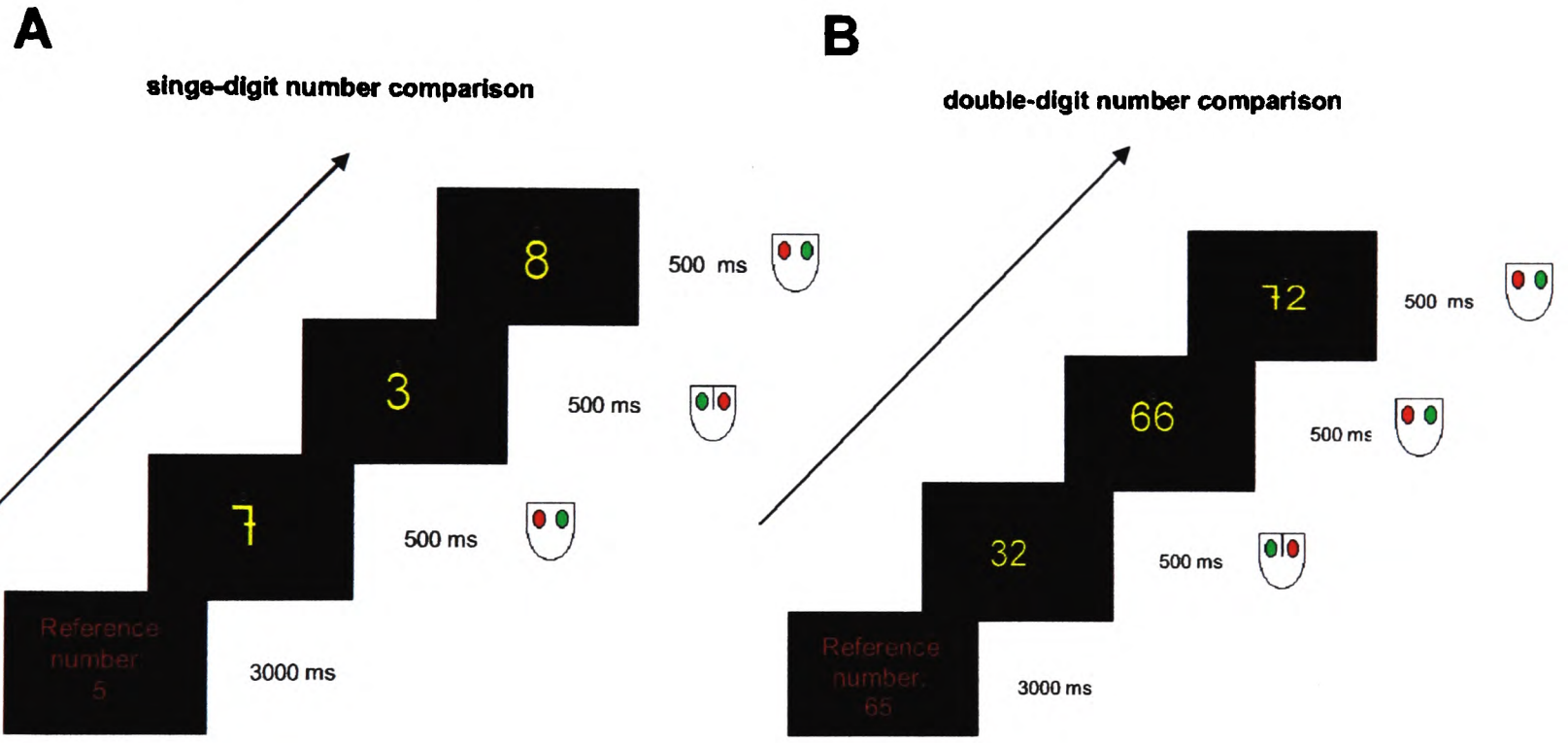



**Figure 7-2:** Number comparison blocks with (a) single-digit stimuli and (b) double-digit stimuli. Subjects had to indicated with one of two possible key presses whether the displayed number was larger or smaller than a reference number (reference number for a: 5, b: 65). The intertrial interval varied between 1.4 and 1.6 s.

When the visual instruction cue was 'vertical line ?', subjects were asked to press the right button with their right index finger, if the stimulus on the screen contains a vertical line (numbers 1, 4, 7 and 9; number 7 and 9 were slightly manipulated to contain a vertical line) and the left button with their left index finger, when the stimulus on the screen does not contain a vertical line (numbers 2, 3 , 5 , 6, 8; see

figure 7-3, figure 7-4). For these blocks, subjects were instructed to completely ignore the fact that the stimuli are numbers and to search through the visual display for a vertical line. For double-digit numbers each stimulus could contain none, one or two vertical lines.

There were two subtypes of blocks with vertical line detection. In vertical-line-control blocks the stimuli were exactly the same as displayed in the number comparison blocks (see figure 7-3a and figure 7-4). In vertical-line-mirror blocks, the same numbers as in the number comparison blocks were used to generate the stimuli. The numbers, however, were rotated, flipped and cut in a way to make them as different from numbers as possible while still keeping the vertical line intact and the height and width of the stimuli constant across conditions (see figure 7-3b and figure 7-4). All block types were balanced for button response side.

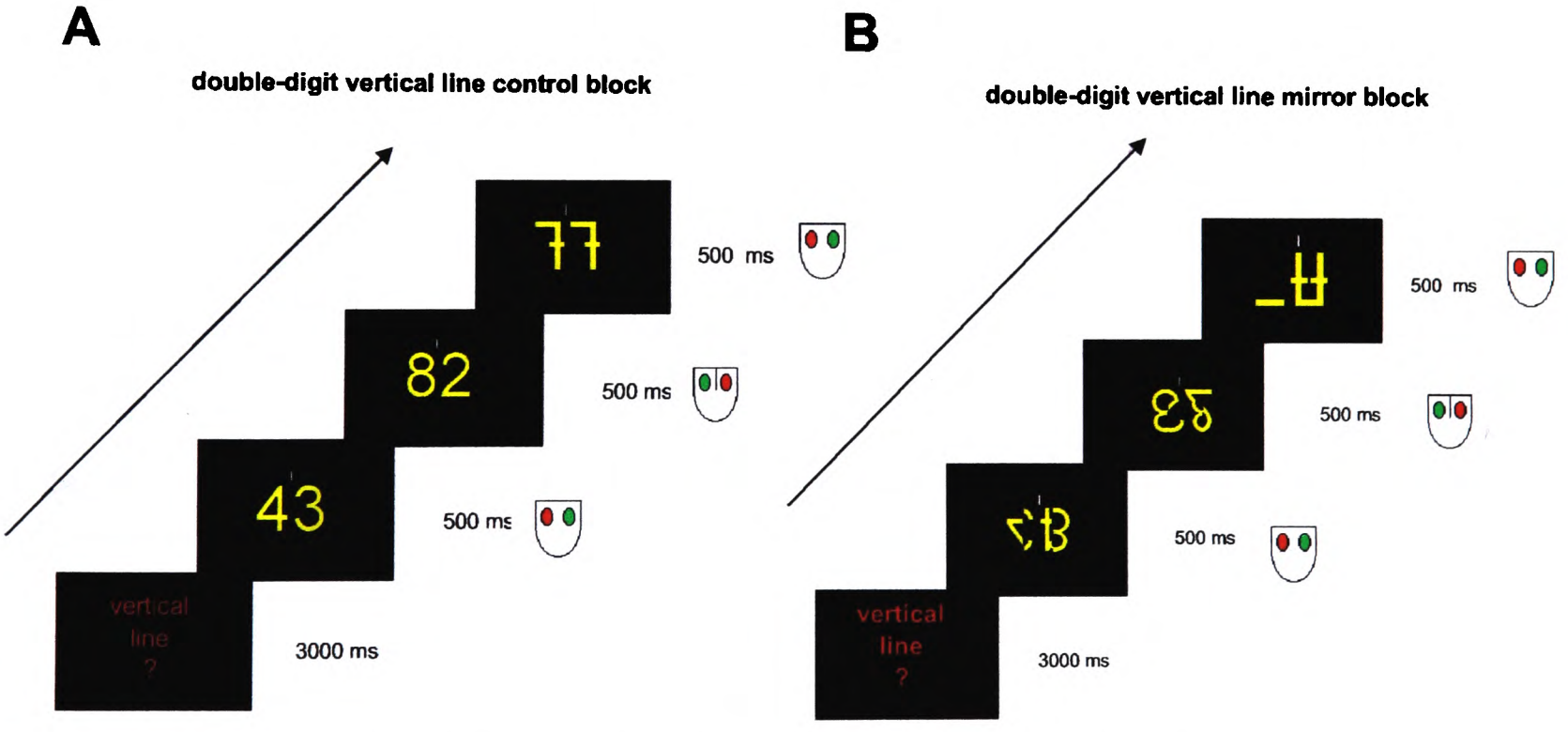



**Figure 7-3:** Control blocks with (a) numerical and (b) mirror stimuli. Subjects had to indicated with one of two possible key presses whether the target (a yellow vertical line) was present or absent. The intertrial interval varied between 1.4 and 1.6 s.

In total there were 16 number comparison blocks (4 double-digit blocks with distance close, 4 double-digit blocks with distance far, 4 single-digit blocks with

distance close and 4 single-digit blocks with distance far), 32 vertical line judgement blocks (16 vertical-line control blocks and 16 vertical-line-mirror blocks) and eight rest periods. The order of these blocks was generated pseudo-randomly once and then hold constant for each subject. The paradigm took roughly 30 minutes.

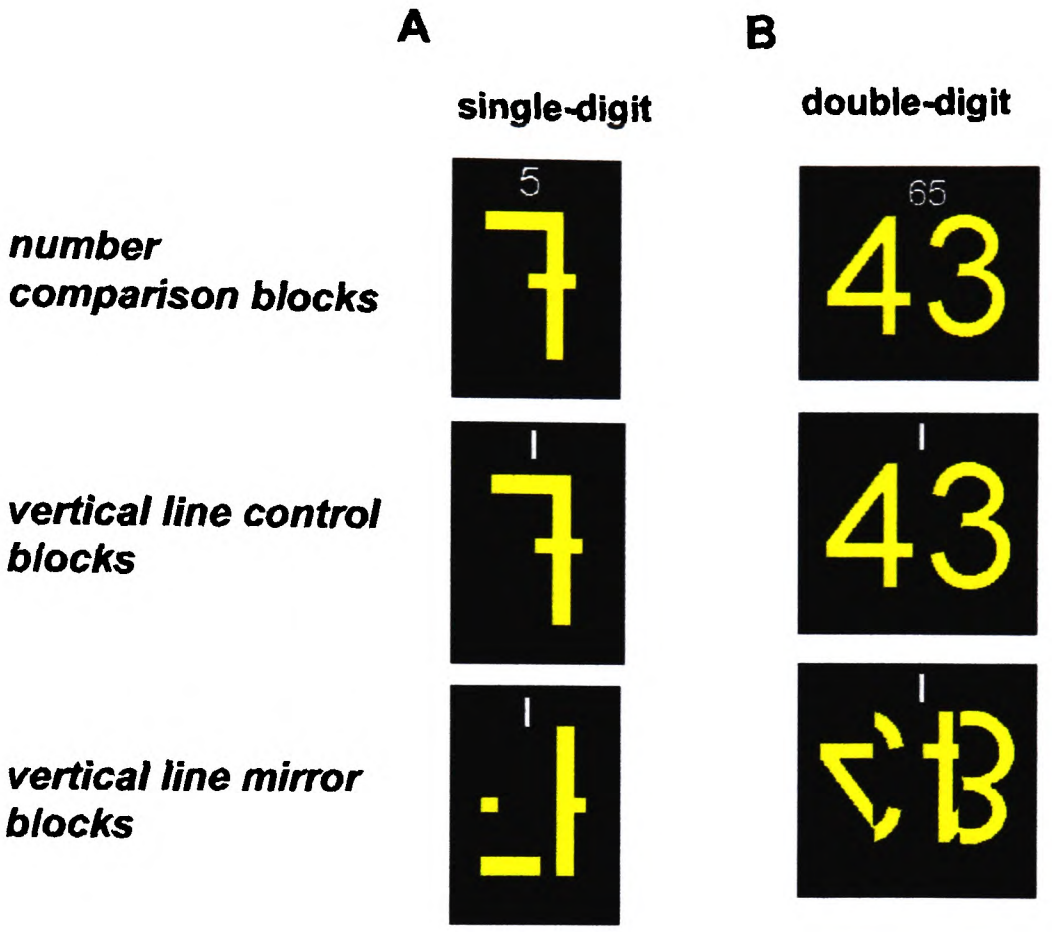



**Figure 7-4:** Overview of stimuli used. There were three judgement types (number comparison, vertical line control, vertical line mirror) and two stimulus types (single-digit and double-digit)

Exact timing of stimulus presentation and button responses were measured with Spike 2, version 4.00 (Cambridge Electronic Design).

### *7.3.4 Behavioural data analysis*

Reaction times from erroneous responses (3.7% of all responses) were not included in the behavioural analysis. A repeated-measures three-way ANOVA on median reaction times with judgement type (number comparison, vertical line judgement, mirror stimuli), stimulus type (single-digit stimulus, double-digit-stimulus) and distance to reference number (close, far) was carried out. In some cases ANOVA

results were followed up with paired samples t-tests. Only significant two-tailed results of these t-tests will be reported.

### *7.3.5 Image analysis*

Image analysis was performed using tools from the FMRIB Software Library, FSL 1.4 (FMRIB, Oxford, UK, www.fmrib.ox.ac.uk/fsl). First, a slice dropout detection procedure was carried out. In three subjects slice dropouts were detected and corrected. The following pre-statistic processing was applied: motion correction using MCFLIRT (Jenkinson & Smith, 2001), spatial smoothing using a Gaussian kernel of full width half maximum 5 mm; mean-based intensity normalisation of all volumes by the same factor; non-linear high pass filtering (Gaussian-weighted least squares straight line fitting with sigma = 700 s). For each subject then, statistical analysis was carried out within FEAT 4.10, the FMRI Expert Analysis Tool (FMRIB, Oxford, UK) using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001).

Fourteen explanatory variables were entered in to the general linear model: (1) number comparison judgement with reference number 5 distance close; (2) number comparison judgement with reference number 5 distance far; (3) number comparison judgement with reference number 65 distance close; (4) number comparison judgement with reference number 65 distance far; (5) vertical line judgement with stimuli from reference number 5 distance close; (6) vertical line judgement with stimuli from reference number 5 distance far; (7) vertical line judgement with stimuli from reference number 65 distance close; (8) vertical line judgement with stimuli from reference number 65 distance far; (9) vertical line judgement with mirror stimuli produced from reference number 5 distance close; (10) vertical line judgement with mirror stimuli produced from reference number 5

distance far; (11) vertical line judgement with mirror stimuli produced from reference number 65 distance close; (12) vertical line judgement with mirror stimuli produced from reference number 65 distance far; (13) visual instruction cues, (14) reaction times. Except EV14 all EVs were binary. For EV14, median reaction times for each paradigm block were computed and normalised for each subject, so that the maximum reaction time was 1. The normalised reaction times were then entered into the design matrix and orthogonalised with respect to EVs 1 to 12. Figure 7-5 shows a typical design matrix for one subject.

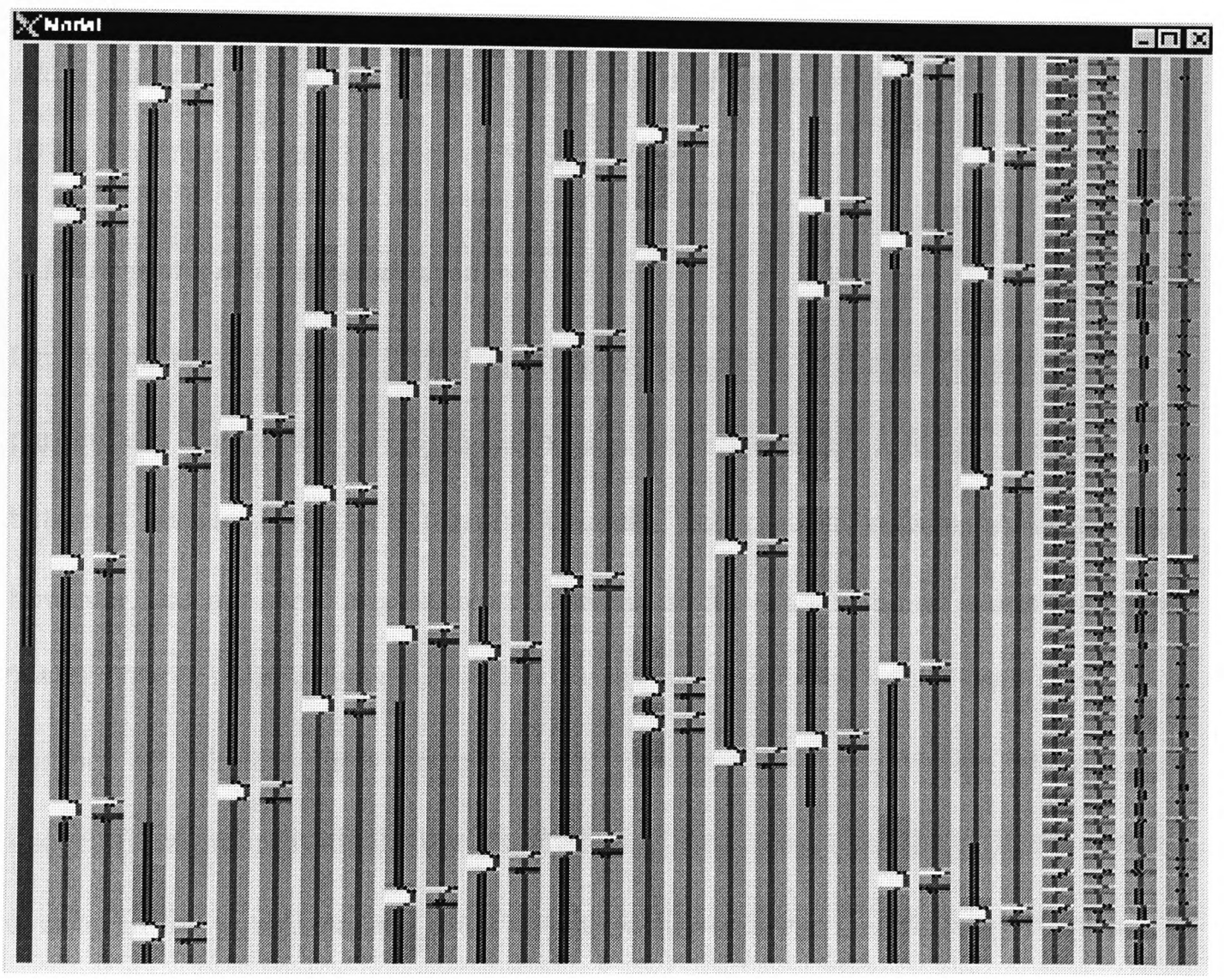


**Figure 7-5:** Example of a subject's design matrix in FEAT 4.10

Z values were calculated for contrasts of experimental conditions versus rest and between experimental conditions. The Z (Gaussianised T/F) statistic images for the individual subjects were thresholded using clusters determined by $Z > 1.8$ and a

cluster significance threshold of P = 0.05 (Forman, et al., 1995; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992).

Registration of EPI images to high-resolution images and into standard space (Talairach & Tournoux, 1988) was carried out using FLIRT (FMRIBs Linear Image Registration Tool; Jenkinson & Smith, 2001).

### *7.3.6 Group analysis*

Group analysis was carried out using a random effects analysis. Cluster detection was applied to the group Z (Gaussianised T) statistic images determined by Z > 2.7 and a cluster significance threshold of P = 0.01 (Forman et al., 1995; Friston, et al., 1994; Worsley, Evans, Marrett, & Neelin, 1992).

### *7.3.7 Regions of interest analysis*

On the basis of previous TMS experiments described in chapter 4 and 5 we were particularly interested in brain activation differences in inferior parietal areas between certain types of numerical stimuli. The random effects group analysis, however, did not yield any of these differences (for random effect group results see 7.4.2). The random effects analysis is a strict test as it requires not only that a large number of subjects show an effect, but also that after registration of activation images from the individual subjects, the loci of that effect from the different subjects overlap in the same standard brain space (Johansen-Berg, Christensen, Woolrich, & Matthews, 2000). To allow for individual variation in the location and magnitude of response in inferior parietal and intraparietal areas, we performed an additional analysis based on signal change in regions of interest. To define the regions of interest we used the random effect brain activations found for the contrast number

comparison judgement versus rest. Only those activations were used which were in and/or around the lateral or medial bank of the IPS.

These activations were further divided into anterior and posterior activations. Anatomically, the IPL is divided into SMG and ANG by the sulcus intermedius primus of Jensen, a descending ramus of the IPS (Duvernoy, Bourgouin, Cabanis, & Cattin, 1999). Therefore, I first identified Jensen's sulcus on sagittal sections of subjects' high-resolution T1 weighted anatomical scans in standard space. In each subject and for each hemisphere separately, I then measured the minimum and maximum y co-ordinates of this sulcus. The mean y co-ordinate of all subjects (left hemisphere: y = - 48, right hemisphere: y = - 45) was subsequently used to split the parietal activation mask into two masks, an anterior inferior parietal mask and a posterior inferior parietal mask. Thus, four ROIs were defined: left aIPS, left pIPS, right aIPS and right pIPS.

These ROIs were then applied to each subject's signal change images comparing activation conditions to rest. A five-way ANOVA on mean percentage signal changes with hemisphere (left, right), site (aIPS, pIPS), judgement type (number comparison, vertical line judgement, mirror stimuli), stimulus type (single-digit stimuli, double-digit stimuli) and distance (distance close, distance far) was carried out. This was followed up by a more detailed analysis of differences in mean percentage signal change separately for each ROI. I carried out four independent three-way ANOVAs with judgement type (number comparison, vertical line judgement, mirror stimuli), stimulus type (single-digit stimulus, double-digit-stimulus) and distance to reference number (close, far). In some cases ANOVA results were followed up with two-tailed paired samples t-tests.

## 7.4 Results

### *7.4.1 Behavioural results*

Subjects missed on average 0.4% of all trials.

*7.4.1.1 Task specific results*

Median reaction times varied between 471 and 756 ms for number comparison blocks with a mean of 586 ms, 460 and 750 ms with a mean of 592 ms for mirror control blocks and between 465 and 704 ms with a mean of 597 ms for vertical line judgement blocks (see figure 7-6). There was no significant difference in reaction times between these three block types ($F(2,22) = 1.347$, $p = 0.27$).

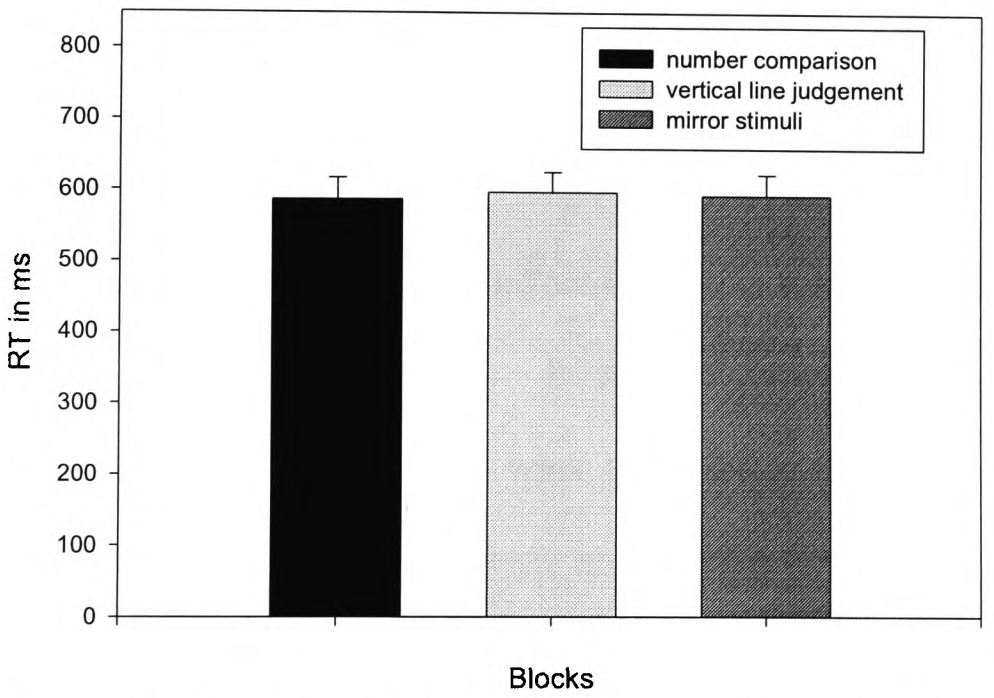



**Figure 7-6:** Reaction times in ms for number comparison blocks, vertical line judgement blocks and blocks with mirror stimuli

*7.4.1.2 Single-digit blocks versus double-digit blocks*

There was a main effect of stimulus type on reaction times ($F(1, 11) = 114.74$, $p < 0.001$). Irrespective of judgement type, on average subjects responded 66 ms faster to single-digit stimuli (mean reaction time = 576 ms) than to double-digit stimuli (mean reaction time = 642 ms) (see figure 7-7). This difference was significant for

all judgement types (number comparison: t = - 8.42, df = 11, p < 0.001; vertical line judgement: t = - 6.19, df = 11, p < 0.001; mirror stimuli : t = - 6.09, df = 11, p < 0.001).

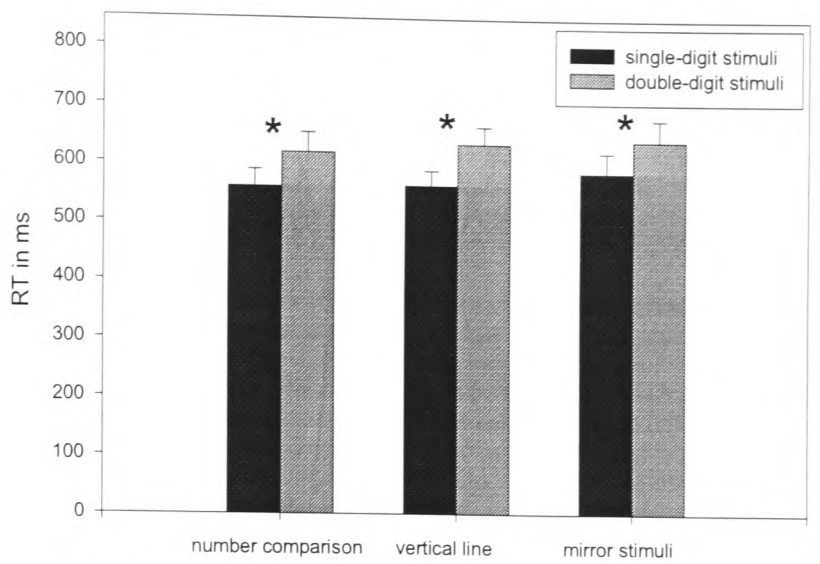



**Figure 7-7:** Reaction times in ms for single- and double-digit stimuli in number comparison blocks, vertical line judgement blocks and blocks with mirror stimuli

*7.4.1.3 Effect of distance*

The effect of distance varied between judgement types (interaction judgement type × distance: F(2,22) = 10.812, p= 0.001). In number judgement blocks subjects responded on average 33 ms more slowly when the distance to the reference number was close than when distance to the reference number was far (t = 3.64, df = 11, p = 0.004). The opposite pattern was observed in vertical line judgement blocks. Here, it took subjects 21 ms longer to respond to stimuli that were far from the reference number than to those that were closer (t = - 2.40, df = 11, p = 0.04; see figure 7-8). Distance showed no effect in blocks with mirror stimuli.

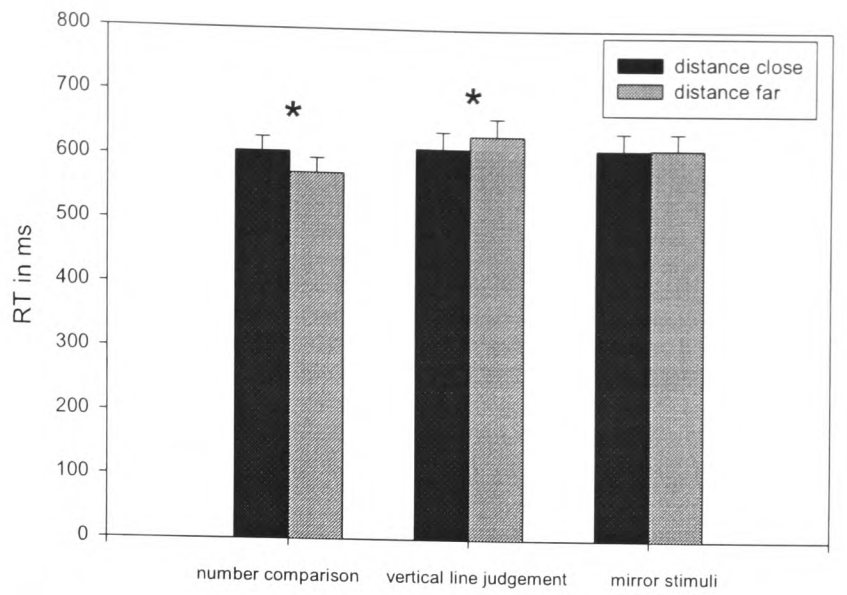



**Figure 7-8:** Reaction times in ms for number comparison blocks, vertical line judgement blocks and blocks with mirror stimuli for stimuli close to reference number in comparison to those far from the reference number

The behavioural distance effect was modified by stimulus type (interaction judgement type × stimulus type × distance: $F(2,22) = 8.245$, $p = 0.002$). In order to follow up this interaction, two ANOVAs on median reaction times were carried out separately for single-digit and double-digit blocks, contrasting judgement type (number comparison, vertical line judgement, mirror stimuli) and distance to reference number (close, far).

For the single-digit blocks, there were no significant main effects (judgement type: $F(2,22) = 0.72$, $p= 0.50$; distance: $F(1,11) = 0.58$, $p = 0.46$) nor was there a significant interaction ($F(2,22) = 1.72$, $p = 0.20$). In number comparison blocks, there was only a difference of 7 ms between responses to single-digit stimuli with close versus far distance to the reference number. For vertical line judgement blocks, it took subjects 10 ms longer to respond to single-digit stimuli further away from the reference number than to those close to the reference. For mirror stimuli, subjects in single-digit blocks were faster to respond to stimuli that were further away (by 15 ms). None of these differences were significant.

In double-digit blocks, there was no general effect of judgement type ($F(2,22) = 2.27$, $p = .15$) or distance ($F(1,11) = 0.08$, $p = .78$). The distance effect, however, was significantly modulated by judgement type ($F(2,22) = 13.78$, $p < .001$). It took subjects in number comparison blocks 59 ms longer to answer to double-digit stimuli that were close to the reference number than to those that were further away ($t = -2.86$, $df = 11$, $p = 0.02$). In vertical line judgement blocks, subjects responded 33 ms more quickly to stimuli that were closer to the reference number ($t = 2.58$, $df = 11$, $p = 0.03$). In blocks with mirror stimuli subjects responded on average 17 ms later to stimuli further away than to those close to the reference number (see figure 7-9). This difference was non-significant.

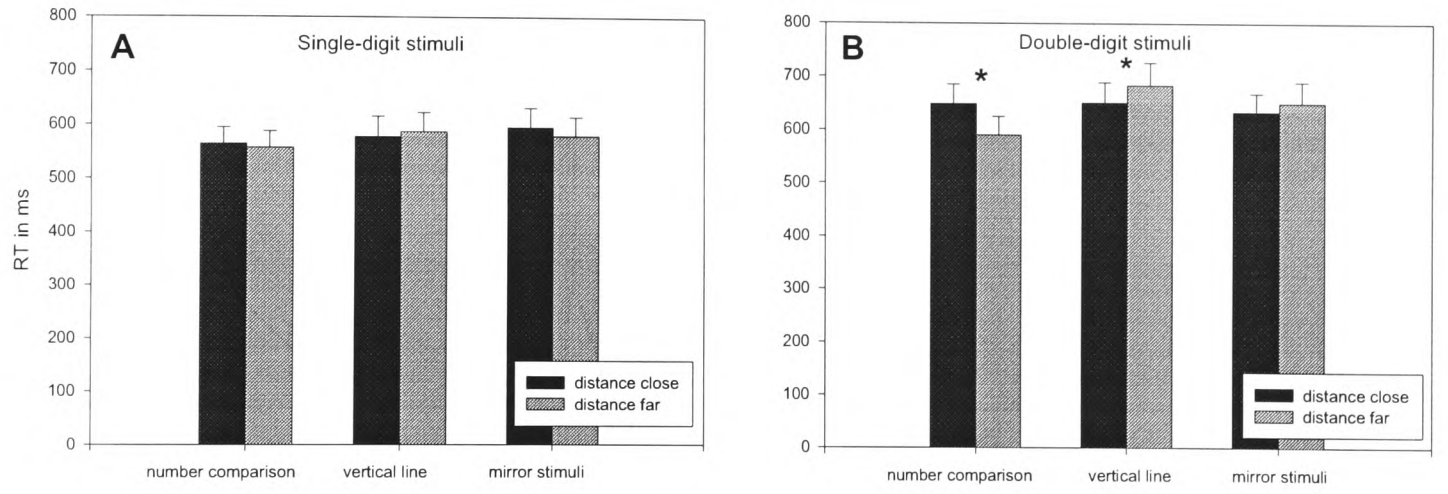



**Figure 7-9:** Reaction times in ms for number comparison blocks, vertical line judgement blocks and blocks with mirror stimuli for stimuli close to reference number in comparison to those far from the reference number for (a) single-digit stimuli and (b) double-digit stimuli

*7.4.1.4 Summary of main behaviour effects*

It took subjects on average the same time to respond to number comparison trials as to vertical line judgement or mirror stimuli trials, thus suggesting that overall the three tasks were of equal difficulty. For each task the reaction times were longer for double-digit stimuli than for single-digit stimuli.

Only for stimuli during number comparison trials were the reactions times longer for stimuli that were closer to the reference number than for those that were

further away. This pattern was specific to the number comparison block and was not observed for vertical line judgement or mirror stimuli blocks. Hence, subjects showed a behavioural distance effect during number comparison inside the scanner. The distance effect, however, was mainly due to differences in reaction time for far and close double-digit stimuli. Although for single-digit stimuli it took subjects longer to respond to stimuli that were close to the reference number than those further away, the difference was smaller and did not reach significance.

### *7.4.2 Whole brain analysis*

#### *7.4.2.1 Task specific results*

When number comparison judgement was compared versus rest there were significant clusters of activation (table 7-3). As can be seen in figure 7-10 a large bilateral parietal patchwork was active during number comparison.

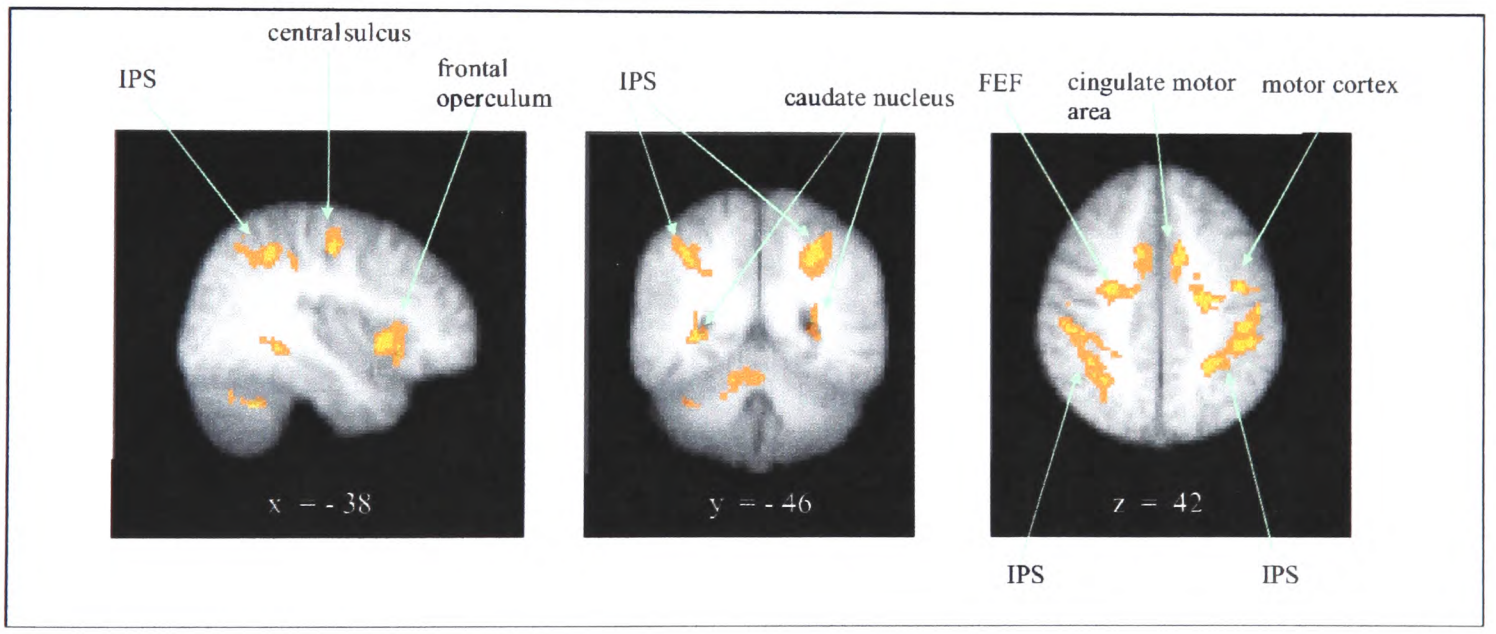



**Figure 7-10:** Brain activations for number comparison versus rest on the mean average structural image of all 12 subjects registered in standard space (sagittal, coronal and axial view from left to right)

This patchwork includes the posterior part of IPS, the medial bank of the IPS extending into the superior parietal lobule and the postcentral sulcus.

**Table 7-3:** Talairach co-ordinates of activation peaks* for number comparison versus rest

| Brain Area | Left hemisphere | | | | Right hemisphere | | | |
|---|---|---|---|---|---|---|---|---|
| | x | y | z | Z | x | y | z | Z |
| *medial bank of IPS/SPL* | -42 | -36 | 44 | 4.03 | 32 | -50 | 36 | 3.94 |
| | -30 | -46 | 48 | 3.91 | 40 | -42 | 46 | 3.65 |
| | -44 | -26 | 42 | 3.75 | | | | |
| *posterior IPS* | | | | | 28 | -54 | 36 | 3.65 |
| | | | | | 34 | -60 | 48 | 3.51 |
| *postcentral sulcus/SPL* | -48 | -20 | 44 | 3.58 | 40 | -30 | 38 | 3.80 |
| *central sulcus/motor cortex* | -42 | -4 | 40 | 4.36 | 46 | -12 | 52 | 3.56 |
| *premotor area* | -46 | -2 | 32 | 4.16 | | | | |
| *supplementary motor area (SMA)* | | | | | 8 | -4 | 58 | 3.89 |
| *PreSMA* | -8 | 4 | 62 | 4.25 | 2 | 2 | 54 | 4.33 |
| *cingulate motor area* | -14 | 12 | 40 | 4.46 | 12 | 16 | 46 | 3.78 |
| | -10 | 8 | 46 | 4.30 | 12 | 14 | 34 | 3.77 |
| *superior precentral sulcus/superior frontal sulcus (probably FEF)* | -26 | -8 | 50 | 4.62 | 28 | -6 | 42 | 4.11 |
| | -24 | -10 | 40 | 4.47 | | | | |
| *middle temporal gyrus/inferior temporal sulcus* | | | | | 50 | -34 | 8 | 3.14 |
| *inferior occipital gyrus/fusiform gyrus* | | | | | 46 | -60 | -24 | 3.23 |
| *frontal operculum of the insula* | -56 | 10 | 4 | 3.44 | 58 | 20 | -2 | 3.95 |
| *anterior insula* | | | | | 40 | 14 | -2 | 4.10 |
| *Putamen* | -30 | 8 | 8 | 4.85 | 26 | 18 | 0 | 4.34 |
| | -20 | 8 | 14 | 4.58 | 26 | 0 | 16 | 4.07 |
| *tail of caudate/thalamus* | | | | | 22 | -24 | 20 | 4.23 |
| *Caudate* | | | | | 8 | -22 | 20 | 4.83 |
| *Cerebellum* | -6 | -62 | -26 | 4.19 | 22 | -56 | -30 | 4.75 |
| | | | | | 2 | -56 | -16 | 4.44 |
| | | | | | 24 | -64 | -28 | 3.95 |

* Activation peaks were determined by using cluster analysis ($Z > 2.7$, cluster significance threshold of $P = 0.01$). Only activation peaks with $Z > 3.0$ are reported in this table.

We failed, however, to find any significant activation in inferior parietal areas at any distance from the IPS. Several motor regions were active: bilateral motor cortex, left premotor area, right supplementary motor area (SMA), bilateral preSMA, bilateral cingulate motor areas and bilateral superior precentral sulcus/superior frontal sulcus (probably FEF). In the right hemisphere, a region in the middle temporal gyrus/inferior temporal sulcus also showed significant activation. The right fusiform

gyrus was activated. Other regions of activation were bilateral insula and putamen, left caudate nucleus and bilateral cerebellum.

No significant clusters of activation were found when number comparison blocks were contrasted with either vertical line judgement blocks or blocks with mirror stimuli.

*7.4.2.2 Single-digit versus double-digit number comparison blocks*

There were no brain areas significantly more active for single-digit number comparison than for double-digit comparison. For the opposite contrast (double-digit number comparison versus single-digit comparison) there were significant clusters of activation only within the extrastriate visual areas (see figure 7-11, table 7-4).

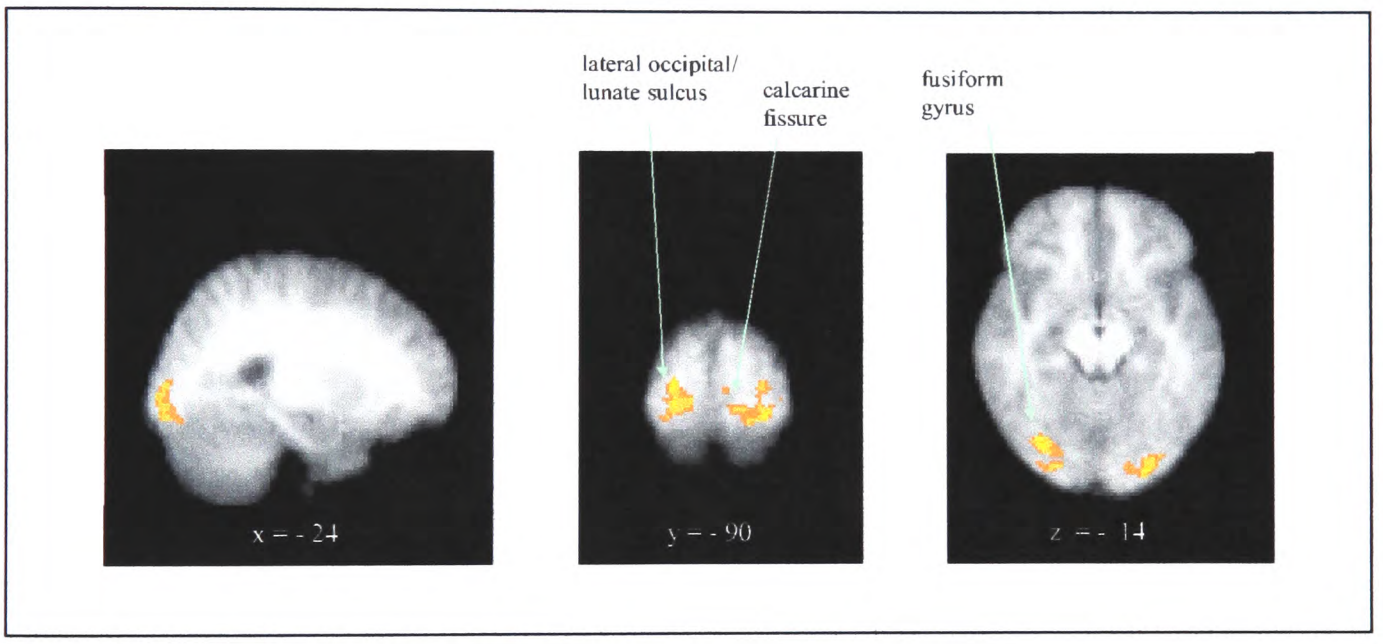



**Figure 7-11:** Brain activations for double-digit versus single-digit stimuli during number comparison on the mean average structural image of all 12 subjects registered in standard space (sagittal, coronal and axial view from left to right)

Brain areas that showed more activation during double-digit than during single-digit comparison were located bilaterally around the lateral occipital/lunate sulci, the fusiform gyri and in the left hemisphere around the inferior occipital sulcus and the calcarine fissure (see table 7-4).

**Table 7-4:** Talairach co-ordinates of activation peaks* for double-digit versus single-digit stimuli in number comparison blocks

| Brain Area | Left hemisphere | | | | Right hemisphere | | | |
|---|---|---|---|---|---|---|---|---|
| | x | y | z | Z | x | y | z | Z |
| *lateral occipital/lunate sulcus* | -24 | -92 | 2 | 3.43 | 22 | -92 | 2 | 4.34 |
| | -30 | -84 | 2 | 3.33 | 24 | -92 | -6 | 4.17 |
| *Inferior occipital sulcus* | -28 | -90 | -14 | 4.17 | | | | |
| | -16 | -94 | -8 | 3.33 | | | | |
| *Fusiform gyrus* | -18 | -90 | -16 | 3.24 | 36 | -70 | -18 | 4.46 |
| | | | | | 34 | -72 | -14 | 4.45 |
| | | | | | 36 | -71 | -22 | 4.22 |
| | | | | | 24 | -78 | -18 | 3.75 |
| *Calcarine sulcus* | -10 | -92 | -10 | 3.38 | | | | |

* Activation peaks were determined by using cluster analysis ($Z > 2.7$, cluster significance threshold of $P = 0.01$). Only activation peaks with $Z > 3.0$ are reported in this table.

### *7.4.2.3 Effect of distance*

We failed to find any significant clusters of activation for the contrast of number comparison blocks with stimuli that were close to the reference number versus those that were far from the reference number. Neither were there any areas more active during number comparison of stimuli with a longer distance than during number comparison of stimuli that were on average much closer to the reference number.

### *7.4.2.4 Reaction time effects*

Figure 7-12 shows brain areas that vary with reaction time. Several parietal activations were found in the left hemisphere. The activation found in the left SMG extends into the lateral bank of the IPS. There is a second cluster of activation in the lateral bank of the IPS, but it is located more posteriorly. We also found activation in the left superior parietal lobule that extends into the medial bank of the IPS and a cluster around the left postcentral sulcus.

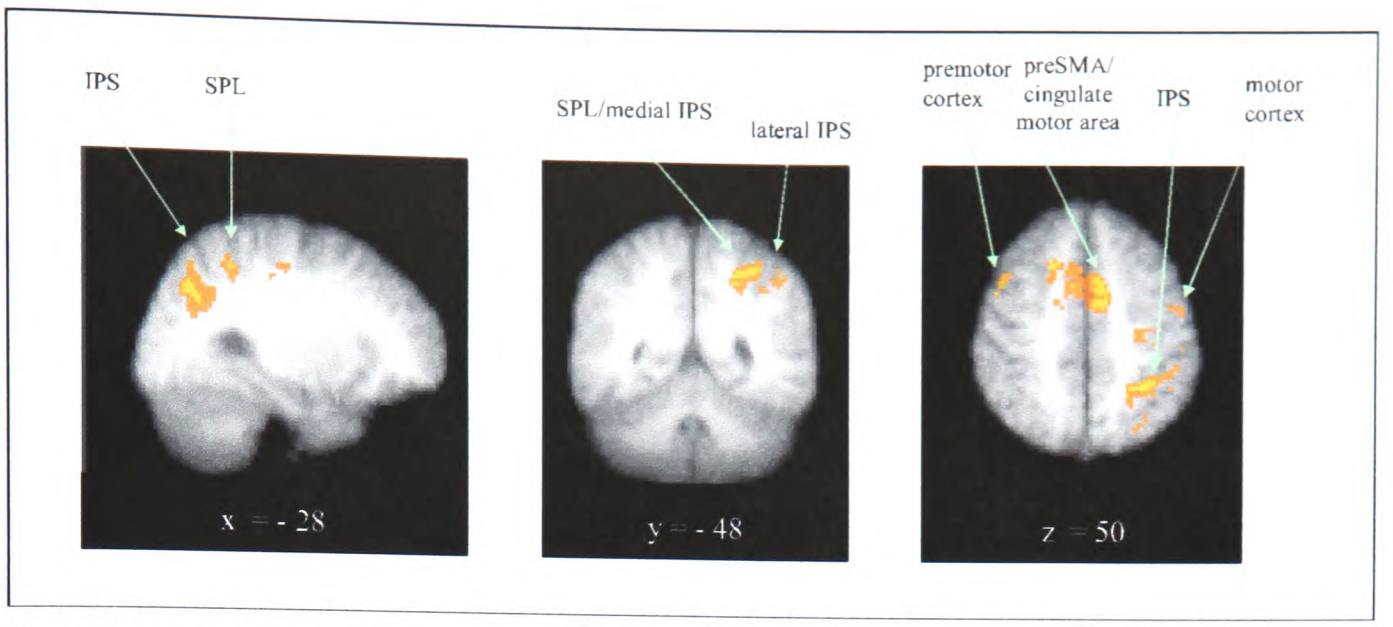



**Figure 7-12:** Brain activations correlated with reaction times versus rest on the mean average structural image of all 12 subjects registered in standard space (sagittal, coronal and axial view from left to right)

**Table 7-5:** Talairach co-ordinates of activation peaks* for reaction time effects versus rest

| Brain Area | Left hemisphere | | | | Right hemisphere | | | |
|---|---|---|---|---|---|---|---|---|
| | x | y | z | Z | x | y | z | Z |
| *SMG/lateral bank of IPS* | -56<br>-52 | -42<br>-24 | 44<br>54 | 3.92<br>3.41 | | | | |
| *lateral bank of posterior IPS* | -28<br>-26<br>-32 | -70<br>-64<br>-58 | 36<br>30<br>32 | 4.05<br>3.81<br>3.72 | | | | |
| *SPL/medial bank of IPS* | -34<br>-22 | -46<br>-46 | 52<br>48 | 3.90<br>3.73 | | | | |
| *postcentral sulcus* | -46 | -18 | 56 | 3.25 | | | | |
| *motor cortex/central sulcus* | -48<br>-34<br>-42 | -4<br>-22<br>-12 | 50<br>54<br>52 | 3.22<br>3.12<br>3.10 | | | | |
| *premotor cortex* | | | | | 52<br>52<br>48<br>54<br>44 | 10<br>10<br>10<br>18<br>10 | 36<br>44<br>48<br>18<br>14 | 5.03<br>4.30<br>4.03<br>3.93<br>3.76 |
| *SMA* | -2<br>-4 | -8<br>10 | 58<br>66 | 4.22<br>4.05 | 6<br>4 | -10<br>-6 | 64<br>54 | 4.27<br>4.04 |
| *preSMA* | | | | | 10 | 4 | 56 | 4.05 |
| *cingulate sulcus/ motor area* | -6<br>-8<br>-8 | 10<br>0<br>6 | 48<br>48<br>40 | 3.98<br>3.98<br>3.72 | 8 | 22 | 46 | 3.31 |
| *inferior frontal sulcus* | | | | | 52 | 30 | 20 | 3.05 |
| *frontal operculum of the insula* | | | | | 38 | 22 | 16 | 3.64 |

* Activation peaks were determined by using cluster analysis ($Z > 2.7$, cluster significance threshold of $P = 0.01$). Only activation peaks with $Z > 3.0$ are reported in this table.

Several motor regions were also active: left motor cortex, right premotor area, bilateral supplementary motor areas (SMA), right PreSMA and bilateral cingulate motor areas. Other regions of activation were in the right hemisphere around the inferior frontal sulcus and in the left frontal operculum.

*7.4.2.5 Summary of main findings of the whole-brain analysis*

Firstly, no area was significantly more active during number comparison than during the control tasks. Secondly, there was more extrastriate activity during presentation of double-digit stimuli than during presentation of single-digit stimuli. Thirdly, brain areas that are modulated by differences in reaction time include not only motor areas, but also several left parietal lobe regions.

### *7.4.3 ROIs analysis*

When overall mean percentage signal change was compared between the four ROIs in and around the IPS (left anterior IPS, left posterior IPS, right anterior IPS and right posterior IPS) there was no significant difference in signal change neither between left and right hemispheres ($F(1,11) = 1.24$, $p = 0.29$) nor between anterior or posterior regions ($F(1,11) = 2.61$, $p = 0.14$). There were however significant differences between the mean percentage signal change between left anterior and posterior regions and right anterior and posterior regions ($F(1,11) = 17.92$, $p = .001$). In the left hemisphere the mean percentage signal change in the anterior part was 1.71 % and hence higher than in the left posterior part where it was 1.44 % (but not significant: $t = 0.98$, $df = 11$, $p = 0.35$). The pattern was reversed for the right hemisphere. Here the higher percentage signal change was in the posterior part with 2.32 % while mean percentage signal in the anterior part was only 1.34 %. This difference was significant ($t = -4.00$, $df = 11$, $p = 0.002$).

*7.4.3.1 Task comparisons*

Overall, there was no significant difference in signal change between the three types of judgement for any of the four ROIs ($F(2,22) = 1.63$, $p = 0.22$) nor did judgement type interact with site ($F(2,22) = 0.51$, $p = 0.55$), hemisphere ($F(2,22) = 1.15$, $p = 0.33$) or site and hemisphere ($F(2,22) = 0.31$, $p = 0.73$) .

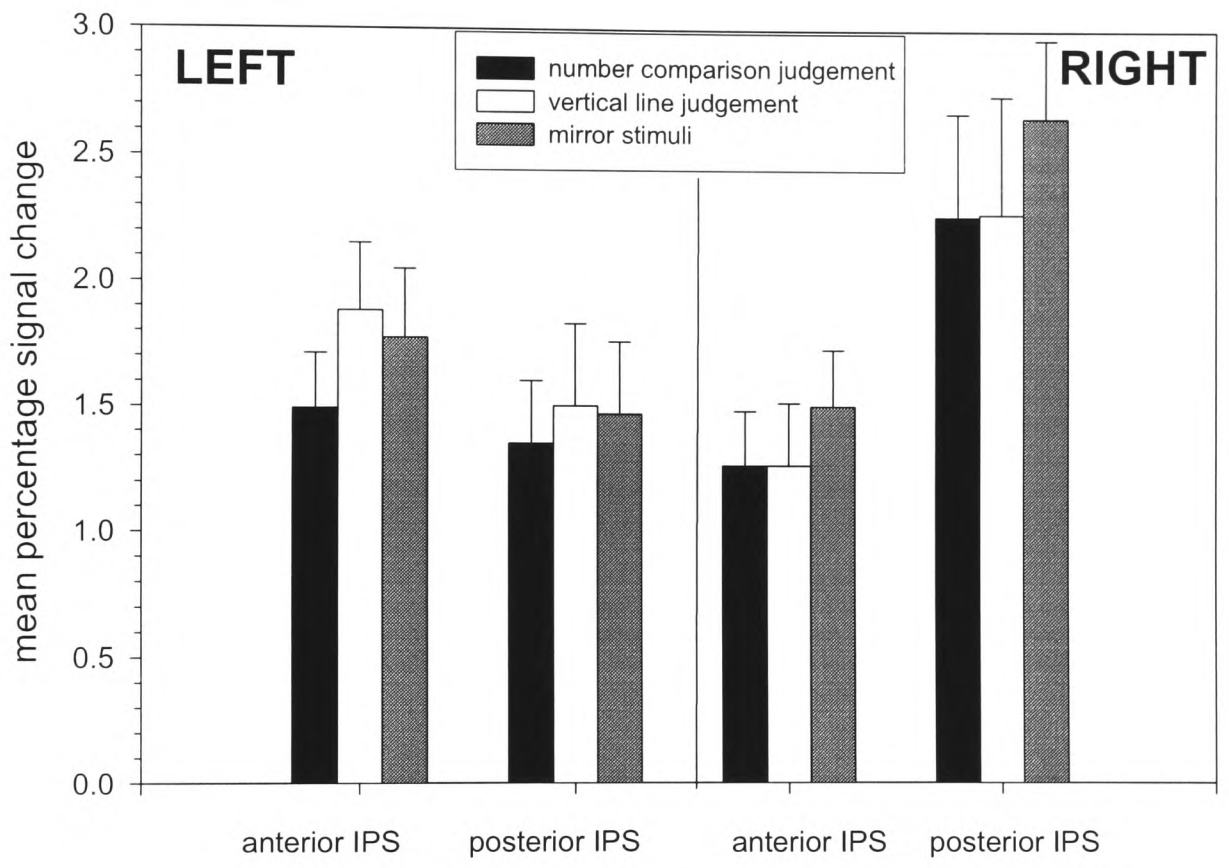



**Figure 7-13:** Mean percentage of signal change in four regions of interest (left anterior and posterior, right anterior and posterior regions in and around the intraparietal sulcus) during three types of judgement (number comparison, vertical line judgement and judgement of mirror stimuli).

*7.4.3.2 Single-digit blocks versus double-digit blocks*

For all ROIs the mean percentage of signal change averaged over all tasks was higher for double-digit stimuli than for single-digit stimuli blocks ($F(1,11) = 8.47$, $p = 0.02$; see figure 7-14). The effect of stimulus type on signal change varied with judgement type ($F(2,22) = 3.53$, $p = 0.05$), site ($F(1,11) = 11.24$, $p = 0.006$) and hemiphere and site ($F(1,11) = 5.05$, $p = 0.05$). We therefore analysed each ROI

separately. The difference in mean percentage of signal change between single-digit and double-digit stimuli only reached significance for the posterior regions in both hemispheres (left: $F(1,11) = 10.32$, $p = 0.008$; right: $F(1,11) = 18.08$, $p = 0.001$). Although for the right anterior IPS region there was no significant difference between signal change for double-digit versus single-digit stimuli ($F(1,11) = 0.19$, $p = 0.67$), stimulus type had an effect on signal change that varied between judgement type ($F(2,22) = 5.11$, $p = 0.02$; see figure 7-14b). There were no significant differences in signal change for double-digit versus single-digit stimuli during mirror stimuli judgement. For number comparison the mean signal change in the right anterior IPS was higher during single-digit stimulus presentation (0.68 %) than during double-digit stimulus presentation (0.57 %; $t = -1.55$, $df = 11$, $p = 0.15$). In contrast, during vertical line judgement the signal change was higher for double-digit stimuli (0.73%) than for single-digit stimuli (0.53%) ($t = 2.00$, $df = 11$, $p = 0.07$).

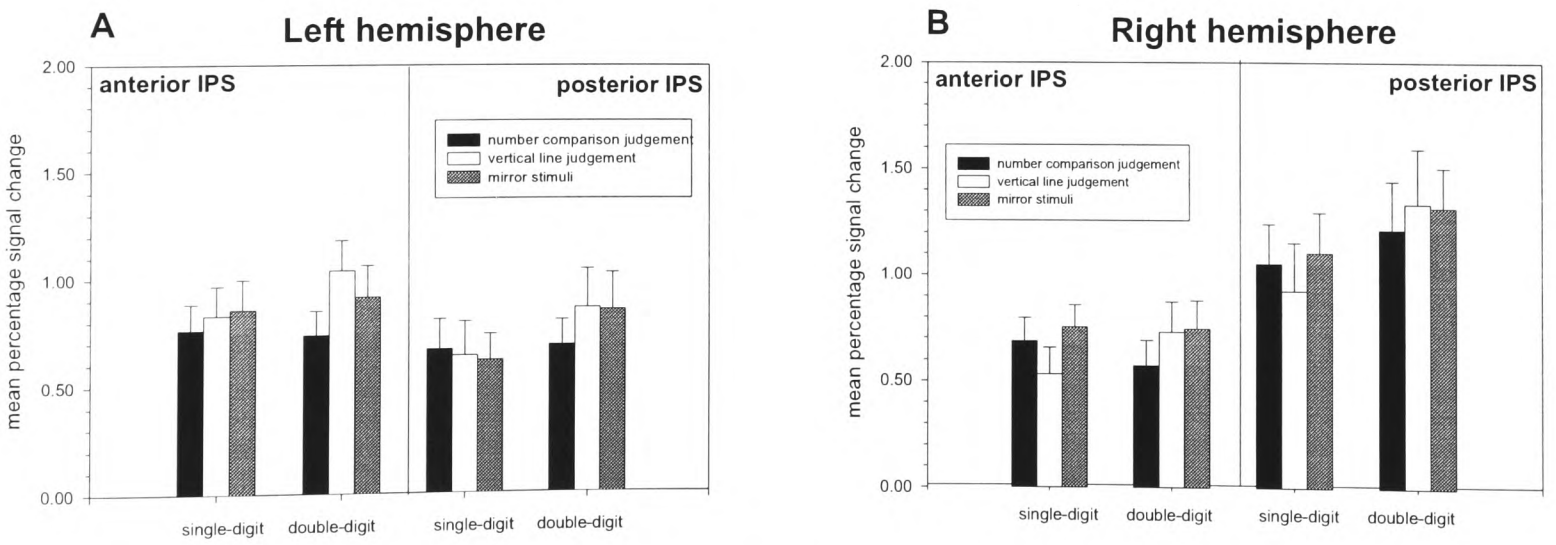



**Figure 7-14:** Mean percentage of signal change in anterior versus posterior regions around the IPS in the left hemisphere (a) and the right hemisphere (b). Results are shown for single-digit and double-digit stimuli during three types of judgement (number comparison, vertical line judgement and judgement of mirror stimuli).

*7.4.3.3 Effect of distance*

Overall, distance did not show a significant effect on mean percentage signal change ($F(1,11) = 2.13$, $p = 0.17$). However, distance interacted significantly with hemisphere ($F(1,11) = 6.81$, $p = 0.03$), site and judgement type ($F(2,22) = 4.81$, $p = 0.02$) and site, judgement type and stimulus type ($F(2,22) = 4.05$, $p = 0.03$). We followed up these interactions by analysing each ROI separately.

The only region of interest which showed a main effect of distance on signal change was the left posterior region around the IPS ($F(1,11) = 9.66$, $p = 0.01$). In this region the mean percentage of signal change increased from 1.98 % for stimuli with distance close to 2.33 % for stimuli with distance far. The effect of distance in this region is mainly due to differences in the control tasks (number comparison: $t = -0.39$, $df = 11$, $p = 0.71$; vertical line judgement: $t = -1.69$, $df = 11$, $p = 0.12$; mirror stimuli: $t = -2.07$, $df = 11$ $p = 0.06$).

For the left anterior region of interest there was no main effect of distance on signal change. The effect of distance in this region, however, varied significantly between single-digit and double-digit stimuli ($F(1,11) = 4.90$, $p = 0.05$). For stimuli with distance far the mean percentage signal change to both double-digit and single-digit stimuli was 1.35 %. In contrast, for stimuli with distance close the mean signal change in this region is higher for double-digit stimuli (1.33 %) than for single-digit stimuli (1.12 %).

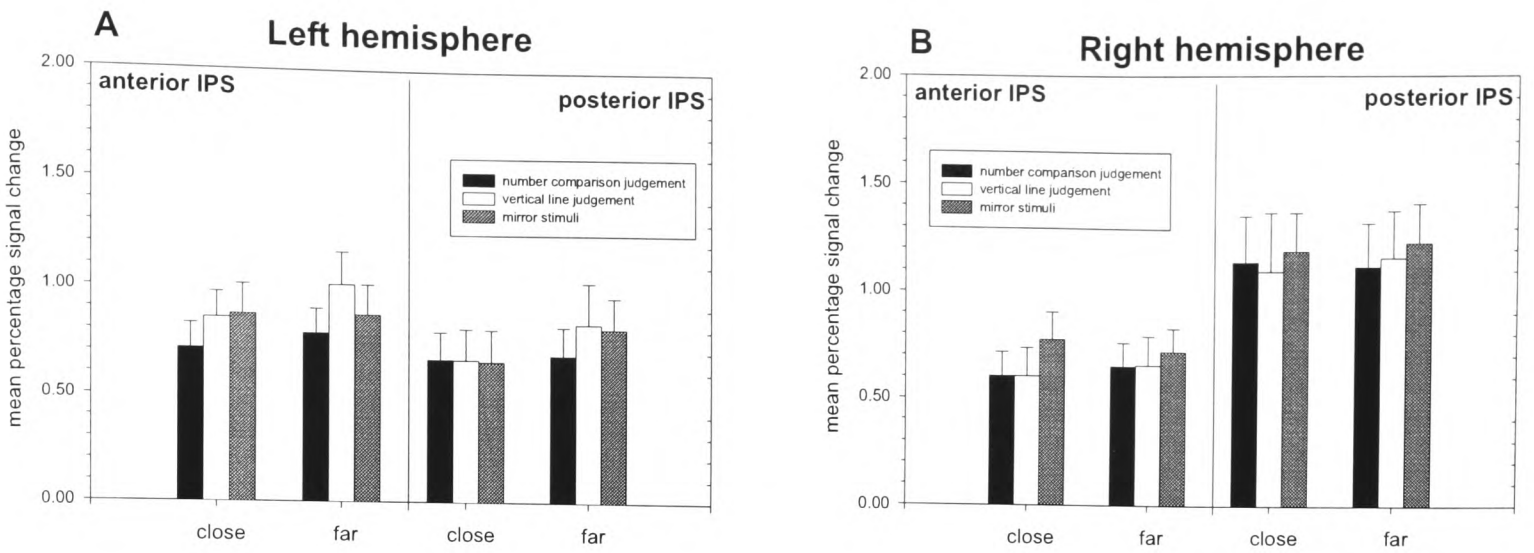



**Figure 7-15:** Mean percentage of signal change in anterior versus posterior regions around the IPS in the left hemisphere (a) and the right hemisphere (b). Results are shown for blocks in which the distance of the stimuli to the reference number was either close or far during three types of judgement (number comparison, vertical line judgement and judgement of mirror stimuli).

In the right posterior IPS region, modulation of the effect of distance by judgement type varied significantly between single-digit and double-digit stimuli ($F(2,22) = 3.5$, $p = 0.05$; see figure 7-16).

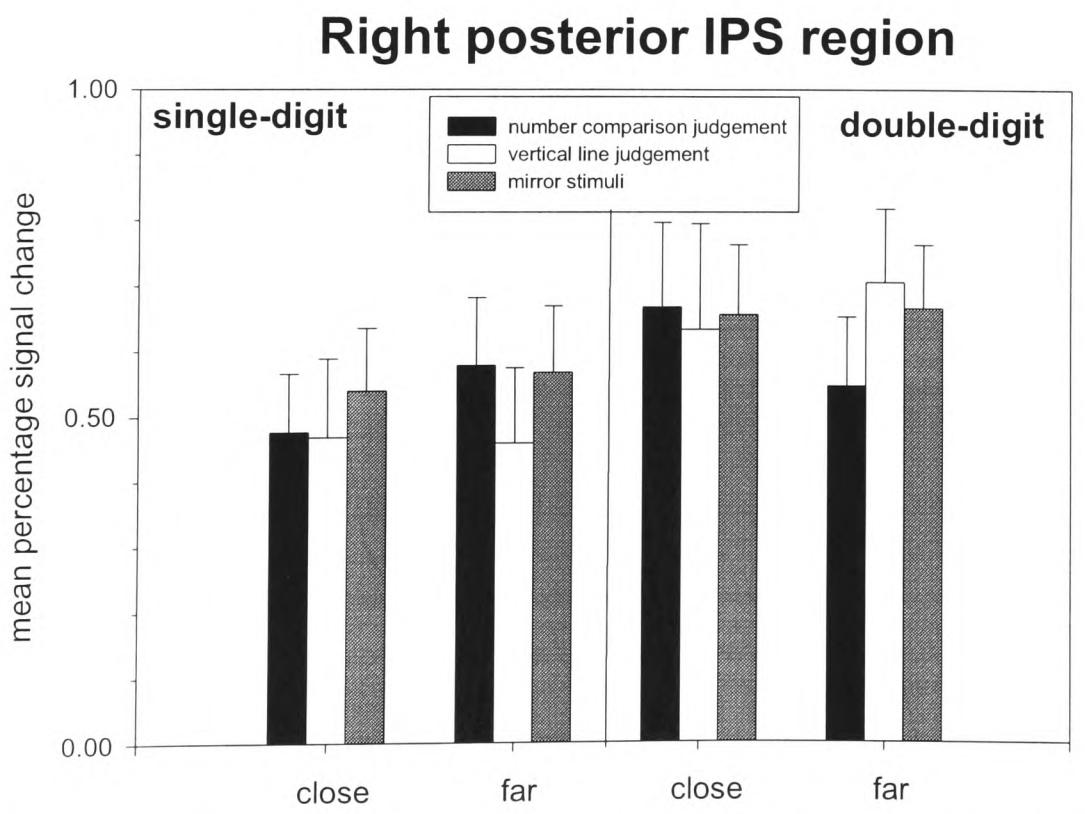



**Figure 7-16:** Mean percentage of signal change in the right posterior region around the IPS for single-digit stimuli (on the left) versus double-digit stimuli (on the right). Results subdivided into blocks in which the distance of the stimuli to the reference number was either close or far during three types of judgement (number comparison, vertical line judgement and judgement of mirror stimuli).

For single-digit stimuli the signal change was higher for distance far than for distance close for number comparison ($t = -1.85$, $df = 11$, $p = 0.09$). In contrast, for double-digit stimuli there was more signal change in this region during number comparison for distance close than distance far ($t = 1.95$, $df = 11$, $p = 0.08$).

*7.4.3.4 Summary of main findings of the ROI analysis*

Overall, the mean percentage of signal change is highest in the right posterior IPS region. None of the four regions of interest show higher mean percentage signal change during number comparison than during the control tasks.

Signal change is in general higher for double-digit than for single-digit stimuli, particularly in the posterior regions. These differences in percentage signal change again were not task-specific. However, in the right anterior IPS region there is a slight trend indicating that mean percentage of signal change during number comparison specifically might be higher during single-digit than double-digit stimuli presentation.

Distance affects the signal change in the left posterior IPS. For stimuli that are close to the reference number there is less signal change than for those that are further away. This difference, however, is mainly driven by differences in the control tasks. In the right posterior region of interest, signal changes for single-digit stimuli are also smaller for distance close than distance far for all three tasks. Signal change for double-digits in this region however varies with distance differently for task. During number comparison of double-digit stimuli there is more signal change in the right posterior IPS region for distance close than distance far. In contrast during vertical line judgement or mirror stimulus presentation of double-digits the

signal change in the right posterior region is again higher for larger distances than shorter distances.

## 7.5 Discussion

In line with other neuroimaging studies of number comparison this study showed that during number comparison versus rest a large bilateral parietal patchwork was active. This patchwork includes the posterior part of IPS, the medial bank of the IPS extending into the superior parietal lobule and the postcentral sulcus. Other activations during number comparison were found in bilateral motor cortex, left premotor area, right supplementary motor area (SMA), bilateral PreSMA, bilateral cingulate motor areas and bilateral superior precentral sulcus/superior frontal sulcus (probably FEF), right middle temporal gyrus/inferior temporal sulcus, right fusiform gyrus, bilateral insula and putamen, left caudate nucleus and bilateral cerebellum. All of these activations have been reported before during number comparison (see table 7-2). These results seem to point toward an important role for the parietal lobe, and the IPS in particular, in number comparison, which is in line with results from TMS experiments discussed in chapters 4 and 5.

### *7.5.1 No difference in activation between number comparison and control tasks*

However, no brain areas were more active during number comparison than during visuospatial control tasks, neither in the whole brain analysis nor when we analysed regions of interest around the IPS. These results indicate that the activations seen for number comparison versus rest are not specific to number comparison. It is perhaps not that surprising, that no areas were found to be more active during number comparison than during vertical line judgement on numerical stimuli. In a number stroop task, Besner & Coltheart (1979) have shown that numerical stimuli often

automatically activate a magnitude representation, if even subjects are asked to perform a non-numerical task with these stimuli. None of the imaging studies on number comparison, with the exception of Chochon et al. (1999), have compared activation during number comparison explicitly with activation during numerical stimulus presentation. Therefore the parietal activation previous studies found during number comparison could be due to numerical stimulus presentation, magnitude judgement or both. When Chochon et al. (1999) compared number comparison with digit naming, they only found one area that was more activated during number comparison: the right postcentral sulcus.

### *7.5.2 Choice of control tasks*

Most imaging studies on number comparison have compared either numerical stimuli with very different stimuli (such as letters or body parts) or they compared trials with numerical stimuli that vary on reaction times. Our study was designed to disentangle reaction times effects from the distance effect. Additonally, we employed visuospatial control tasks that were more closely matched to the number comparison stimuli than in previous imaging studies. But perhaps this experiment did not use the best control tasks. In principle there are two types of control tasks that can be used during fMRI experiments with block designs: tight control tasks or loose control tasks. In tight task comparisons, as many variables as possible are held constant between the two tasks being compared (e.g. stimulus display, response and response selection characteristics, performance level, eye movements). Scott et al. (2000), for example, investigated speech perception in a PET study, in which they presented sentences auditorily to their subjects. As control tasks they used speech-like stimuli with equivalent acoustic complexity. A loose task comparison involves a situation in which much broader comparisons are made and not all variables are held

constant. During loose task comparisons, usually, a low-level reference task is used that allows a more extensive activation pattern to be observed. For example, a loose control task for speech perception would be listening to white noise.

For this fMRI study, tight task comparisons were chosen. Stimuli and motor responses in both our control tasks were closely matched to the number comparison task. In both control tasks, subjects had to judge the orientation of a line. There is, however, some evidence that areas in the inferior parietal lobe/IPS are also active during spatial orientation judgements (Walsh & Perrett, 1994). Therefore, the activation in the inferior parietal lobe/IPS could be due to number magnitude representation during the number comparison tasks and due to visuospatial orientation judgements in the control tasks. Also, one could argue that during the control tasks subjects searched through a visual array for a yellow vertical line and therefore engaged in visual search. Ashbridge, Walsh, & Cowey (1997) showed that a region in the posterior part of the IPL/IPS is important during visual search. Research by Ashbridge, Cowey, & Wade (1999), however, also indicates that the contribution of this area is specific to conjunction visual search (i.e. finding a yellow vertical line in red and yellow horizontal lines). Our control tasks can certainly not be described as conjunction visual search tasks. Furthermore, even if one assumes that the activation in the control tasks in the posterior part of the IPS can be accounted for by a visual search explanation, this does not explain why also the activations in the anterior part of the IPS were higher during control tasks than during number comparison. There is no evidence for a role of the anterior IPS region in visual search.

Alternatively, IPS activation during the control task with mirror stimuli could be related to mental rotation. During the vertical line judgement of mirror stimuli,

subjects could have tried to rotate the stimuli in order to identify them. Several researchers (Alivisatos & Petrides, 1997; Gauthier et al., 2002; Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001; Richter et al., 2000) found parietal activation around the IPS during mental rotation. Walsh & Butler (1996) emphasized the role of the parietal lobe for perception of rotated shapes if they were rotated by large angles (by more than 60°). Bestmann et al. (2002) showed that TMS over IPS prolonged the reaction period during visuomotor rotation for large angles of rotation.

When the vertical line task on mirror stimuli was explained to the subjects, however, the word mirror stimuli was never used. They were only asked to perform a vertical line judgement on non-numerical stimuli. None of these stimuli would appear as a number once they are rotated. Furthermore, stimulus rotation would not help to perform the task, quite to the contrary. None of the subjects reported that they tried to rotate the stimuli. Additional, there were no differences in reaction times between vertical line judgement of numerical and mirror stimuli, thus suggesting that subjects did not rotate stimuli, at least not before making a response. It can, however, not completely be excluded that subjects mentally rotated the mirror stimuli.

In summary, it could be argued that both the control tasks were too similar to the number comparison task. During vertical line judgement on numerical stimuli the magnitude representation could have been activated automatically. Furthermore, during the vertical line judgement on mirror stimuli, it could have been possible that subjects still saw stimuli that looked to them very similar to numbers. Perhaps they even automatically found the corresponding number for some of the mirror stimuli thus activating a magnitude representation. In order to find out whether the control

tasks were too tightly matched, it would be interesting to repeat the current experiment and to include a control task with a loose match, i.e. a language task.

### *7.5.3 The parietal cortex activation might not be exclusive for numbers*

There were no significant over-all differences in activation between the three tasks we used. This finding suggests that the contribution of the parietal lobe to all three tasks is very similar. As argued before, this could be due to the similarities shared by all three tasks. Alternatively, perhaps there is no brain area that is exclusively specialised for representing number magnitude. Parietal activations consistently reported during number comparison could be due to a more general process, that may also be recruited by other visuospatial tasks.

The ROI analyses provide some evidence for this account. The highest signal change for all tasks was in the right posterior IPS region. It is well know that the right posterior parietal lobe is of particular importance for visuospatial tasks. That the highest activation change for all three tasks was observed in this region suggests that the brain processes underlying all three tasks were very similar and were perhaps mainly driven by visuospatial stimulus characteristics. Recently, several researchers suggested that the IPS might also have a more general role in selecting responses to graded visual information (Gold & Shadlen, *2001*). Bunge et al. (2002), for example, showed that the IPS is involved in activating possible responses on the basis of learned stimulus-response associations.

Unless one makes a clear distinction between number comparison and calculation, this explanation, however, is in contrast to findings from acalculic patients, which show that calculation abilities can be impaired independently from visuospatial processing.

### *7.5.4 Number-specific results*

This fMRI experiment was also designed to compare brain activation during number comparison of small stimuli to activations during number comparison of large stimuli. However, we did not find any areas that were more active during number comparison than during control tasks. On the basis of this finding, any interpretation of number-specific results has to be handled with care.

There was more activation in extra-striate areas during double-digit stimulus presentation than during single-digit stimulus presentation. These two stimulus types differed in visual angle, so this activation difference might just have reflected the fact that during double-digit stimulus presentation there was more visual information on the screen. It took subjects longer to respond to double-digit stimuli in all three tasks. For all four ROIs around the IPS, especially the posterior regions, there was in general more signal change related to double-digit stimuli than to single-digit stimuli. Activations found in IPS and the inferior parietal lobe in both neurophysiology and neuroimaging have been related to the selection of motor responses, sometimes in ways that are related to reaction time (Caminiti, et al., 1999; Deiber, Ibanez, Sadato, & Hallett, 1996; Winstein, Grafton, & Pohl, 1997). The differences in IPS activation between double-digit and single-digit stimuli are very likely to be related to differences in reaction time.

However, in the right anterior IPS region there was a trend for higher mean signal change for single-digit stimuli than for double-digit. This result is particularly interesting, because it is specific to number comparison blocks and can not be explained by differences in reaction times. It might mirror TMS findings described in chapter 5, showing that numbers 1 to 9 might be represented more anterior than larger numbers.

### *7.5.5 Distance effect*

The behavioural reaction time analysis showed that even in a scanner environment it took subjects significantly longer to respond to numbers close to the reference number than to those further away. Therefore, the numerical distance effect again could be replicated. In double-digit blocks with distance far the mean distance from the reference number was 26.5, while in blocks with distance close it was 7.6. In single-digit blocks the difference was less pronounced (distance far: 3.1; distance close: 2.0). This might explain why the distance effect was behaviourally stronger for double-digit stimuli.

In the whole brain analysis we failed to find any area that was more active during distance close than during distance far blocks and vice versa. In the left posterior IPS regions, however, in general there was more signal change during blocks with distance far than blocks with distance close. For the number comparison, this finding is in tight anti-parallel with the reaction times which are significantly longer for closer distance. It could be argued that during number comparison subjects had to redirect attention in space along the mental number line. In this case one would expect greater parietal activation for numbers that are further away from the reference number, because subjects have to redirect their attention further. They are, so to say, travelling further on the mental number line.

Reaction times during the vertical line judgement on numerical stimuli were significantly longer during distance far than during distance close. This effect perhaps can be explained by the fact that during these blocks subjects were asked to completely ignore the fact that the stimuli were numbers. Perhaps it was easier for them to ignore the numerical value of the stimuli for numbers closer to the reference number than for those further away form the reference number. It is quite likely that

the higher IPS activation during vertical line judgement blocks for distance far than distance close is related to these reaction time differences, i.e. task difficulty. However, there was also more signal change for distance far than distance close during vertical line judgement on mirror stimuli. This difference in signal change cannot be explain by reaction time differences, because there were no reaction time differences between distance far and distance close blocks for mirror stimuli.

In the right posterior IPS region, there was more signal change for distance far than for distance close with the exception of double-digit stimuli presentation during number comparison judgement. In these blocks there was more signal change in the right posterior IPS region for distance close than for distance far. This is in parallel with the reaction time data, thus suggesting that during number comparison activity in this region might be related rather to task difficulty than to redirecting attention along the mental number line.

### *7.5.6 Reaction times*

As our parametric whole brain analysis showed, reaction times are associated with a large left-lateralised parietal patchwork of activations which is not correlated with any of the three task manipulations. In fact, the parietal patchwork found to be significantly associated with reaction time (left SMG, left lateral and medial banks of the IPS, left superior parietal lobule medial bank of the IPS and the left postcentral sulcus) is very similar to many patchworks previously described for either number comparison or distance effects (see table 7-2). Therefore reaction time differences could partially account for parietal activations found during number comparison. In order to further investigate the role of reaction times, it would be interesting to analyse the current experiment with reaction times as the main

explanatory variable and then to evaluate how much independent explanation of variance can be added by number comparison and control blocks.

## *7.6 Conclusion*

This fMRI experiment on number comparison successfully replicated activations in a large bilateral parietal-motor patchwork during number comparison versus rest. However, it failed to find any activations specific to number comparison blocks that were not seen during visuospatial control tasks. This finding suggests that either the control tasks were too closely matched or that there might be no brain areas specifically and solely dedicated to number comparison.

# 8. General Discussion

## 8.1 Main findings

### 8.1.1 TMS is a useful neuroimaging tool to investigate numerical cognition

This thesis confirms rTMS as a neuroimaging tool that can successfully be used to investigate number comparison and calculation in normal subjects. The first experiment showed that rTMS can be used on normal subjects to mimic the behaviour of patients with deficits in calculation. Magnetic stimulation over the left inferior parietal lobe produced deficits in simple addition that are similar to deficits seen in acalculic patients. TMS over the right inferior parietal lobe, however, did not lead to deficits in behaviour. This is in line with results from patient studies showing that acalculia is mostly related to brain damage in the left posterior parietal lobe.

TMS was then used to investigate basic numerical processes (chapters 4 and 5). Number comparison is a basic numerical process, that is rarely impaired in patients. The experiments on number comparison showed further that TMS can be used successfully to disrupt these basic processes. TMS affected comparison of double-digit numbers when subjects were stimulated over the posterior part of the right or left IPS, but not when stimulated over the anterior part. In contrast, in the number comparison experiment with single-digit numbers, TMS had a disruptive effect when used over the anterior right and left IPS/SMG, but not when used over the posterior part of the IPS/ANG.

### 8.1.2 The IPL plays an important role in calculation and number comparison

Results from the TMS experiments (chapters 3, 4 and 5) as well as from the fMRI study on number comparison (chapter 7) show clearly that the inferior parietal lobule and the IPS are involved in number processing. Because magnetic stimulation is an

interference technique, an impaired performance in calculation and number comparison when magnetic stimulation was applied over the inferior parietal lobule, emphasises that the inferior parietal lobe is not merely associated with the patchwork used for number processing, but also that it is indispensable for optimal performance.

### *8.1.3 Evidence for visuospatial number representation*

In chapter 6, a single case of a person (HS) with an explicit mental number line was described. His number representation is clearly visuospatial in nature. Evidence for a visuospatial number representation in subjects without an explicit mental number line stems from the SNARC effect. In a parity judgement task, Dehaene, Bossini & Giraux (1993) found a left-hand preference for low number responding and right-hand preference for high number responding. On the basis of this SNARC (spatial-numerical-association of response codes) effect they proposed that the mental number line has a specific spatial orientation as a left-right continuum of ascending magnitude.

In both TMS experiments on number comparison (chapters 4 and 5), the TMS effect varied with distance from the reference number. For stimulation over the left IPL the TMS effect was stronger for numbers larger than the reference number, but close to the reference number. This effect was not observed for stimulation over the right hemisphere. The SNARC effect implies that numbers smaller than the reference number are represented on the left side of space while numbers that are larger than the reference number are represented on the right side of space (Dehaene, Bossini, & Giraux, 1993; Dehaene, Dupoux, & Mehler, 1990). The TMS findings therefore can be interpreted as showing that left IPL TMS particularly affects

numbers represented on the contralateral side of space, thus providing evidence for a spatial representation of number in the left IPL.

Further evidence for a visuospatial number representation stems from recent neuroimaging studies. Several researchers reported activity in a bilateral parietal patchwork during number comparison (Chochon, Cohen, van de Moortele, & Dehaene, 1999; LeClec'H, et al., 2000; Pinel, Dehaene, Riviere, & LeBihan, 2001; Rickard, et al., 2000). However, when visuospatial tasks (e.g. comparing angles in Fias, Lammertyn, Reynvoet, Dupont, & Orban, in press) were used as control tasks, only left hemispheric activation was reported during number comparison. These findings suggest, that visuospatial processes may play an important role during number comparison and are in line with findings of the fMRI study reported in chapter 7. There were no areas more active during number comparison than during closely matched visuospatial tasks, thus again suggesting that number comparison is closely related to visuospatial tasks.

### *8.1.4 Evidence for IPL/IPS activity specific to number comparison*

On the basis of findings reported in this thesis it is impossible to decide whether there are number-specific areas in the parietal lobes as implied by several researchers (Dehaene, Dehaene-Lambertz, & Cohen, 1998; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002) or whether parietal activation during number comparison is not number-specific. That no differences between visuospatial tasks and number comparison were found in the fMRI study, for example, could also be interpreted as evidence that there are no brain areas that are exclusively active during number comparison. This interpretation suggests that IPL/IPS plays a more general role common to all these tasks. As discussed in the introduction, parietal activation generalises across a wide variety of cognitive functions, of which three in particular

might be related to number comparison: visual search, stimulus-response selection and task difficulty.

Several studies have shown that the ANG/posterior IPS is involved in visual search (Ashbridge, Walsh, & Cowey, 1997; Corbetta & Shulman, 1999; Ellison, 2000; Nobre, et al., 1997). Signal changes reported during all three tasks in that area could have been related to the visual search component of these tasks. Similarly, findings from the TMS experiment on number comparison of double-digit stimuli could partly be explained by a visual search account. In previous studies of visual search tasks, TMS over right posterior IPS/ANG has been shown to have a greater effect than TMS over left posterior IPS/ ANG. The lateralisation of the TMS effect on double-digit number classification was reversed (i.e. larger over left). Therefore, it is impossible to argue that TMS over posterior IPS/ANG simply disrupted any task that included visual search as a component process. One could nevertheless still argue that while left posterior IPS/ANG TMS actually disrupted a spatial representation of numbers, right ANG stimulation might have actually disrupted processes used to search this representation. However, in the number comparison experiment with single-digit numbers, there was only a TMS effect for stimulation over the anterior IPS/SMG. These results cannot be explained on the basis of a visual search account, because the anterior IPS or SMG have never been found to be so important for visual search. Similarly, a visual search account could not explain why there were no task differences in fMRI signal change in the anterior IPS region in the fMRI study reported in chapter 7.

None of the experiments that used magnetic stimulation employed a non-numerical control task. Therefore, it could be that parietal TMS actually disrupted and limited basic sensory-motor processes on which number comparison depends

rather than a process specific to just number comparison. Andersen et al. (1997) and Snyder, Batista, & Andersen (1997) showed that the parietal cortex is involved in activating motor responses on the basis of learned stimulus-response associations. This could mean the parietal cortex is involved in the representation of responses and the selection of an appropriate response from among competing response alternatives. However, evidence is mounting, that the parietal cortex represents possible responses rather than being specifically involved in response selection. For example, cells in parietal cortex of nonhuman primates are active in response to cues instructing them to withhold a response as well as by cues instructing them to make a response (Kalaska & Crammond, 1995). This finding has been replicated with neuroimaging in humans (Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001). Bunge et al. (2002) showed that left parietal cortex was activated by either of two manipulations that increased the need to maintain a representation of possible responses. Furthermore, in a fMRI study by Thoenissen et al. (2002) the posterior parietal cortex showed delay-related activity in a prelearned associative visuomotor task regardless of the movement probability. These studies suggest that in prelearned visuomotor tasks the parietal cortex serves to represent candidate responses.

During number comparison tasks, one could argue that subjects were asked to map responses onto numbers that are represented spatially. So the cognitive requirement here would also be a stimulus-response representation and selection. In such a case it could be argued that this stimulus-response representation was altered by parietal magnetic stimulation, rather than a representation limited to numbers. Furthermore it could be argued that it was the stimulus-response representation that produced parietal activation common to all three tasks in the fMRI study.

The hypothesis that IPL activation during number comparison is due to stimulus-response representation can account for the findings of the fMRI study. It, however, cannot account for differences between the role of the anterior IPL region and the posterior IPL region in number comparison that were found in the experiments with magnetic stimulation, because there should be no differences in stimulus-response representation between single-digit and double-digit comparison.

Response-selection can also account for the findings of the first TMS experiment on number comparison in another way. It is possible that the posterior part of the IPL, and not the anterior part, is important during double-digit number comparison. Recent studies have shown that the more difficult it is to select a response, the more activity is reported in parietal areas (Duncan et al., 2000; Gold & Shadlen, 2001). However, a priori, it is not clear why double-digit selection is more difficult.

In the number comparison task the most difficult responses, as indicated by reaction times, are to numbers close to the reference number. The effect of TMS depended on distance from the reference number. Furthermore, magnetic stimulation over the left hemisphere had its strongest effect close to the reference number. Also, double-digit numbers took longer to respond to than single-digit numbers. Therefore, the involvement of the posterior IPL region during double-digit but not single-digit comparison could be explained by task difficulty, i.e. the posterior parietal lobe could be more active during tasks with higher demands. However, a simple task difficulty explanation for the observed differences between the neural representation of single- and double-digit numbers, cannot accommodate combined findings from the first and second TMS experiment on number comparison. The second experiment showed that during number comparison of single-digits, TMS only had a

disruptive effect over the anterior IPS/IPL region and not over the posterior IPS/IPL region. If that finding were related to task difficulty, then a TMS effect over SMG would also be expected during a more difficult task, e.g. during double-digit comparison. During double-digit comparison, however, magnetic stimulation only showed an effect when applied over posterior IPL/IPS.

It is difficult to think of an explanation of these complementary findings that is not related to number representation. The finding that small numbers might be represented differently from larger, provides tentative evidence for at least some degree of number-specificity in brain activations.

### *8.1.5 Small numbers are represented differently*

TMS affected comparison of double-digit numbers when subjects were stimulated over the posterior part of the IPS/IPL, but not when stimulated over the anterior part. In contrast, magnetic stimulation during number comparison of single-digits only disrupted performance when applied over the anterior part of the IPS/IPL, not when applied over the posterior part.

These findings suggest that small numbers are represented separately from larger numbers, or at least that small numbers are processed differently from larger numbers. There was some evidence for a similar effect in the TMS experiment on simple addition reported in chapter 3. In a second analysis of this experiment I analysed the reactions times for sums larger than ten and sums smaller than ten separately. In this analysis the data showed a trend for differences between the role of supramarginal gyrus/anterior IPS and angular gyrus/posterior IPS in simple addition. The strongest increase in RTs for the posterior IPL could be seen when TMS was applied over posterior IPL and the sum size was *over* 10. In contrast, magnetic stimulation over anterior IPL did not lead to an increase in RTs for sums

with a sum size *larger* than 10, but for sums *smaller* than 10. Again, this seems to point towards a role for anterior IPS/supramarginal gyrus in the representation of smaller numbers and for the posterior IPS/angular gyrus for larger numbers, even when the task is adding numbers rather than comparing number size.

This is partly in line with findings from Stanescu-Cosson et al. (2000) showing greater BOLD activation in bilateral intraparietal regions for numerical problems involving larger numbers. In the fMRI experiment reported in chapter 7 higher signal change was found for double-digit than single-digit numbers in posterior regions. However, differences in activation between larger and smaller numbers found in both studies could have been due to the greater difficulty associated with processing double-digit as opposed to single-digit stimuli (as implied by longer reaction times for larger numbers). Any findings of specificity for smaller numbers (for example reported for the TMS experiment in chapter 4 and the imaging study in chapter 7), however, cannot be explained by invoking task difficulty.

This suggests that there is something special about the representation of small numbers. Whether this might be related to the fact that small numbers can be represented motorically (Butterworth, 1999) while large numbers clearly cannot, has to be investigated by further research.

## *8.2 Unanswered questions*

### *8.2.1. Are the findings specific to visual presentation?*

In all presented experiments, numbers were presented visually as Arabic numerals. So the question arises as to whether the effects I have described might be notation-specific. Some number processing models would certainly predict that. Therefore it would be worthwhile to repeat the experiments in different modalities, for example with auditory stimulus presentation, written numbers words or even dot patterns.

The outcome would be interesting on two levels. First, are the behavioural effects notation-specific? To my knowledge several numerical effects, e.g. the SNARC effect, have so far only been carried out in the visual modality and could well disappear for different modalities. Assuming that several basic numerical effects are based on a visuospatial number representation, it would be very interesting to find out whether non-visual stimulus presentation alters the ease with which a visuospatial representation is employed. It might encourage subjects to abandon the use of a visuospatial strategy. Secondly, will there be a common neuroanatomical site that causes an impairment of performance when magnetically stimulated irrespective of notation or will this site vary with notation as some number processing models (see section 1.6) predict?

### *8.2.2 The nature of visuospatial number representations*

In order to judge the importance of a visuospatial number representation it would be valuable to find out, which brain areas are used during number comparison by participants who have never had any visual experience, but still have spatial senses (i.e. congenitally blind participants). When they engage in a mathematical task, which in seeing participants activates visuospatial areas of the brain, will they use similar brain areas? Auditory versions of the numerical distance task or SNARC tasks could be used to investigate number representations in blind participants.

#### *8.2.2.1 Is there a mental number line?*

Recently, Donlan (2002) has questioned the existence of a mental number line. Indeed, one can criticise the studies on subjects with explicit number lines as being introspective, instead of experimental. However, Ramachandran & Hubbard (2001) suggested an experiment to be carried out on subjects with explicit number lines that

could provide experimental evidence for the existence of their mental number lines. In some subjects mental number lines can be highly convoluted, curving back onto itself. Ramachandran et al. (2001) proposed to give these subjects two numbers that are numerically far apart (e.g. 4 and 57), but spatially close together on their convoluted number line. It would be very interesting indeed to analyse the reaction times of this experiment and to see whether the distance effect is modified by the individual spatial arrangement of numbers. Unfortunately, HS had a straight, unconvoluted number line, so this interesting experiment awaits to be carried out with a subject who has a highly convoluted number line.

A study by Zorzi, Priftis & Umilta (2002) provides more evidence for the existence of a visuospatial representation of numbers akin to a mental number line. They reported that patients with hemispatial neglect misplace the midpoint of a numerical interval when asked to bisect it. They tested four right-brain damaged patients with left neglect, four right-brain-damaged patients without spatial neglect and four healthy control subjects. Subjects were auditorily presented with two numbers defining a number interval and were then asked to state the midpoint number without calculating. Neglect patients, in contrast to patients without spatial neglect or control subjects, made many errors. Zorzi et al. interpret this finding as strong evidence

> *"that the mental number line is more than simply a metaphor, and that its spatial nature renders it functionally isomorphic to physical lines."* (page 138).

The main body of evidence for visuospatial number representations similar to number lines in subjects without explicit mental number lines stems from the SNARC effect that was first found on a parity judgement task (Dehaene, Bossini, & Giraux, 1993). One would certainly expect the SNARC effect to generalize to

magnitude comparison tasks. Donlan (2002), however, failed to find a SNARC effect in their reaction time data on number comparison. He investigated number comparison of numbers 1 to 9 and compared it to block judgements (1-9, graded according to area) in 24 normal subjects. The SNARC effect predicts they should find that for target numbers less than 5, the left hand reaction times should be faster than right hand reaction times for number, and for target numbers greater than 5 left hand reaction times should be slower than right hand reaction times. However, there were no differences in reaction times between right and left hand responses. The SNARC effect did not generalise from parity judgement to a comparison task. This finding reduces the plausibilty of a spatially-organised mental number line as basis for number representation.

Furthermore, Donlan's results provide some evidence that comparison of numerical magnitude need not be based on numerically specific representations. He analysed reaction times item-wise as a function of distance, ratio and logarithmic scaling and found common properties of the reaction times for number comparison and block comparison. This suggests that a common mechanism might support comparison of numerical and perceptual inputs. Magnitude representations of this sort need not be numerically specific, but may be characterised as signal strengths proportional to context.

The evidence for more than a metaphorical existence for the mental number line is inconclusive. However, recently several studies on the existence of mental number lines have chosen the experimental approach. As described above, this has led to interesting results and will hopefully inspire more experimental research on mental number lines. Besides this experimental work, a theoretically interesting, but

so far very tentative connection between synaesthesia and number representation has been proposed by Ramachandran et al. (2001).

*8.2.2.2 Relation between synaesthesia and a visuospatial number representation*

Although the subject with the explicit number line decribed in chapter 6 (HS) did not describe any association of colours with specific numbers or parts of his number line, an association between numbers or number lines with colours seems to be quite common (Galton, 1880). Automatic associations of colours specific to certain numbers has also often been described in synaesthetes (Ramachandran & Hubbard, 2001).

Synaesthesia is a phenomenon in which an otherwise normal person experiences sensations in one modality when another modality is stimulated. Cytowic (1989) reported that synaesthetes often show left-right confusion, mathematical problems and an exceptionally good memory for geometrical figures. Aspects of the synaesthetes' are reminiscent of Gerstmann's syndrome. Recently, Ramachandran & Hubbard (2001) looked at the most common type of synaesthesia: grapheme - colour (i.e. number-colour or letter-colour) synaethesia. They claim that at least for this type of synaesthetes there are two forms: a 'lower' form and a 'higher' form. In 'lower' synaesthetes Ramachandran & Hubbard believe it is the actual visual appearance of the grapheme, not the numerical concept that evokes colour. In contrast, for 'higher' synaesthetes they provide some evidence that it might be the concept of numerical magnitude that seemed to generate colours. Interestingly, in their paper they suggest that both types of synaesthesia are caused by hyperconnectivity between colour and number areas, but at different stages in processing. 'Lower' synaesthesia might be caused by cross-wiring within the fusiform gyrus, while 'higher' synaesthesia may rely on cross-activation in the

angular gyrus. It could be hypothesised that at least some of the subjects who presented themselves with coloured number lines belonged to the group of 'higher' synaesthetes. It would be interesting to further investigate the relationship between synaesthesia, mental number lines and the inferior parietal lobe.

### *8.2.3 Motoric number representation*

Earlier in this section, when differences about the representation of small versus larger number were discussed, I put forward the idea that these differences might be related to the fact that small numbers can be represented motorically (Butterworth, 1999) while large numbers clearly cannot. If this is the case, one would certainly expect effects in a dual task on small numbers and attention to movements, that should not appear for larger numbers.

Although motoric representations of numbers during numerical tasks have been shown to have an influence (Fayol, Barrouillet, & Marinthe, 1998), very little attention has been given to them in the literature on numerical cognition. I propose to start investigating motoric number representations by developing simple numerical tasks that mainly activate brain areas that are related to attention to body movements and finger usage. These tasks could be based on activities such as counting a small group of objects and dealing with small numerosities in general. These tasks then could be used to investigate the type of number representation and the brain areas activated by these tasks with neuroimaging tools, e.g. TMS or fMRI.

## *8.3 The future of magnetic stimulation during numerical cognition*

In this thesis TMS was used to investigate the neural patchworks involved in addition and number comparison. In future years, magnetic stimulation could help to

bridge the gap between findings from acalculic patients and from brain imaging studies.

As the first TMS experiment on addition showed, magnetic stimulation can be useful in investigating hemispheric differences. In a recent brain imaging study, for example, Piazza & Butterworth (2001) found that the left hemisphere is active during counting. During estimation, however, they mainly found activations in the right hemisphere. Using TMS while subjects perform either a counting or an estimation task should establish hemispheric differences between counting and estimation more clearly. With TMS the relative contribution of left and right parietal lobes in solving both the estimation and the counting task could be investigated directly. Piazza's & Buterworth's results predict that left parietal TMS should interfere with counting while right parietal TMS should mainly affect performance in estimation.

Furthermore, magnetic stimulation could be used to investigate the validity of models of numerical processing. As discussed in the general introduction, some models of numerical processing make predictions about differences between operations that could explicitly be tested with TMS. For example, if there were separate routes for subtraction and multiplication with underlying anatomical differences, it should be possible to use magnetic stimulation to impair subtraction, but not multiplication or vice versa.

In summary, then, the locations of the areas most critical to theories of cortical processing of quantity are accessible to TMS. This has allowed the investigations detailed in this thesis. It also makes possible further TMS studies on the necessity of areas in number processing. Additionally, in future experiments TMS might be used to investigate the timing of the involvement of an area.

# 9. References


AEEGS (1991). American Electroencephalographic Society guidelines for standard electrode position nomenclature. *Journal of Clinical Neurophysiology*, **8**(2), 200-202.

Agnew, W. F., & McCreery, D. B. (1987). Considerations for safety in the use of extracranial stimulation for motor evoked potentials. *Neurosurgery*, **20**(1), 143-7.

Agnew, W. F., & McCreery, D. B. (1990). Considerations for safety with chronically implanted nerve electrodes. *Epilepsia*, **31 Suppl 2**, S27-32.

Alivisatos, B., & Petrides, M. (1997). Functional activation of the human brain during mental rotation. *Neuropsychologia*, **35**(2), 111-8.

Amassian, V. E. et al. (1994). Human immune functions are differentially affected by left-sided versus right-sided magnetic stimulation of temporo-parieto-occipital cortex. *Neurology*, **44**(Suppl 2), A 133.

Andersen, R. A., & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annu Rev Neurosci*, **25**, 189-220.

Andersen, R. A., Asanuma, C., Essick, G., & Siegel, R. M. (1990). Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. *J Comp Neurol*, **296**(1), 65-113.

Andersen, R. A., Essick, G. K., & Asanuma, C. (1985). Encoding of spatial location by posterior parietal neurons. *Science*, **230**, 456-458.

Andersen, R. A., Snyder, L. H., Bradley, D. C., & Xing, J. (1997). Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annual review of Neuroscience*, **20**, 303-330.

Annas, J. (1976). *Aristotle's Metaphysics: Books M and N.* Oxford: Clarendon Press.

Antell, S. E., & Keating, D. P. (1983). Perception of numerical invariance in neonates. *Child Development*, **54**(3), 695-701.

Aram, D., & Ekelman, B. (1988). Scholastic aptitude and achievement among children with unilateral brain lesions. *Neuropsychologia*, **14**, 903-916.

Arthurs, O. J., & Boniface, S. (2002). How well do we understand the neural origins of the fMRI BOLD signal? *Trends in Neuroscience*, **25**(1), 27-31.

Ashbridge, E., Cowey, A., & Wade, D. (1999). Does parietal cortex contribute to feature binding? *Neuropsychologia*, **37**(9), 999-1004.

Ashbridge, E., Walsh, V., & Cowey, A. (1997). Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia*, **35**(8), 1121-1131.

Ashcraft, M. H. (1995). Cognitive Psychology and simple arithmetic: A Review and Summary of New Directions. *Mathematical Cognition*, **1**(1), 3-34.

Ashcraft, M. H., & Battaglia, J. (1978). Cognitive arithmetic: Evidence for retrieval and decision processes in mental addition. *Journal of Experimental Psychology: Human Learning and Memory*, **4**(5), 527-538.

Ashcraft, M. H., Yamashita, T. S., & Aram, D. M. (1992). Mathematics performance in left and right brain-lesioned children and adolescents. *Brain and Cognition*, **19**(2), 208-252.

Bächtold, D., Baumüller, M., & Brugger, P. (1998). Stimulus-response compatibility in representational space. *Neuropsychologia*, **36**(8), 731-735.

Balakrishnan, J. D., & Ashby, F. G. (1992). Subitizing: Magical numbers or mere superstition? *Psychological Research/Psychologische Forschung*, **54**(2), 80-90.

Bandettini, P. A. (1999). The temporal resolution of functional MRI. In C. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 195-204). Berlin: Springer.

Bandettini, P. A., & Ungerleider, L. G. (2001). From neuron to BOLD: new connections. *Nat Neurosci*, **4**(9), 864-6.

Banks, W. P., Fujii, M., & Kayra-Stuart, F. (1976). Semantic congruity effects in comparative judgements of magnitudes of digits. *Journal of Experimental Psychology: Human Perception and Performance*, **2**, 435-447.

Barker, A. T. (1991). An introduction to the basic principles of magnetic nerve stimulation. *Journal of Clinical Neurophysiology*, **8**, 26-37.

Barker, A. T. (1996). Magnetic Nerve Stimulation - Basic Principles and early development. In J. Nilsson, M. Panizza, & F. Grandori (Eds.), *Advances in Magnetic Stimulation - Mathematical Modeling and Clinical Applications* (Vol. 2, pp. 1-11). Pavia: Fondazione Salvatore Maugeri Edizioni.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex [letter]. *Lancet*, **1**(8437), 1106-7.

Baron-Cohen, S., & Harrison, J.E. (Eds.). (1997). *Synaethesia: classic and contemporary readings* . Oxford: Blackwells.

Batista, A. P., Buneo, C. A., Snyder, L. H., & Andersen, R. A. (1999). Reach plans in eye-centered coordinates. *Science*, **285**(5425), 257-60.

Ben Hamed, S., Duhamel, J. R., Bremmer, F., & Graf, W. (2002). Visual receptive field modulation in the lateral intraparietal area during attentive fixation and free gaze. *Cereb Cortex*, **12**(3), 234-45.

Benacerraf, P., & Putnam, H. (1983). *Philosophy of Mathematics*. Cambridge: Cambridge University Press.

Benson, D. F., & Denckla, M. B. (1969). Verbal paraphasia as a cause of calculation disturbances. *Archives of Neurology*, **21**, 96-102.

Benson, D. F., & Geschwind, N. (1970). Developmental Gerstmann syndrome. *Neurology*, **20**(3), 293-8.

Benton, A. L. (1959). *Right-Left Discrimination and Finger Localization: Development and Pathology*. New York: Hoeber-Harper.

Benton, A. L. (1961). The fiction of the "Gerstmann Syndrome". *Journal of Neurology, Neurosurgery and Psychiatry*, **24**, 176-181.

Benton, A. L. (1992). Gerstmann's Syndrome. *Archives of Neurology*, **49**, 445-447.

Berch, D. B., Foley, E. J., Hill, R. J., & Ryan, P. M. (1999). Extracting parity and magnitude from Arabic numerals: Developmental changes in number processing and mental representation. *Journal of Experimental Child Psychology*, **74**(4), 286-308.

Berger, H. (1926). Über Rechenstörungen bei Herderkrankungen des Grosshirns. *Archiv für Psychiatrie und Nervenkrankheiten*, **78**, 238-263.

Besner, D., & Coltheart, M. (1979). Ideographic and alphabetic processing in skilled reading of English. *Neuropsychologia*, **17**(5), 467-472.

Bestmann, S., Thilo, K. V., Sauner, D., Siebner, H. R., & Rothwell, J. C. (2002). Parietal Magnetic Stimulation Delays Visuomotor Mental Rotation at Increased Processing Demands. *NeuroImage*, **17**, 1512-1520.

Bideaud, J., Meljac, C., & Fischer, J.-P. (Eds.). (1992). *Pathways to number: Children's developing numerical abilities*. Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *J Neurosci*, **17**(1), 353-62.

Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., & Freund, H. (1999a). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur J Neurosci*, **11**(9), 3276-86.

Binkofski, F., Buccino, G., Stephan, K. M., Rizzolatti, G., Seitz, R. J., & Freund, H. J. (1999b). A parieto-premotor network for object manipulation: evidence from neuroimaging. *Exp Brain Res*, **128**(1-2), 210-3.

Binkofski, F., Dohle, C., Posse, S., Stephan, K. M., Hefter, H., Seitz, R. J., & Freund, H. J. (1998). Human anterior intraparietal area subserves prehension: a combined lesion and functional MRI activation study. *Neurology*, **50**(5), 1253-9.

Bisiach, E., & Luzatti, C. (1978). Unilateral neglect of representational space. *Cortex*, **14**, 129-133.

Bisiach, E., & Vallar, G. (1988). Hemineglect in humans. In J. Grafman (Ed.), *Handbook of Neuropsychology* (Vol. 1, pp. 195-222). Amsterdam: Elsevier.

Bohning, D. E., Shastri, A., McConnell, K. A., Nahas, Z., Lorberbaum, J. P., Roberts, D. R., Teneback, C., Vincent, D. J., & George, M. S. (1999). A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. *Biological Psychiatry*, **45**, 385-394.

Boller, F., & Grafman, J. (1983). Acalculia: Historical Development and Current Significance. *Brain and Cognition*, **2**, 205-223.

Brammer, M. J. (2001). Head Motion and its correction. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 243-250). Oxford: Oxford University Press.

Brannon, E. M., & Terrace, H. S. (1998). Ordering of the numerosities 1 to 9 by monkeys. *Science*, **282**(5389), 746-9.

Brasil-Neto, J. P., McShane, L. M., Fuhr, P., Hallett, M., & Cohen, L. G. (1992). Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. *Electroencephalogr Clin Neurophysiol*, **85**(1), 9-16.

Bremmer, F., Schlack, A., Shah, N. J., Zafiris, O., Kubischik, M., Hoffmann, K., Zilles, K., & Fink, G. R. (2001). Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron*, **29**(1), 287-96.

Brissiaud, R. (1992). A tool for number construction: finger symbol sets. In J. Bideaud, C. Meljac, & J.-P. Fischer (Eds.), *Pathways to number: Children's developing numerical abilities* (pp. 41-65). Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.

Brodman, K. (1909). *Vergleichende Lokalisationslehre der Großhirnrinde*. Leipzig: Verlag von Johann Ambrosius Barth.

Brusa, A., Rossi, B., & Tartarini, E. (1960). Syndrome primaire de Gerstmann dans un cas de méningiome frontal de la convexité. *Encéphale*, **49**, 319-328.

Buckley, P. B., & Gillman, C. B. (1974). Comparisons of digits and dot patterns. *Journal of Experimental Psychology*, **103**(6), 1131-1136.

Buneo, C. A., Jarvis, M. R., Batista, A. P., & Andersen, R. A. (2002). Direct visuomotor transformations for reaching. *Nature*, **416**(6881), 632-6.

Bunge, S. A., Hazeltine, E., Scanlon, M. D., Rosen, A. C., & Gabrieli, J. D. E. (2002). Dissociable Contributions of Prefrontal and Parietal Cortices to Response Selection. *NeuroImage*, **17**, 1562-1571.

Burbaud, P., Camus, O., Guehl, D., Bioulac, B., Caille, J. M., & Allard, M. (1999). A functional magnetic resonance imaging study of mental subtraction in human subjects. *Neurosci-Lett*, **273**(3), 195-9.

Burbaud, P., Degreze, P., Lafon, P., Franconi, J. M., Bouligand, B., Bioulac, B., Caille, J. M., & Allard, M. (1995). Lateralization of prefrontal activation during internal mental calculation: a functional magnetic resonance imaging study. *J-Neurophysiol*, **74**(5), 2194-200.

Burton, H., & Sinclair, R. J. (2000). Attending to and remembering tactile stimuli: a review of brain imaging data and single-neuron responses. *J Clin Neurophysiol*, **17**(6), 575-91.

Burton, H., Abend, N. S., MacLeod, A. M., Sinclair, R. J., Snyder, A. Z., & Raichle, M. E. (1999). Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study. *Cereb Cortex*, **9**(7), 662-74.

Butterworth, B. (1999). *The Mathematical Brain*. London: Macmillan Publishers Ltd.

Butterworth, B., Cipolotti, L., & Warrington, E. (1996). Short-term memory impairment and arithmetical ability. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology*, **49A**(1), 251-262.

Butterworth, B., Zorzi, M., Girelli, L., & Jonckheere, A. R. (2001). Storage and retrieval of addition facts: The role of number comparison. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology*, **54A**(4), 1005-1029.

Calkins, M. W. (1892). A statistical study of pseudo-chromesthesia and of mental-forms. *American Journal of Psychology*, **5**, 439-464.

Caminiti, R., Genovesio, A., Marconi, B., Mayer, A. B., Onorati, P., Ferraina, S., Mitsuda, T., Giannetti, S., Squatrito, S., Maioli, M. G., & Molinari, M. (1999). Early coding of reaching: frontal and parietal association connections of parieto-occipital cortex. *Eur J Neurosci*, **11**(9), 3339-45.

Campbell, J. I. D. (1995). Mechanisms of simple addition and multiplication: a modified network-interference theory and simulation. *Mathematical Cognition*, **1**(2), 121-164.

Campbell, J. I. D., & Clark, J. M. (1992). Cognitive number processing: an encoding complex perspective. In J. I. D. Campbell (Ed.), *The Nature and Origins of Mathematical Skills* (pp. 457-491). Amsterdam: Elsevier.

Campbell, J. I. D., & Graham, D. J. (1985). Mental multiplication skill: Structure, process, and acquisition. *Canadian Journal of Psychology*, **39**(2), 338-366.

Cappelletti, M., Butterworth, B., & Kopelman, M. E. (2001). Spared numerical abilities in a case of semantic dementia. *Neuropsychologia*, **39**(11), 1224-1239.

Caramazza, A., & McCloskey, M. (1987). Dissociations of calculation processes. In G. Deloche & X. Seron (Eds.), *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* (pp. 221-233). Hillsdale, NJ: Lawrence Erlbaum.

Caramia, M. D., Gigli, G., Iani, C., Desiato, M. T., Diomedi, M., Palmieri, M. G., & Bernardi, G. (1996). Distinguishing forms of generalized epilepsy using magnetic brain stimulation. *Electroencephalogr. Clin. Neurophysiol.*, **98**(1), 14-19.

Carpenter, P. A., Just, M. A., Keller, T. A., Eddy, W., & Thulborn, K. (1999). Graded functional activation in the visuospatial system with the amount of task demand. *J Cogn Neurosci*, **11**(1), 9-24.

Cavada, C. (2001). The visual parietal areas in the macaque monkey: current structural knowledge and ignorance. *Neuroimage*, **14**(1 Pt 2), S21-6.

Cavada, C., & Goldman-Rakic, P. S. (1989a). Posterior parietal cortex in rhesus monkey: I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J Comp Neurol*, **287**(4), 393-421.

Cavada, C., & Goldman-Rakic, P. S. (1989b). Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J Comp Neurol*, **287**(4), 422-45.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suarez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cereb Cortex*, **10**(3), 220-42.

Chao, L. L., & Martin, A. (2000). Representation of manipulable man-made objects in the dorsal stream. *Neuroimage*, **12**(4), 478-84.
Chochon, F., Cohen, L., van de Moortele, P. F., & Dehaene, S. (1999). Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, **11**(6), 617-30.
Chomsky, N. (1993). *Language and Thought.* Wakefield, RI.: Moyer Bell.
Churchland, P. S., & Sejnowski, T. J. (1988). Perspectives on cognitive neuroscience. *Science*, **242**(4879), 741-5.
Cipolotti, L. (1995). Multiple routes for reading words, why not numbers? Evidence from a case of Arabic numeral dyslexia. *Cognitive Neuropsychology*, **12**(3), 313-342.
Cipolotti, L., & Butterworth, B. (1995). Toward a multiroute model of number processing: Impaired number transcoding with preserved calculation skills. *Journal of Experimental Psychology: General*, **124**(4), 375-390.
Cipolotti, L., & de Lacy Costello, A. (1995). Selective impairment for simple division. *Cortex*, **31**(3), 433-449.
Cipolotti, L., & van Harskamp, N. (2001). Disturbances of number processing and calculation. In R. S. Berndt (Ed.), *Language and Aphasia* (Vol. 3, pp. 305-331): Elsevier Science.
Cipolotti, L., Butterworth, B., & Denes, G. (1991). A specific deficit for numbers in a case of dense acalculia. *Brain*, **114**, 2619-2637.
Cipolotti, L., Butterworth, B., & Warrington, E. K. (1994). From "one thousand nine hundred and forty-five" to 1000,945. *Neuropsychologia*, **32**(4), 503-509.
Cohen, L., & Dehaene, S. (1991). Neglect dyslexia for numbers? A case report. *Cognitive Neuropsychology*, **8**(1), 39-58.
Cohen, L., & Dehaene, S. (1994). Amnesia for arithmetic facts: a single case study. *Brain and Language*, **47**, 214-232.
Cohen, L., & Dehaene, S. (1995). Number processing in pure alexia: the effect of of hemispheric asymmetries and task demands. *Neurocase*, **1**, 121-137.
Cohen, L., & Dehaene, S. (1996). Cerebral networks for number processing: Evidence from a case of posterior callosal lesion. *NeuroCase*, **2**, 155-174.
Cohen, L., & Dehaene, S. (2000). Calculating without reading: Unsuspected residual abilities in pure alexia. *Cognitive Neuropsychology*, **17**(6), 563-583.
Cohen, L., Dehaene, S., & Verstichel, P. (1994). Number words and number non-words: A case of deep dyslexia extending to arabic numerals. *Brain*, **117**(2), 267-279.
Cohen, L., Dehaene, S., Chochon, F., Lehericy, S., & Naccache, L. (2000). Language and calculation within the parietal lobe: a combined cognitive, anatomical and fMRI study. *Neuropsychologia*, **38**(10), 1426-1440.
Cohen, Y. E., & Andersen, R. A. (2002). A common reference frame for movement plans in the posterior parietal cortex. *Nat Rev Neurosci*, **3**(7), 553-62.
Colby, C. L. (1999). Parietal cortex constructs action-oriented spatial representations. In N. Burgess, J. O'Keefe (Ed.), *The hippocampal and parietal foundations of spatial cognition* (pp. 104-126). Oxford: OUP.
Colby, C. L., & Duhamel, J. R. (1996). Spatial representations for action in parietal cortex. *Brain Res Cogn Brain Res*, **5**(1-2), 105-15.
Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annu Rev Neurosci*, **22**, 319-49.
Collignon, R., Leclercq, C., & Mahy, J. (1977). Etude de la sémiologie des troubles du calcul observés au cours des lésions corticales. *Acta Neurologica Belgica*, **77**, 257-275.
Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computer Assisted Tomography*, **18**(2), 192-205.
Constantinidis, C., & Steinmetz, M. A. (2001). Neuronal responses in area 7a to multiple-stimulus displays: I. neurons encode the location of the salient stimulus. *Cereb Cortex*, **11**(7), 581-91.
Corbetta, M., & Shulman, G. L. (1999). Human cortical mechanisms of visual attention during orienting and search. In G. W. Humphreys, J. Duncan, & A. Triesman (Eds.), *Attention, Space and Action: Studies in Cognitive Neuroscience* . Oxford: Oxford University Press.
Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, **3**(3), 292-297.
Corthout, E., Uttl, B., Walsh, V., Hallet, M., & Cowey, A. (2000). Plasticity revealed by transcranial magnetic stimulation of early visual cortex. *NeuroReport*, **11**, 1565-1569.
Corthout, E., Uttl, B., Walsh, V., Hallett, M., & Cowey, A. (1999). Timing of activity in early visual cortex as revealed by transcranial magnetic stimulation. *Neuroreport: For Rapid Communication of Neuroscience Research*, **10**(12), 2631-2634.

Counter, S. A., Borg, E., Lofqvist, L., & Brismar, T. (1990). Hearing loss from the acoustic artifact of the coil used in extracranial magnetic stimulation. *Neurology*, **40**(8), 1159-62.
Cowell, S. F., Egan, G. F., Code, C., Harasty, J., & Watson, J. D. G. (2000). The Functional Neuroanatomy of Simple Calculation and Number Repetition: A Parametric PET Activation Study. *NeuroImage*, **12**(5), 565-573.
Cowey, A., & Walsh, V. (2000). Magnetically induced phosphenes in sighted, blind and blindsighted subjects. *NeuroReport*, **11**(14), 3269-3273.
Cracco, R. Q., Amassian, V. E., Maccabee, P. J., & Cracco, J. B. (1989). Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroenceohalography and Clinical Neurophysiology*, **74**, 417-424.
Cracco, R. Q., Cracco, J. B., Maccabee, P. J., & Amassian, V. E. (1999). Cerebral function revealed by transcranial magnetic stimulation. *J Neurosci Methods*, **86**(2), 209-19.
Critchley, M. (1953). *The parietal lobes*. Oxford, England: Williams and Wilkins.
Critchley, M. (1966). The enigma of Gerstmann's syndrome. *Brain*, **89**, 183-198.
Culham, J. C., & Kanwisher, N. G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Curr Opin Neurobiol*, **11**(2), 157-63.
Curry, H. B. (1954). Remarks on the definition and nature of mathematics. *Dialectica*, **8**, 228-233.
Cytowic, R. E. (1989). *Synethesia: A Union of the Senses*. New York: Springer Verlag.
Dagenbach, D., & McCloskey, M. (1992). The organization of arithmetical facts in memory: evidence from a brain-damaged patient. *Brain and Cognition*, **20**, 345-366.
Dahmen, W., Hartje, W., Bussing, A., & Sturm, W. (1982). Disorders of calculation in aphasic patients: spatial and verbal components. *Neuropsychologia*, **20**, 145-153.
Dale, A. M., & Buckner, R. L. (1997). Selective averaging of rapidly presented individual trials using fMRI. *Human Brain Mapping*, **5**, 329-340.
Dantzig, T. (1962). *Number: The Language of Science*. (4th ed.). London: George Allen & Unwin.
d'Arsonval, M. A. (1896). Dispositifs pour la mesure des courants alternatifs de toutes fréquences. *Comptes Rendus*, **3**, 450-451.
De Renzi, E. (1982). *Disorders of Space Exploration and Cognition*. Chichester: Wiley.
Dehaene, S. (1989). The psychophysics of numerical comparison: A reexamination of apparently incompatible data. *Perception & Psychophysics*, **45**(6), 557-566.
Dehaene, S. (1992). Varieties of numerical abilities. Special Issue: Numerical cognition. *Cognition*, **44**(1-2), 1-42.
Dehaene, S. (1996). The organization of brain activations in number comparison: Event-related potentials and the additive-factors method. *Journal of Cognitive Neuroscience*, **8**(1), 47-68.
Dehaene, S. (1999). *The Number Sense*. London: Penguin Books Ltd.
Dehaene, S. (2000). Cerebral Bases of Number Processing and Calculation. In M. S. Gazzanigga (Ed.), *The new cognitive neurosciences* (pp. 987-998). Cambridge, Mass. London: MIT Press.
Dehaene, S., & Cohen, L. (1991). Two mental calculation systems: A case study of severe acalculia with preserved approximation. *Neuropsychologia*, **29**(11), 1045-1074.
Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical Cognition*, **1**(1), 83-120.
Dehaene, S., & Cohen, L. (1997). Cerebral pathways for calculation: double dissociation between rote verbal and quantitative knowledge of arithmetic. *Cortex*, **33**(2), 219-50.
Dehaene, S., Bossini, S., & Giraux, P. (1993). The mental representation of parity and number magnitude. *Journal of Experimental Psychology: General*, **122**(3), 371-396.
Dehaene, S., Dehaene-Lambertz, G., & Cohen, L. (1998). Abstract representations of numbers in the animal and human brain. *Trends in Neuroscience*, **21**, 355-361.
Dehaene, S., Dupoux, E., & Mehler, J. (1990). Is numerical comparison digital? Analogical and symbolic effects in two-digit number comparison. *Journal of Experimental Psychology: Human Perception & Performance*, **16**(3), 626-641.
Dehaene, S., Spelke, E., Pinel, P., Stanescu, R., & Tsivkin, S. (1999). Sources of mathematical thinking: Behavioral and brain-imaging evidence. *Science*, **284**(5416), 970-974.
Dehaene, S., Tzourio, N., Frak, V., Raynaud, L., & et al. (1996). Cerebral activations during number multiplication and comparison: A PET study. *Neuropsychologia*, **34**(11), 1097-1106.
Deiber, M.-P., Ibanez, V., Sadato, N., & Hallett, M. (1996). Cerebral structures participating in motor preparation in humans: A positron emission tomography study. *Journal of Neurophysiology*, **75**(1), 233-247.
Delazer, M., & Benke, T. (1997). Arithmetic facts without meaning. *Cortex*, **33**(4), 697-710.

Delazer, M., & Butterworth, B. (1997). A dissociation of number meanings. *Cognitive Neuropsychology*, **14**(4), 613-636.
Delazer, M., & Denes, G. (1998). Writing Arabic numerals in an agraphic patient. *Brain and Language*, **64**, 257-266.
Delazer, M., & Girelli, L. (1997). When 'Alfa Romeo' facilitates 164 semantic effects in verbal number production. *Neurocase*, **3**, 461-475.
Deloche, G., & Seron, X. (1982). From one to 1: An analysis of a transcoding process by means of neuropsychological data. *Cognition*, **12**(119-149).
Deloche, G., & Seron, X. (1987). *Mathematical Disabilities: A Cognitive Neuropsychological Perspective*. Hillsdale, NJ: Lawrence Erlbaum.
Deloche, G., Souza, L., Willadino-Braga, L., & Dellatolas, G. (1999). Assessment of calculation and number processing by adults: cognitive and neuropsychological issues. *Perceptual and Motor Skills*, **89**, 707-738.
Devlin, J. T., Moore, C. J., Mummery, C. J., Gorno-Tempini, M. L., Phillips, J. A., Noppeney, U., Frackowiak, R. S., Friston, K. J., & Price, C. J. (2002). Anatomic constraints on cognitive theories of category specificity. *Neuroimage*, **15**(3), 675-85.
Dhuna, A., Gates, J., & Pascual-Leone, A. (1991). Transcranial magnetic stimulation in patients with epilepsy. *Neurology*, **41**, 1067-7.
Diederich, A. (1995). Intersensory facilitation of reaction time: Evaluation of counter and diffusion coactivation models. *Journal of Mathematical Psychology*, **39**(2), 197-215.
Donaldson, D. L., & Buckner, R. L. (2001). Effective paradigm design. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 177-195). Oxford: Oxford University Press.
Donlan, C. (1998). *The development of mathematical skills*. Hove: Psychology Press.
Donlan, C. (2002). *Perceptual bases of number representation or what if there isn't a mental number line?* Presentation at the ICN, London and personal communication.
Donlan, C., & Gourlay, S. (1999). The importance of non-verbal skills in the acquisition of place-value knowledge: Evidence from normally-developing and language-impaired children. *British Journal of Developmental Psychology*, **17**(1), 1-19.
Donner, T., Kettermann, A., Diesch, E., Ostendorf, F., Villringer, A., & Brandt, S.-A. (2000). Involvement of the human frontal eye field and multiple parietal areas in covert visual selection during conjunction search. *European Journal of Neuroscience*, **12**(9), 3407-3414.
Dowker, A. (1997). Young children's addition estimates. *Mathematical Cognition*, **3**(4), 141-154.
Dowker, A., Flood, A., Griffiths, H., Harriss, L., & Hook, L. (1995). Estimation strategies of four groups. *Mathematical Cognition*, **2**(2), 113-135.
Dufft, C., & Ulrich, R. (1999). Intersensorische Erleichterung: Auch visuelle Begleitreize können die Reaktionszeit verkürzen. *Zeitschrift für Experimentelle Psychologie*, **46**(1), 16-27.
Duncan, J., Seitz, R. J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F. N., & Emslie, H. (2000). A neural basis for general intelligence. *Science*, **289**(5478), 457-60.
Duong, T. Q., Kim, D. S., Ugurbil, K., & Kim, S. G. (2001). Localized cerebral blood flow response at submillimeter columnar resolution. *Proc Natl Acad Sci U S A*, **98**(19), 10904-9.
Duvernoy, H. M., Bourgouin, P., Cabanis, E. A., & Cattin, F. (1999). *The Human Brain: Surface, Three-Dimensional Sectional Anatomy With MRI, and Blood Supply*. New York: Springer.
Edgley, S. A., Eyre, J. A., Lemon, R. N., & Miller, S. (1997). Comparison of activation of corticospinal neurons and spinal motor neurons by magnetic and electrical transcranial stimulation in the lumbosacral cord of the anaesthetized monkey. *Brain*, **120**(Pt 5), 839-53.
Eidelberg, D., & Galaburda, A. M. (1984). Inferior parietal lobule. Divergent architectonic asymmetries in the human brain. *Arch Neurol*, **41**(8), 843-52.
Ellison, A. (2000). What does the parietal cortex contribute to visual search? Sixth International Conference on Functional Mapping of the Human Brain. *NeuroImage*, **10**, S6.
Engel, S. A., Glover, G. H., & Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cerebral Cortex*, **7**(2), 181-92.
Epstein, C. M. (1998). Transcranial Magnetic Stimulation: Language function. *Journal of Clinical Neurophysiology*, **15**, 325-332.
Ettlinger, G., & Kalsbeck, J. E. (1962). Changes in tactile discrimination and in visual reaching after successive and simultaneous bilateral posterior parietal ablations in the monkey. *Journal of Neurology, Neurosurgery and Psychiatry*, **25**, 256-268.

Evans, A. C., Collins, D. L., & Milner, B. (1992). An MRI-based stereotaxic atlas from 250 normal young subjects. *Society for Neuroscience Abstract*, **18**, 408.
Faillenot, I., Toni, I., Decety, J., Gregoire, M. C., & Jeannerod, M. (1997). Visual pathways for object-oriented action and object recognition: functional anatomy with PET. *Cereb Cortex*, **7**(1), 77-85.
Faraday, M. (1832). *Experimental researches in electricity*. London: Richard & John Edward Taylor.
Faugier-Grimaud, S., Frenois, C., & Peronnet, F. (1985). Effects of posterior parietal lesions on visually guided movements in monkeys. *Exp Brain Res*, **59**(1), 125-38.
Faugier-Grimaud, S., Frenois, C., & Stein, D. G. (1978). Effects of posterior parietal lesions on visually guided behavior in monkeys. *Neuropsychologia*, **16**(2), 151-68.
Fayol, M., Barrouillet, P., & Marinthe, C. (1998). Predicting arithmetical achievement from neuro-psychological performance: A longitudinal study. *Cognition*, **68**(2), B63-B70.
Ferrier, D. (1875). Experiments on the brains of monkeys. *Philosophical Transactions of the Royal Society London*, **165**, 433.
Ferrier, D. (1876). *The functions of the brain*. London: Dawsons.
Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orabn, G. A. (in press). Parietal representation of symbolic and non-symbolic magnitude. *Journal of Cognitive Neuroscience*.
Fischer, J. P. (1992). Subitizing: the discontinuity after three. In J. Bideaud, C. Meljac, & J.-P. Fischer (Eds.), *Pathways to number: Children's developing numerical abilities* (pp. 191-208). Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.
Fischer, M. H. (in press). Number processing induces spatial performance biases. *Neurology*.
Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine*, **33**, 636-647.
Forrest, D. (2000). *Hyponotism: A History*. London: Penguin Books.
Frackowiak, R. S. (1997). Functional Imaging with Magnetic Resonance. In R. S. Frackowiak, K. J. Friston, C. D. Frith, R. J. Donlan, & J. C. Mazziotta (Eds.), *Human Brain Function* (pp. 467-486). Academic press.
Frege, G. (1903). *Grundgesetze der Arithmetik 2*. Hildesheim: Olms.
Friedman-Hill, S. R., Robertson, L. C., & Treisman, A. (1995). Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions. *Science*, **269**(5225), 853-5.
Friston, K. J. (1997). Imaging cognitive anatomy. *Trends in Cognitive Sciences*, **1**(1), 21-27.
Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995a). Spatial registration and normalization of images. *Human Brain Mapping*, **2**, 165-189.
Friston, K. J., Holmes, A., Worsley, K., Poline, J.-B., Frith, C., & Frackowiak, R. (1995b). Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping*, **2**, 189-210.
Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the Significance of Focal Activations Using their Spatial Extent. *Human Brain Mapping*, **1**, 214-220.
Friston, K. J., Zarahn, E., Josephs, O., Henson, R. N., & Dale, A. M. (1999). Stochastic designs in event-related fMRI. *Neuroimage*, **10**(5), 607-19.
Fulbright, R. K., Molfese, D. L., Stevens, A. A., Skudlarski, P., Lacadie, C. M., & Gore, J. C. (2000). Cerebral Activation during Multiplication: A Functional MR Imaging Study of Number Processing. *American Journal of Neuroradiology*, **21**, 1048-1054.
Gadsby, A. (Ed.). (1995). *Dictionary of Contemporary English* (third edition). München: Langenscheidt-Longman GmbH.
Gallese, V., Murata, A., Kaseda, M., Niki, N., & Sakata, H. (1994). Deficit of hand preshaping after muscimol injection in monkey parietal cortex. *Neuroreport*, **5**(12), 1525-9.
Galletti, C., Fattori, P., Battaglini, P. P., Shipp, S., & Zeki, S. (1996). Functional demarcation of a border between areas V6 and V6A in the superior parietal gyrus of the macaque monkey. *Eur J Neurosci*, **8**(1), 30-52.
Galletti, C., Fattori, P., Gamberini, M., & Kutz, D. F. (1999). The cortical visual area V6: brain location and visual topography. *Eur J Neurosci*, **11**(11), 3922-36.
Galletti, C., Fattori, P., Kutz, D. F., & Gamberini, M. (1999). Brain location and visual topography of cortical area V6A in the macaque monkey. *Eur J Neurosci*, **11**(2), 575-82.
Gallistel, C. R., & Gelman, R. (1991). Subitizing: The preverbal counting process. In W. Kessen & A. Ortony (Eds.). *Memories, thoughts, and emotions: Essays in honor of George Mandler*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc
Gallistel, C. R., & Gelman, R. (1992). Preverbal and verbal counting and computation. *Cognition*, **44**(1-2), 43-74.
Galton, F. (1880a). Visualised numerals. *Nature*, **21**, 252-256.

Galton, F. (1880b). Visualised numerals. *Nature*, **11**, 494-495.
Galvani, L. (1894). Abhandlung über die Kräfte der Elektrizität bei der Muskelbewegung (De viribus electricitatis in motu musculari. 1791). *Ostwald's Klassiker der exakten Wissenschaften* (Vol. 52). Leipzig.
Garner, W. R., Podgorny, P., & Frasca, E. M. (1982). Physical and cognitive dimensions in stimulus comparison. *Perception and Psychophysics*, **31**(6), 507-522.
Gates, J. R., Dhuna, A., & Pascual-Leone, A. (1992). Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. *Epilepsia*, **33**(3), 504-8.
Gattis, M. (Ed.). (2001). *Spatial schemas and abstract thought*. Cambridge, MA, US: The MIT Press.
Gauthier, I., Hayward, W. G., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (2002). BOLD activity during mental rotation and viewpoint-dependent object recognition. *Neuron*, **34**(1), 161-71.
Gazzaniga, M. S., & Smylie, C. E. (1984). Dissociation of language and cognition: A psychological profile of two disconnected right hemispheres. *Brain*, **107**, 145-153.
Gelman, R., & Gallistel, C. R. (1978). *The child's understanding of number*: Cambridge, MA, Harvard U Press. (1978).
George, M. S., Wassermann, E. M., Williams, W. A., Steppel, J., Pascual-Leone, A., Basser, P., Hallett, M., & Post, R. M. (1996). Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neuropsychiatry Clin Neurosci*, **8**(2), 172-80.
George, M. S., Nahas., Z., Kozel, F. A., Goldman, J., Molloy, M., & Oliver, N. (1999). Improvement of depression following transcranial magnetic stimulation. *Current Psychiatry Reports*, **1**(2), 114-124.
Gerstmann, J. (1924). Eine umschriebene Störung der Orientierung am eigenen Körper. *Wiener Klinische Wochenzeitschrift*, **40**, 1010 - 1012.
Gerstmann, J. (1930). Zur Symptomatologie der Hirnläsionen in Übergangsgebiet der unteren Parietal- und mittleren Occipitalwindung. *Nervenarzt*, **3**, 691-695.
Giaquinto, M. (1993). Visualizing in arithmetic. *Philosophy and Phenomenological Research*, **LIII**(2), 385-396.
Girelli, L., & Delazer, M. (1996). Subtraction bugs in an acalculic patient. *Cortex*, **32**, 547-555.
Girelli, L., Delazer, M., Semenza, C., & Denes, G. (1996). The representation of arithmetical facts: evidence from two rehabilitation studies. *Cortex*, **32**, 49-66.
Gitelman, D. R., Nobre, A. C., Parrish, T. B., LaBar, K. S., Kim, Y. H., Meyer, J. R., & Mesulam, M. (1999). A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. *Brain*, **122**(Pt 6), 1093-106.
Gjedde, A. (2001). Brain energy metabolism and the physiological basis of the haemodynamic response. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 37-65). Oxford: Oxford University Press.
Gold, J. I., & Shadlen, M. N. (2001). Neural computations that underlie decisions about sensory stimuli. *Trends in Cognitive Science*, **5**(1), 10-16.
Gonzales, E., & Kolers, P. (1982). Mental manipulation of arithmetic symbols. *Journal of Experimental Psychology: Learning, Memory and Cognition*, **8**, 308-319.
Gonzales, E., & Kolers, P. (1987). Notational constraints on mental operations. In G. Deloche & X. Seron (Eds.), *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* (pp. 27-42). Hillsdale, NJ: Lawrende Erlbaum.
Gordon, B., Lesser, R. P., Rance, N. E., Hart, J., Jr., Webber, R., Uematsu, S., & Fisher, R. S. (1990). Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation. *Electroencephalogr Clin Neurophysiol*, **75**(5), 371-7.
Gottlieb, J. P., Kusunoki, M., & Goldberg, M. E. (1998). The representation of visual salience in monkey parietal cortex. *Nature*, **391**(6666), 481-4.
Grafman, J., Kampen, D., Rosenberg, J., Salazar, A., & Boller, F. (1989). The progressive breakdown of number processing and calculation ability: A case study. *Cortex*, **25**, 121-133.
Grafman, J., Passafiume, D., Faglioni, P., & Boller, F. (1982). Calculation disturbances in adults with focal hemispheric damage. *Cortex*, **18**(1), 37-50.
Graziano, M. S., Cooke, D. F., & Taylor, C. S. (2000). Coding the location of the arm by sight. *Science*, **290**(5497), 1782-6.
Greenberg, B. D., Ziemann, U., Cora-Locatelli, G., Harmon, A., Murphy, D. L., Keel, J. C., & Wassermann, E. M. (2000). Altered cortical excitability in obsessive-compulsive disorder. *Neurology*, **54**(1), 142-7.
Groen, G.-J., & Parkman, J.-M. (1972). A chronometric analysis of simple addition. *Psychological Review*, **79**(4), 329-343.

Gruber, O., Indefrey, P., Steinmetz, H., & Kleinschmidt, A. (2001). Dissociating Neural Correlates of Cognitive Components in Mental Calculation. *Cerebral Cortex*, **11**, 350-359.
Grüsser, O.-J., & Landis, T. (Eds.). (1991). *Visual Agnosias and other disturbances of visual perception and cognition* (Vol. 12). Houndsmills: The Macmillian Press Ltd.
Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Review Neuroscience*, **2**(10), 685-94.
Guttman, E. (1936). Congenital arithmetic disability and acalculia. *British Journal of Medical Psychology*, **16**, 16-35.
Halligan, P. W., & Marshall, J. C. (1994). Completion in visuo-spatial neglect: a case study. *Cortex*, **30**(4), 685-94.
Hamann, M..S., & Ashcraft, M. H. (1985). Simple and complex mental addition across development. *Journal-of-Experimental-Child-Psychology.*, **40**(1), 49-72.
Hatta, T., Hirose, T., Ikeda, K., & Fukuhara, H. (1989). Digit Memory of Soroban Experts: Evidence of Utilization of Mental Imagery. *Applied Cognitive Psychology*, **3**, 23-33.
Hauser, M. D., Carey, S., & Hauser, L. B. (2000). Spontaneous number representation in semi-free-ranging rhesus monkeys. *Proc R Soc Lond B Biol Sci*, **267**(1445), 829-33.
Hayes, J. R. (1973). On the function of visual imagery in elementary mathematics. In W. G. Chase (Ed.), *Visual Information Processing* (pp. 177-214). New York: Academic Press.
Hécaen, H., Angelergues, R., & Houllier, S. (1961). Les variétés cliniques des acalculias au cours des lésions rétrolandiques: Approche statistique du problème. *Rev. Neurol. (Paris)*, **102**, 85-103.
Heeger, D. J., & Ress, D. (2002). What does fMRI tell us about neuronal activity? *Nature Review Neuroscience*, **3**(2), 142-51.
Heeger, D. J., Huk, A. C., Geisler, W. S., & Albrecht, D. G. (2000). Spikes versus BOLD: what does neuroimaging tell us about neuronal activity? *Nature Neuroscience*, **3**(7), 631-3.
Heilman, K. M. (1979). Neglect and related disorders. In K. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (pp. 268-307). Oxford: OUP.
Heimburger, R. F., DeMeyer, W., & Reitan, R. M. (1964). Implications of the Gerstmann syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 52-57.
Henschen, E. (1919). Über Sprach-, Musik- und Rechenmechanismen und ihre Lokalisationen im Großhirn. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **52**, 273-298.
Henschen, S. E. (1920). *Klinische und anatomische Beiträge zur Pathologie des Gehirns*. Stockholm: Nordiska.
Hermelin, B., & O'Connor, N. (1990). Factors and primes: a specific numerical ability. *Psychol Med*, **20**(1), 163-9.
Hershenon, M. (1962). Reaction time as a measure of intersensory facilitation. *Journal of Experimental Psychology*, **63**(289-93).
Hittmaier-Delazer, M., Sailer, U., & Benke, T. (1995). Impaired arithmetic facts but intact conceptual knowledge - a single case study of dyscalculia. *Cortex*, **31**, 139-148.
Hittmaier-Delazer, M., Semenza, C., & Denes, G. (1994). Concepts and facts in calculation. *Brain*, **117**, 715-728.
Hoge, R. D., & Pike, G. B. (2001). Quantitative measurement using fMRI. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 159-174). Oxford: Oxford University Press.
Hunter, M. L. (1964). *Memory*. (revised edition ed.). Harmondsworth: Penguin.
Hyvärinen, J. (1982). *The parietal cortex of monkey and man*. Berlin, Heidelberg, New York: Springer.
Hyvärinen, J., & Poranen, A. (1974). Functions of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain*, **97**, 673-692.
Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science*, **286**(5449), 2526-8.
Ifrah, G. (1994). *The universal history of numbers*. London: The Harvill Press Ltd.
Iggo, A. (Ed.). (1973). *Somatosensory System* (Vol. 2). New York: Springer Verlag.
Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport*, **10**, 3537-3540.
Iriki, A., Tanaka, M., & Iwamura, Y. (1996). Coding of modified body schema during tool use by macaque postcentral neurones. *Neuroreport*, **7**(14), 2325-30.
Isaacs, E. B., Edmonds, C. J., Lucas, A., & Gadian, D. G. (2001). Calculation difficulties in children of very low birthweight: a neural correlate. *Brain*, **124**(Pt 9), 1701-7.
Jackson, M., & Warrington, E. K. (1986). Arithmetic skills in patients with unilateral cerebral lesions. *Cortex*, **22**(4), 611-20.
Jaquette, D. (2001). *Philosophy of mathematics : an anthology*. Malden, MA: Blackwell Publishers.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frakowiak, R. S. J., & Passingham, R. E. (1994). Motor Sequence Learning: A study with Positron Emission Tomography. *Neuroscience*, **14**, 3775-3790.

Jenkinson, M. (2001). Registration, brain atlases and cortical flattening. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 271-294). Oxford: Oxford University Press.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, **5**, 143-156.

Jensen, E. M., Reese, E. P., & Reese, T. W. (1950). The subitizing and counting of visually presented fields of dots. *Journal of Psychology*, **30**, 363-392.

Jezzard, P., & Clare, S. (2001). Principles of nuclear magnetic resonance and MRI. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 67-92). Oxford: Oxford University Press.

Johansen-Berg, H., & Lloyd, D. M. (2000). The physiology and psychology of selective attention to touch. *Front Biosci*, **5**, D 894-904.

Johansen-Berg, H., Christensen, V., Woolrich, M., & Matthews, P. M. (2000). Attention to touch modulates activity in both primary and secondary somatosensory areas. *Neuroreport*, **11**(6), 1237-41.

Jones, R. A., Brookes, J. A., & Moonen, C. T. W. (2001). Ultra-fast fMRI. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 93-108). Oxford: Oxford University Press.

Jordan, K., Heinze, H. J., Lutz, K., Kanowski, M., & Jancke, L. (2001). Cortical activations during the mental rotation of different visual objects. *Neuroimage*, **13**(1), 143-52.

Kalaska, J. F., & Crammond, D. J. (1995). Deciding not to GO: neuronal correlates of response selection in a GO/NOGO task in primate premotor and parietal cortex. *Cereb Cortex*, **5**(5), 410-28.

Kalaska, J. F., & Hyde, M. L. (1985). Area 4 and area 5: differences between the load direction-dependent discharge variability of cells during active postural fixation. *Exp Brain Res*, **59**(1), 197-202.

Kant, I. (1900). *Kant's gesammelte Schriften*. Berlin: G. Reimer.

Karmiloff-Smith, A. (1992). *Beyond modularity: a developmental perspective on cognitive science*. London: MIT Press.

Karnath, H. O. (2001). New insights into the functions of the superior temporal cortex. *Nat Rev Neurosci*, **2**(8), 568-76.

Kaufman, E. L., Lord, M. W., Reese, T. W., & Volkmann, J. (1949). The discrimination of visual number. *American Journal of Psychology*, **62**, 498-525.

Kazui, H., Kitagaki, H., & Mori, E. (2000). Cortical activation during retrieval of arithmetical facts and actual calculation: a functional magnetic resonance imaging study. *Psychiatry Clin Neurosci*, **54**(4), 479-85.

Kelly, S. J., Macaruso, P., & Sokol, S. M. (1997). Mental calculation in an autistic savant: a case study. *Journal of Clinical and Experimental Neuropsychology*, **19**, 172-184.

Kerkhoff, G. (2001). Spatial hemineglect in humans. *Progress in Neurobiology*, **63**(1), 1-27.

Kertzman, C., Schwarz, U., Zeffiro, T. A., & Hallett, M. (1997). The role of posterior parietal cortex in visually guided reaching movements in humans. *Exp Brain Res*, **114**(1), 170-83.

Kew, J. J., Ridding, M. C., Rothwell, J. C., Passingham, R. E., Leigh, P. N., Sooriakumaran, S., Frackowiak, R. S., & Brooks, D. J. (1994). Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation. *Journal of Neurophysiology*, **72**(5), 2517-24.

Kim, D. S., Duong, T. Q., & Kim, S. G. (2000). High-resolution mapping of iso-orientation columns by fMRI. *Nature Neuroscience*, **3**(2), 164-9.

Kim, S. G., Tsekos, N. V., & Ashe, J. (1997). Multi-slice perfusion-based functional MRI using the FAIR technique: comparison of CBF and BOLD effects. *NMR in Biomedicine*, **10**(4-5), 191-6.

Kinsbourne, M., & Warrington, E. (1962). A study on finger agnosia. *Brain*, **85**, 47-66.

Krapf, E. (1937). Über Akalkulie. *Neurologie und Psychologie*, **39**, 330-334.

Krueger, L.-E., & Hallford, E.-W. (1984). Why 2 + 2 = 5 looks so wrong: On the odd-even rule in sum verification. *Memory and Cognition*, **12**(2), 171-180.

Laiacona, M., & Lunghi, A. (1997). A case of concomitant impairment of operational signs and punctuation marks. *Neuropsychologia*, **35**, 325-332.

Lampl, Y., Eshel, Y., Gilad, R., & Sarova-Pinhas, I. (1994). Selective acalculia with sparing of the subtraction process in a patient with left parieto-temporal haemorrhage. *Neurology*, **44**, 1759-1761.

Lawler, K. A., & Cowey, A. (1987). On the role of posterior parietal and prefrontal cortex in visuo- spatial perception and attention. *Exp Brain Res*, **65**(3), 695-8.

LeClec'H, G., Dehaene, S., Cohen, L., Mehler, J., Dupoux, E., Poline, J. B., Lehéricy, S., Moortele, P. F., & Bihan, D. L. (2000). Distinct Cortical Areas for Names of Numbers and Body Parts Independent of Language and Input Modality. *NeuroImage*, **12**(4), 381-391.

Lee, K. M. (2000). Cortical areas differentially involved in multiplication and subtraction: a functional magnetic resonance imaging study and correlation with a case of selective acalculia. *Ann Neurol*, **48**(4), 657-61.
LeFevre, J. A., & Kulak, A. G. (1994). Individual differences in the obligatory activation of addition facts. *Memory and Cognition*, **22**(2), 188-200.
LeFevre, J. A., Bisanz, J., Daley, K. E., Buffone, L., & et al. (1996). Multiple routes to solution of single-digit multiplication problems. *Journal of Experimental Psychology: General*, **125**(3), 284-306.
LeFevre, J. A., Sadesky, G. S., & Bisanz, J. (1996). Selection of procedures in mental addition: Reassessing the problem size effect in adults. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **22**(1), 216-230.
Leinonen, L., & Nyman, G. (1979). II. Functional properties of cells in anterolateral part of area 7 associative face area of awake monkeys. *Exp Brain Res*, **34**(2), 321-33.
Levinovitz, A. W., & Ringertz, N. (Eds.). (2001). *The Nobel Prize: The First 100 Years*: Imperial College Press and World Scientific Publishing Co.
Lewandowsky, M., & Stadelmann, E. (1908). Über einen bemerkenswerten Fall von Hirnblutung und über Rechenstörungen bei Herderkrankungen des Gehirns. *Zeitschrift für Psychologie und Neurologie*, **11**, 249ß265.
Livingston, J. D. (1996). *Driving force: the natural magic of magnets*. Cambridge: Harvard University Press.
Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, **412**(6843), 150-7.
Luchelli, F., & De Renzi, E. (1993). Primary dyscalculia after a medial frontal lesion of the left hemisphere. *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 304-307.
Luria, A. (1966). *Higher cortical functions in man*. New York: Basic Books.
Lynch, J. C., & McLaren, J. W. (1983). Optokinetic nystagmus deficits following parieto-occipital cortex lesions in monkeys. *Exp Brain Res*, **49**(1), 125-30.
Lynch, J. C., & McLaren, J. W. (1989). Deficits of visual attention and saccadic eye movements after lesions of parietooccipital cortex in monkeys. *J Neurophysiol*, **61**(1), 74-90.
Lynch, J. C., Graybiel, A. M., & Lobeck, L. J. (1985). The differential projection of two cytoarchitectonic subregions of the inferior parietal lobule of macaque upon the deep layers of the superior colliculus. *J Comp Neurol*, **235**(2), 241-54.
Macaruso, P., McCloskey, M., & Aliminosa, D. (1993). The functional architecture of the cognitive numerical processing system: evidence from a patient with multiple impairments. *Cognitive Neuropsychology*, **10**, 341-376.
Malonek, D., & Grinvald, A. (1996). Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. *Science*, **272**(5261), 551-4.
Mandler, G., & Shebo, B.-J. (1982). Subitizing: An analysis of its component processes. *Journal of Experimental Psychology: General*, **111**(1), 1-22.
Martins, I. P., Parreira, J., Albuquerque, L., & Ferro, J. M. (1999). Capacités de calcul chez des enfants scolarisés avec des lésions cérébrales acquises. *A.N.A.E.*, **51**, 6-12.
Marzi, C. A., Miniussi, C., Maravita, A., Bertolasi, L., Zanette, G., Rothwell, J. C., & Sanes, J. N. (1998). Transcranial magnetic stimulation selectively impairs interhemispheric transfer of visuo-motor information in humans. *Exp Brain Res*, **118**(3), 435-8.
Masur, H., Papke, K., & Oberwittler, C. (1993). Suppression of visual perception by transcranial magnetic stimulation: Experimental findings in healthy subjects and patients with optic neuritis. *Electroencephalography & Clinical Neurophysiology*, **86**(4), 259-267.
Matsuzawa, T. (1985). Use of numbers by a chimpanzee. *Nature*, **315**(6014), 57-59.
Matthews, P. M. (2001). An introduction to functional magnetic resonance imaging of the brain. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 3-34). Oxford: Oxford University Press.
Mayer, E., Martory, M. D., Pegna, A. J., Landis, T., Delavelle, J., & Annoni, J. M. (1999). A pure case of Gerstmann syndrome with a subangular lesion. *Brain*, **122**(Pt 6), 1107-20.
Mazzoni, M., Pardoni, L., Giorgetti, V., & Arena, R. (1990). Gerstmann syndrome: a case report. *Cortex*, **26**, 459-467.
McCloskey, M. (1992). Cognitive mechanisms in numerical processing: evidence from acquired dyscalculia. *Cognition*, **44**, 107-157.

McCloskey, M., Aliminosa, D., & Sokol, S. M. (1991). Facts, rules, and procedures in normal calculation: Evidence from multiple single-patient studies of impaired arithmetic fact retrieval. *Brain and Cognition*, **17**, 154-203.

McCloskey, M., Caramazza, A., & Basili, A. (1985). Cognitive mechanisms in number processing and calculation: evidence from dyscalculia. *Brain and Cognition*, **4**, 171-196.

McCloskey, M., Sokol, S. M., & Goodman, R. A. (1986). Cognitive processes in verbal-numeral production: inferences from the performance of brain-damaged subjects. *Journal of Experimental Psychology: General*, **115**(4), 307-330.

McCloskey, M., Sokol, S. M., Goodman-Schulman, R. A., & Caramazza, A. (1990). Cognitive representations and processes in number production: evidence from cases of acquired dyscalculia. In A. Caramazza (Ed.), *Advances in Cognitive Neuropsychology and Neurolinguistics* (pp. 1-32). Hillsdale, NJ: Lawrence Erlbaum.

McKeown, M. J., Makeig, S., Brown, G. G., Jung, T. P., Kindermann, S. S., Bell, A. J., & Sejnowski, T. J. (1998). Analysis of fMRI data by blind separation into independent spatial components. *Human Brain Mapping*, **6**(3), 160-88.

McNeal, D. R. (1977). 2000 years of electrical stimulation. In T. F. Hambrecht & J. B. Reswick (Eds.), *Functional Electrical Stimulation* (pp. 3-35). New York: Marcel Dekker.

McNeil, J., & Warrington, E. K. (1994). A dissociation between addition and subtraction with written calculation. *Neuropsychologia*, **32**, 717-728.

Menninger, K. (1969). *Number Words and Number Symbols: A Cultural History of Numbers*. Cambridge, MA: MIT Press.

Menon, R. S. (2001). Imaging function in the working brain with fMRI. *Current Opinion in Neurobiology*, **11**(5), 630-6.

Menon, R. S., & Goodyear, B. G. (1999). Submillimeter functional localization in human striate cortex using BOLD contrast at 4 Tesla: implications for the vascular point-spread function. *Magn Reson Med*, **41**(2), 230-5.

Menon, R. S., & Goodyear, B. G. (2001). Spatial and temporal resolution in fMRI. In P. M. M. Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 145-158). Oxford: Oxford University Press.

Menon, R. S., & Kim, S. G. (1999). Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends in Cognitive Science*, **3**(6), 207-216.

Menon, V., Rivera, S. M., White, C. D., Eliez, S., Glover, G. H., & Reiss, A. L. (2000). Functional optimization of arithmetic processing in perfect performers. *Cognitive Brain Research*, **9**(3), 343-345.

Menon, V., Rivera, S. M., White, C. D., Glover, G. H., & Reiss, A. L. (2000). Dissociating Prefrontal and Parietal Cortex Activation during Arithmetic Processing. *NeuroImage*, **12**, 357-365.

Mesulam, M. M. (1981). A cortical network for directed attention and unilateral neglect. *Ann Neurol*, **10**(4), 309-25.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage*, **11**(6 Pt 1), 735-59.

Miller, K., Perlmutter, M., & Keating, D. (1984). Cognitive arithmetic: Comparison of operations. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **10**(1), 46-60.

Millett, N. B. (1990). The Narmer Macehead and Related Objects. *Journal of the American Research Center in Egypt*, **27**, 53-59.

Milner, A. D., & Goodale, M. A. (1995). *The visual brain in action*. Oxford: OUP.

Morris, H. H., Lüders, H., Lesser, R. P., Dinner, D. S., & Hahn, J. (1984). Transient neuropsychological abnormalities (including Gerstmann's syndrome) during cortical stimulation. *Neurology*, **34**, 877-883.

Mortifee, P., Stewart, H., Schulzer, M., & Eisen, A. (1994). Reliability of transcranial magnetic stimulation for mapping the human motor cortex. *Electroencephalography & Clinical Neurophysiology: Electromyography & Motor Control*, **93**(2), 131-137.

Morton, D. M. (1936). Number forms and arithmetical ability in children. *British Journal of Educational Psychology*, **6**, 58-73.

Mountcastle, V. B., Lynch, J. C., Georgopoulus, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: command function of operations within extrapersonal space. *Journal of Neurophysiology*, **38**, 871-907.

Moyer, R. S., & Landauer, T. K. (1967). Time Required For Judgements of Numerical Inequality. *Nature*, **215**(5109)), 1519-1520.

Naccache, L., & Dehaene, S. (2001). The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cereb Cortex*, **11**(10), 966-74.

Natorp, P. (1910). *Die logischen Grundlagen der exakten Wissenschaften*. Berlin: B.G. Teubner.

Nickerson, R. S. (1973). Intersensory facilitation of reaction time: energy summation or preparation enhancement? *Psychol Rev*, **80**(6), 489-509.

Nobre, A. C., Gitelman, D. R., Dias, E. C., & Mesulam, M. M. (2000). Covert visual spatial orienting and saccades: overlapping neural systems. *Neuroimage*, **11**(3), 210-6.

Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain*, **120**(Pt 3), 515-33.

Noël, M. P., & Seron, X. (1993). Arabic number reading deficit: a single case study. *Cognitive Neuropsychology*, **10**, 317-339.

Noël, M. P., & Seron, X. (1995). Lexicalization errors in writing Arabic numerals: A single-case study. *Brain and Cognition*, **29**(2), 1-25.

Nose, I., Itsukushima, Y., & Masato, T. (2002). Brain activations during mental comparison. *NeuroImage*, **16**(2), Poster No.: 20581.

Nuerk, H. C., Weger, U., & Willmes, K. (2001). Decade breaks in the mental number line? Putting the tens and units back in different bins. *Cognition*, **82**(1), 25-33.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A*, **87**(24), 9868-72.

Ogawa, S., Lee, T. M., Stepnoski, R., Chen, W., Zhu, X. H., & Ugurbil, K. (2000). An approach to probe some neural systems interaction by functional MRI at neural time scale down to milliseconds. *Proc Natl Acad Sci U S A*, **97**(20), 11026-31.

Ojemann, J. G., Buckner, R. L., Akbudak, E., Snyder, A. Z., Ollinger, J. M., McKinstry, R. C., Rosen, B. R., Petersen, S. E., Raichle, M. E., & Conturo, T. E. (1998). Functional MRI studies of word-stem completion: reliability across laboratories and comparison to blood flow imaging with PET. *Human Brain Mapping*, **6**(4), 203-15.

Oliveri, M., Rossini, P. M., Traversa, R., Cicinelli, P., Filippi, M. M., Pasqualetti, P., Tomaiuolo, F., & Caltagirone, C. (1999). Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. *Brain*, **122**(Pt 9), 1731-9.

Oswald, I. (1960). Number-forms and kindred visual images. *Journal of General Psychology*, **63**, 81-88.

Owen, A. M., Epstein, R., & Johnsrude, I. S. (2001). fMRI: applications to cognitive neuroscience. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 311-327). Oxford: Oxford University Press.

Pascual-Leone, A., Gates, J. R., & Dhuna, A. (1991). Induction of speech arrest and counting errors with rapid rate transcranial magnetic stimulation. *Neurology*, **41**, 697-702.

Pascual-Leone, A., Gomez-Tortosa, E., Grafman, J., & Alway, D. (1994). Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology*, **44**(3), 494-498.

Pascual-Leone, A., Houser, C. M., Reese, K., Shotland, L. I., & et al. (1993). Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalography & Clinical Neurophysiology: Electromyography & Motor Control*, **89**(2), 120-130.

Pascual-Leone, A., Tarazona, F., Keenan, J., Tormos, J. M., Hamilton, R., & Catala, M. D. (1999). Transcranial magnetic stimulation and neuroplasticity. *Neuropsychologia*, **37**(2), 207-217.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology*, **10**, 232-237.

Passingham, R. E. (1998). The specializations of the human neocortex. In A. D. Milner (Ed.), *Comparative Neuropsychology* (pp. 271-298). Oxford: OUP.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature*, **362**(6418), 342-345.

Pauling, L., & Coryell, C. D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbomonoxyhemoglobin. *Proc Natl Acad Sci USA*, **22**, 210-216.

Paus, T. (1999). Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia*, **37**(2), 219-24.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *Journal of Neuroscience*, **17**, 3178-84.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1998). Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. *J Neurophysiol*, **79**(2), 1102-7.

Pear, T. H. (1922). *Remembering and Forgetting*. London: Methuen.

Penfield, W., & Rasmussen, T. (1950). *The cerebral cortex of man*. London: Macmillan Press.

Perenin, M. T., & Vighetto, A. (1988). Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain*, **111**(Pt 3)), 643-74.

Peritz, G. (1918). Zur Pathopsychologie des Rechnens. *Deutsche Zeitschrift für Nervenheilkunde*, **61**, 234-340.

Perry, R. J., & Zeki, S. (2000). The neurology of saccades and covert shifts in spatial attention: an event-related fMRI study. *Brain*, **123**(Pt 11), 2273-88.

Pesenti, M., Seron, X., & Van Der Linden, M. (1994). Selective impairment as evidence for mental organisation of arithmetical facts: BB, a case of preserved subtraction? *Cortex*, **30**, 661-671.

Pesenti, M., Seron, X., Samson, D., & Duroux (1999). Basic and exceptional calculation abilities in a calculating prodigy. *Mathematical Cognition*, **5**(2), 97-148.

Pesenti, M., Thioux, M., Seron, X., & De-Volder, A. (2000). Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: A PET study. *Journal of Cognitive Neuroscience*, **12**(3), 461-479.

Pesenti, M., Zago, L., Crivello, F., Mellet, E., Samson, D., Duroux, B., Seron, X., Mazoyer, B., & Tzourio-Mazoyer, N. (2001). Mental calculation in a prodigy is sustained by right prefrontal and medial temporal areas. *Nature Neuroscience*, **4**(1), 103-107.

Piazza, M., Mechelli, A., Butterworth, B., & Price, C. J. (2002). Are subitizing and counting implemented as separate or functionally overlapping processes? *Neuroimage*, **15**(2), 435-46.

Piazza, M. & Butterworth, B. (2001). Personal communication.

Pinel, P., Dehaene, S., Riviere, D., & LeBihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage*, **14**(5), 1013-26.

Pinel, P., Le Clec'H, G., Moortele, P.-F., Naccache, L., Bihan, D. L., & Dehaene, S. (1999). Event-related fMRI analysis of the cerebral circuit for number comparison. *NeuroReport*, **10**(7), 1473-1479.

Poeck, K., & Orgass, B. (1966). Gerstmann's syndrome and aphasia. *Cortex*, **2**, 421-437.

Polson, M. J. R., Barker, A. T., & Freeston, I. L. (1982). Stimulation of nerve trunks with time-varying magnetic fields. *Med & Biol Eng & Comput*, **20**, 243-244.

Poppelreuter, W. (1917). *Die psychischen Schädigungen durch Kopfschuss im Kriege 1914/1916*. Leipzig: Voss.

Price, C. J., Howard, D., Patterson, K., Warburton, E. A., Friston, K. J., & Frackowiak, S. J. (1998). A functional neuroimaging description of two deep dyslexic patients. *J Cogn Neurosci*, **10**(3), 303-15.

Pridmore, S., Fernandes Filho, J. A., Nahas, Z., Liberatos, C., & George, M. S. (1998). Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *Journal of Electroconvulsive Therapy*, **14**(1), 25-7.

Pugh, K. R., Offywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Byrd, D., Skudlarski, P., Shankweiler, D. P., Katz, L., Constable, R. T., Fletcher, J., Lacadie, C., Marchione, K., & Gore, J. C. (1996). Auditory selective attention: an fMRI investigation. *Neuroimage*, **4**(3 Pt 1), 159-73.

Raichle, M. E. (1998). Behind the scenes of functional brain imaging: a historical and physiological perspective. *Proc Natl Acad Sci U S A*, **95**(3), 765-72.

Ramachandran, V. S., & Hirstein, W. (1998). The perception of phantom limbs. The D. O. Hebb lecture. *Brain*, **121**(Pt 9), 1603-30.

Ramachandran, V. S., & Hubbard, E. M. (2001). Synaethesia - a window into perception, thought and language. *Journal of Consciousness Studies*, **8**(12), 3-34.

Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nature Neuroscience*, **3**(7), 716-23.

Reilly, J. P. (1992). *Electrical Stimulation and Electropathology*: Cambridge University Press.

Remond-Besuchet, C., Noel, M.-P., Seron, X., Thioux, M., Brun, M., & Aspe, X. (1999). Selective Preservation of Exceptional Arithmetical Knowledge in a Demented Patient. *Mathematical Cognition*, **5**(1), 41-63.

Richter, W., Somorjai, R., Summers, R., Jarmasz, M., Menon, R. S., Gati, J. S., Georgopoulos, A. P., Tegeler, C., Ugurbil, K., & Kim, S. G. (2000). Motor area activity during mental rotation studied by time-resolved single-trial fMRI. *J Cogn Neurosci*, **12**(2), 310-20.

Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: an fMRI study. *Neuropsychologia*, **38**, 325-335.

Rinck, P. A. (Ed.). (1993). *Magnetic Resonance in Medicine* (3rd ed.). Oxford: Blackwell Scientific Publications.

Robertson, I. H., & Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol Bull*, **125**(5), 544-75.

Robinson, C. J., & Burton, H. (1980). Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory and granular insula of M. fascicularis. *J Comp Neurol*, **192**(1), 69-92.

Robinson, D. L., Goldberg, M. E., & Stanton, G. B. (1978). Parietal association cortex in the primate: sensory mechanisms and behavioral modulations. *J Neurophysiol*, **41**(4), 910-32.

Roeltgen, D. P., Sevush, S., & Heilman, K. M. (1983). Pure Gerstmann's syndrome from a focal lesion. *Archives of Neurology*, **40**, 46-47.

Roland, P. E., & Friberg, L. (1985). Localization of cortical areas activated by thinking. *Journal of Neurophysiology*, **53**(5), 1219-43.

Roland, P. E., Levin, B., Kawashima, R., and Åkerman, S. (1993). Three-dimensional analysis of clustered voxels in 15O-butanol activation images. *Human Brain Mapping*, **1**, 3-19.

Romaiguere, P., Possamai, C. A., & Hasbroucq, T. (1997). Motor cortex involvement during choice reaction time: a transcranial magnetic stimulation study in man. *Brain Res*, **755**(2), 181-92.

Rossor, M. N., Warrington, E. K., & Cipolotti, L. (1995). The isolation of calculation skills. *J Neurol*, **242**(2), 78-81.

Roth, B. J. (1991). A theoretical calculation of the electrical field induced in the cortex during magnetic stimulation. *Electroencephalography & Clinical Neurophysiology*, **81**, 47-56.

Rueckert, L., Lange, N., Partiot, A., Appollonio, I., Litvan, I., Le Bihan, D., & Grafman, J. (1996). Visualizing cortical activation during mental calculation with functional MRI. *Neuroimage*, **3**(2), 97-103.

Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience*, **4**(6), 656-661.

Rushworth, M. F. S., Krams, M., & Passingham, R. E. (2001). The attentional role of the left parietal cortex: The distinct lateralization and localization of motor attention in the human brain. *Journal of Cognitive Neuroscience*, **13**(5), 698-710.

Rushworth, M. F. S., Paus, T., & Sipila, P. K. E. (2001). Attention systems and the organization of the human parietal cortex. *Journal of Neuroscience*, **21**(14), 5262-5271.

Russell, B. (1919). *Introduction to mathematical philosophy.* London: George Allen & Unwin, Ltd.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The TINS Lecture. The parietal association cortex in depth perception and visual control of hand action. *Trends Neurosci*, **20**(8), 350-7.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., Tsutsui, K., Tanaka, Y., Shein, W. N., & Miyashita, Y. (1999). Neural representation of three-dimensional features of manipulation objects with stereopsis. *Exp Brain Res*, **128**(1-2), 160-9.

Sakurai, Y., Momose, T., Iwata, M., Sasaki, Y., & Kanazawa, I. (1996). Activation of prefrontal and posterior superior temporal areas in visual calculation. *Journal of Neurological Sciences*, **139**(1), 89-94.

Sathian, K., Simon, T. J., Peterson, S., Patel, G. A., Hoffman, J. M., & Grafton, S. T. (1998). Neural evidence linking visual object enumeration and attention. *Journal of Cognitive Neuroscience*, **11**(1), 36-51.

Sawamura, H., Shima, K., & Tanji, J. (2002). Numerical representation for action in the parietal cortex of the monkey. *Nature*, **415**(6874), 918-22.

Schluter, N. D., Rushworth, M. F. S., Mills, K. R., & Passingham, R. E. (1999). Signal-, set-, and movement-related activity in the human premotor cortex. *Neuropsychologia*, **37**(2), 233-244.

Schluter, N. D., Rushworth, M. F. S., Passingham, R. E., & Mills, K. R. (1998). Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements: A study using transcranial magnetic stimulation. *Brain*, **121**(5), 785-799.

Schwartz, A. S., & Eidelberg, E. (1968). 'Extinction' to bilateral simultaneous stimulation in the monkey. *Neurology*, **18**, 61-68.

Scott, S. K., Blank, C. C., Rosen, S., & Wise, R. J. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain*, **123**(Pt 12), 2400-6.

Semenza, C., Miceli, L., & Girelli, L. (1997). A deficit for arithmetical procedures: lack of knowledge or lack of monitoring? *Cortex*, **33**, 483-498.

Seron, X., Pesenti, M., Noel, M.-P., Deloche, G., & Cornet, J.-A. (1992). Images of numbers: or "When 98 is upper left and 6 sky blue." *Cognition*, **44**(1-2), 159-196.

Sgro, J. A., Ghatak, N. R., Stanton, P. C., Emerson, R. G., & Blair, R. (1991). Repetitive high magnetic field stimulation: the effect upon rat brain. *Electroencephalogr Clin Neurophysiol Suppl*, **43**, 180-5.

Shallice, T., & Vallar, G. (1990). The impairment of auditory-verbal short-term storage. In G. Vallar & T. Shallice (Eds.), *Neuropsychological Impairments of Short-term Memory* (pp. 11-53). Cambridge: Cambridge University Press.

Shapiro, S. (2000). *Thinking about mathematics - the philosophy of mathematics*. New York: Oxford University Press.

Shellock, F. G., & Kanal, E. (1996). *Magnetic resonance: bio-effects, safety and patient management*. (2 ed.). New York: Lippincott-Raven.

Shepard, R. N., Kilpatrick, D. W., & Cunningham, J. P. (1975). The internal representation of numbers. *Cognitive Psychology*, **7**, 82-138.

Shepard, R. N., & Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science*, **171**(3972), 701-703.

Siebner, H. R., Willoch, F., Peller, M., Auer, C., Boecker, H., Conrad, B., & Bartenstein, P. (1998). Imaging brain activation induced by long trains of repetitive transcranial magnetic stimulation. *Neuroreport*, **9**(5), 943-8.

Simon, O., Mangin, J. F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, **33**(3), 475-87.

Simon, T.-J., & Vaishnavi, S. (1996). Subitizing and counting depend on different attentional mechanisms: Evidence from visual enumeration in afterimages. *Perception and Psychophysics*, **58**(6), 915-926.

Sittig, O. (1917). Über Störungen des Ziffernschreibens bei Aphasischen. *Zeitschrift für Pathopsychologie*, **2**, 298-306.

Smith, E. E., Jonides, J., Marshuetz, C., & Koeppe, R. A. (1998). Components of verbal working memory: evidence from neuroimaging. *Proc Natl Acad Sci, USA*, **95**, 876-882.

Smith, S. M. (2001a). Overview of fMRI analysis. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 215-227). Oxford: Oxford University Press.

Smith, S. M. (2001b). Preparing fMRI data for statistical analysis. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 229-242). Oxford: Oxford University Press.

Snyder, L. H., Batista, A. P., & Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, **386**(6621), 167-70.

Sokol, S. M., & McCloskey, M. (1988). Levels of representation in verbal number production. *Applied Psycholinguistics*, **9**, 267-281.

Sokol, S. M., & Ruzecki, V. I. (1991). Number impairments following hypokalemia: A case study. *Cortex*, **27**(3), 447-452.

Sokol, S. M., McCloskey, M., Cohen, N.-J., & Aliminosa, D. (1991). Cognitive representations and processes in arithmetic: Inferences from the performance of brain-damaged subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **17**(3)

Spalding, J. M. K., & Zangwill, O. L. (1950). Disturbances of Number-form in a case of brain injury. *Journal of Neurology, Neurosurgery and Psychiatry*, **13**, 24-29.

Spelke, E. (2001). Core knowledge and human intelligence: the case of number. *What is special about Human Cognition*? Lecture at the Institute of Cognitive Neuroscience, 02.03.2001, London.

Stanescu-Cosson, R., Pinel, P., Moortele, P. F., Bihan, D. L., Cohen, L., & Dehaene, S. (2000). Understanding dissociations in dyscalculia: A brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. *Brain*, **123**(11), 2240-2255.

Starkey, P., & Cooper, R. G. (1980). Perception of Numbers by Human Infants. *Science*, **210**, 1033-1035.

Starkey, P., Spelke, E.-S., & Gelman, R. (1990). Numerical abstraction by human infants. *Cognition*, **36**(2), 97-127.

Stein, J. F. (1978). Effects of parietal lobe cooling on manipulation in the monkey. In G. Gordon (Ed.), *Active touch* (pp. 79-90). Oxford: Pergamon.

Stein, J. F. (1991). Space and the parietal association areas. In J. Paillard (Ed.), *Brain and Space* (pp. 185-223). Oxford: OUP.

Stengel, E. (1944). Loss of spatial orientation, constructional apraxia and Gerstmann's syndrome. *J Ment Sci*, **90**, 753-760.

Stigler, J. W. (1984). "Mental abacus": The effect of abacus training on Chinese children's mental calculation. *Cognitive Psychology*, **16**(2), 145-176.

Strub, R., & Geschwind, N. (1974). Gerstmann syndrome without aphasia. *Cortex*, **10**(4), 378-387.

Sulkowski, G. M., & Hauser, M. D. (2001). Can rhesus monkeys spontaneously subtract? *Cognition*, **79**(3), 239-62.

Talairach, J., & Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging* (M. Rayport, Trans.). New York: Thieme.

Terao, Y., Ugawa, Y., Suzuki, M., Sakai, K., Hanajima, R., Gemba-Shimizu, K., & Kanazawa, I. (1997). Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. *Exp Brain Res*, **115**(3), 541-5.

Thoenissen, D. , Zilles, K., & Toni, I. (2002). Differential involvement of parietal and precentral regions in movement preparation and motor intention. *Journal of Neuroscience*, **22**(20), 9024-9034.

Thompson, S. P. (1881). *Electricity and Magnetism*. London: Macmillan and Co.

Thulborn, K. R., & Gisbert, A. (2001). Clinical applications of mapping neurocognitive processes. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 329-349). Oxford: Oxford University Press.

Tomasello, M., & Call, J. (1997). *Primate cognition*. New York, NY, US: Oxford University Press.

Toni, I., Ramnani, N., Josephs, O., Ashburner, J., & Passingham, R. E. (2001). Learning arbitrary visuomotor associations: temporal dynamic of brain activity. *Neuroimage*, **14**(5), 1048-57.

Tootell, R. B. H., Hadjikhani, N. K., Mendola, J. D., Marrett, S., & Dale, A. M. (1998). From retinotopy to recognition: fMRI in human visual cortex. *Trends in Cognitive Science*, **2**, 174-183.

Trick, L. M., & Pylyshyn, Z. W. (1993). What enumeration studies can show us about spatial attention: Evidence for limited capacity preattentive processing. *Journal of Experimental Psychology: Human Perception and Performance*, **19**(2), 331-351.

Vallar, G. (2001). The methodological foundations of human neuropsychology: studies in brain-damaged patients. In R. S. Berndt (Ed.), *Language and Aphasia* (Vol. 3, pp. 305-344): Elsevier Science.

Vallar, G., & Papagno, C. (1995). Neuropsychological impairments of short-term memory. In A. D. Baddeley, B. A. Wilson, & F. Watts (Eds.), *Handbook of Memory Disorders* (pp. 135-165). Chichester: Wiley.

Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia*, **24**(5), 609-22.

Vallar, G., & Perani, D. (1987). The anatomy of spatial neglect. In M. Jeannerod (Ed.), *Neurophysiological and neuropsychological aspects of spatial neglect* (pp. 235-258). Amsterdam: North-Holland.

van Harskamp, N. & Cipolotti. L. (2001). Selective impairments for addition, subtraction and multiplication: Implications for the organisation of arithmetical facts. *Cortex*, **37**(3), 363-388.

van Harskamp, N. J., Rudge, P., & Cipolotti, L. (2002). Are multiplication facts implemented by the left supramarginal and angular gyri? *Neuropsychologia*, **40**, 1786 -1793.

van Oeffelen, M. P., & Vos, P. G. (1982). Configurational effects on the enumeration of dots. *Memory & Cognition*, **10**(4), 396-404.

Van Loosbroek, E., & Smitsman, A.-W. (1990). Visual perception of numerosity in infancy. *Developmental Psychology*, **26**(6), 911-922.

Varney, N. R. (1984). Gerstmann syndrome without aphasia: a longitudinal study. *Brain and Cognition*, **3**, 1-9.

Vogt, O. (1911). Die Myeloarchitektonik des Isocortex parietalis. *J. Psychol. Neurol.*, **18**, 107-118.

von Bonin, G., & Bailey, P. (1947). *The neocortex of Macaca mulatta*. Urbana, IL: University of Illinois.

Vuilleumier, P., & Rafal, R. (1999). "Both" means more than "two": localizing and counting in patients with visuospatial neglect. *Nat-Neurosci*, **2**(9), 783-4.

Waldvogel, D., van Gelderen, P., Muellbacher, W., Ziemann, U., Immisch, I., & Hallett, M. (2000). The relative metabolic demand of inhibition and excitation. *Nature*, **406**(6799), 995-8.

Walsh, V. (1998). Faradization of the mind. *Current Biology*, **8**(1), R8-R11.

Walsh, V. (in press). The nuts and bolts of transcranial magnetic stimulation. In V. Walsh & A. Pascual-Leone (Eds.), *Transcranial magnetic stimulation: a neurochronometrics of mind*. MIT Press.

Walsh, V., & Butler, S. R. (1996). The effects of visual cortex lesions on the perception of rotated shapes. *Behav Brain Res*, **76**(1-2), 127-42.

Walsh, V., & Cowey, A. (2000) Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience*, **1**, 73-79.

Walsh, V., & Cowey, A. (1998). Magnetic stimulation studies of visual cognition. *Trends in Cognitive Sciences*, **2**(3), 103-110.

Walsh, V., & Perrett, D. I. (1994). Visual attention in the occipitotemporal processing stream of the macaque. *Cognitive Neuropsychology*, **11**(2), 243-263

Walsh, V., & Rushworth, M. F. S. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, **37**, 125-135.

Walsh, V., Ashbridge, E., & Cowey, A. (1998). Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. *Neuropsychologia*, **36**, 45-49.

Walsh, V., Ellison, A., Battelli, L., & Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proc R Soc Lond B Biol Sci*, **265**(1395), 537-43.

Warrington, E. K. (1982). The fractionation of arithmetical skills: A single case study. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology*, **34A**(1), 31-51.

Warrington, E. K., & James, M. (1967). Tachistoscopic Number Estimation in Patients With Unilateral Cerebral Lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**(5), 468-474.

Warrington, E. K., James, M., & Maciejewski, C. (1986). The WAIS as a lateralizing and localizing diagnostic instrument: A study of 656 patients with unilateral cerebral lesions. *Neuropsychologia*, **24**(2), 223-239.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology: Evoked Potentials*, **108**(1), 1-16.

Wassman, J., & Dasen, P. R. (1994). Yupno number system and counting. *Journal of Cross-Cultural Psychology*, **25**(1), 78-94.

Waxman, D. (1986). The development of Hypnosis as a psychotherapeutic force. In P. L. N. Naish (Ed.), *What is hypnosis? Current theories and research.* (pp. 13-36). Milton Keynes: Open University Press.

Weddel, R. A., & Davidoff, J. B. (1991). A dyscalculic patient with selectively impaired processing of the numbers 7, 9 and 0. *Brain and Cognition*, **17**, 240-271.

Whetstone, T. (1998). The representation of arithmetic facts in memory: Results from retraining a brain-damaged patient. *Brain and Cognition*, **36**(3), 290-309.

Winstein, C. J., Grafton, S. T., & Pohl, P. S. (1997). Motor task difficulty and brain activity: investigation of goal-directed reciprocal aiming using positron emission tomography. *J Neurophysiol*, **77**(3), 1581-94.

Wojciulik, E., & Kanwisher, N. (1999). The generality of parietal involvement in visual attention. *Neuron*, **23**(4), 747-64.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*, **14**(6), 1370-86.

Worsley, K. J. (2001). Statistical analysis of activation images. In Peter Jezzard, Stephen M. Smith (Ed.), *Functional MRI - an introduction to methods* (pp. 251-270). Oxford: Oxford University Press.

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*, **12**, 900-918.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant voxels in images of cerebral activation. *Human Brain Mapping*, **4**, 58-73.

Wynn, K. (1996). Infants' individuation and enumeration of actions. *Psychological Science*, **7**(3), 164-169.

Zago, L., Pesenti, M., Mellet, E., Crivello, F., Mazoyer, B., & Tzourio-Mazoyer, N. (2001). Neural Correlates of Simple and Complex Mental Calculation. *NeuroImage*, **13**(2), 314-327.

Zatorre, R.-J., Evans, A.-C., Meyer, E., & Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. *Science*, **256**(5058), 846-849.

Ziemann, U., Paulus, W., & Rothenberger, A. (1997). Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. *American Journal of Psychiatry*, **154**(9), 1277-84.

Zorzi, M., Priftis, K., & Umilta, C. (2002). Brain damage: neglect disrupts the mental number line. *Nature*, **417**(6885), 138-9.

**Page d'écriture**

*Deux et deux quatre*
*quatre et quatre huit*
*huit et huit font seize...*
*Répétez ! dit le maître*
*Deux et deux quatre*
*quatre et quatre huit*
*huit et huit font seize.*
*Mais voilà l'oiseau-lyre*
*qui passe dans le ciel*
*l'enfant le voit*
*l'enfant l'entend*
*l'enfant l'appelle :*
*Sauve-moi*
*joue avec moi*
*oiseau !*
*Alors l'oiseau descend*
*et joue avec l'enfant*
*Deux et deux quatre...*
*Répétez ! dit le maître*
*et l'enfant joue*
*l'oiseau joue avec lui...*
*quatre et quatre huit*
*huit et huit font seize*
*et seize et seize qu'est-ce qu'ils font ?*
*Ils ne font rien seize et seize*
*et surtout pas trente-deux*
*de toute façon*
*et ils s'en vont.*
*Et l'enfant a caché l'oiseau*
*dans son pupitre*
*et tous les enfants*
*entendent sa chanson*
*et tous les enfants*
*entendent la musique*
*et huit et huit à leur tour s'en vont*
*et quatre et quatre et deux et deux*
*à leur tour fichent le camp*
*et un et un ne font ni une ni deux*
*un à un s'en vont également.*
*Et l'oiseau-lyre joue*
*et l'enfant chante*
*et le professeur crie :*
*Quand vous aurez fini de faire le pitre !*
*Mais tous les autres enfants*
*écoutent la musique*
*et les murs de la classe*
*s'écroulent tranquillement.*
*Et les vitres redeviennent sable*
*l'encre redevient eau*
*les pupitres redeviennent arbres*
*la craie redevient falaise*
*le porte-plume redevient oiseau.*

from "Paroles" by Jacques Prevert

# Appendix A

This appendix has notes of the first interview held with HS in December 2000 (see chapter 6). The interview was conducted in German. A translation of the notes is provided first, followed by the original notes in German.

# First interview with HS: His Visual Number Form

*December 2000*

English translation:

"Illuminated from all sides – I can move in or out of it – three-dimensional, 1 to 10 are on a slope, I don't see any written numbers, but know that dots are numbers, I mostly see it from the front, slightly tilted. Numbers are like mountains, 100-1000 are foggy, with shadows, dark – very difficult to calculate. 1 to 10 used for fractions, subtraction, good for magnitude understanding and calculating. Line is continuous, but natural numbers are more easily found. Numbers 20 to 100 as if the sun were shining on them – not much contrast. At 10 the integral is not continuos. It goes till one billion – after that very blurred."

„I was born in 75, centuries go back from one hundred, goes back till birth of Christ, also a timeline, at 1890 – it makes an abrupt change in direction and then goes further down."

„I have this since I can remember, certainly since secondary school, perhaps primary school. In focus → numbers close to zero: looks differently, e.g. can change automatically into sixth (7/3 – 3/2)."

"year as circle. Distortion depends on importance (e.g. 3 months in advance etc.) blurred or concise → thoughts about future; many thoughts → clear structure

image frayed on the side, e.g. in August a giant slope → already planned

end of March: exams → afterwards it falls because no stress anymore

two month of dissertation are floating inbetween like a block."

"depends on timeline – like spiral around the timeline"

"not coloured, each year has a spiral structure: weeks, months, but not really for days– weekends are like mountains– tilted to the right as if it were to drive out of the thing.

Planning of my week:" (he closes his eyes) "days are clear units: 12 o'clock – lines like on a barcode – goes down – day ends: "



„put appointments on mountains → what is tomorrow ?" (eyes closed)

Original German notes:

"Von allen Seiten beleuchten – kann Art Kamerafahrt machen – dreidimensional, 1-10 deutlich auf Bahn, sieht keine Ziffern, aber weiß, daß die Punkte für Zahlen stehen, blickt meistens von vorne schräg drauf.Ebene - Zahlen als Gebirge, 100-1000 vernebelt, Schatten drüber, dunkel, schwer zu rechnen.Brüche adieren, subtrahieren 1-10, gut für Größnevorstellungen – benutzt es manchmal zum Rechnen, kontinuierlich aber natürliche Zahlen haben höhere Präsenz.

20-100 als ob die Sonne drauf scheinthebt sich nicht viel ab

bei 10: Ableitung nicht stetig, geht glatt bis Milliarde – danach verschwommen"

„75 geboren, Jahrhundert von Hundert zurückschauen, bis Christi Geburt – Jahrhundert – Zeitbedeutung, letzter Punkt: Christi Geburt, 1890 – Kehrtwende unter der 10, dann weiter runter."

„Habe es seitdem ich mich erinnern kann, auf jeden Fall seit Mittelstufe - evtl . Grundschule. Nahaufnahme → Zahlen um Null : sieht wieder anders aus, z. B. automatisch in Sechstel (7/3 – 3/2)."

"Jahr als Kreis. Verzerrung je nach Wichtigkeit (z.B. 3 Monate voraus..usw.) –schwammig oder klar → Gedanken über die Zukunft

wenn viel Gedanken → klare Struktur,

Vorstelllung schwammig, faserig an der Seite

z.B. bei August- Riesen nach oben → schon vorprogrammiert

Ende März: Prüfung → danach geht nach unten, weil entlastet,

Zwischendrin schwimmt 2monatige Seminararbeit wie ein Block."

"hängt mit Zeitlinie zusammen – wie Spirale um Zeitlinie"

"nicht in Farbe

Spiralstruktur von Jahr: Wochen, Monate auf jeden Fall, Tage eher nicht- Wochenende ist Gebirge – rechtsgekrümmt als ob es auf dem Ding herausfahren würde.

Wochenplanung:" (macht die Augen zu) "Tage klare Einheit: 12 Uhr- Linie wie bei Strichcode – setzt sich- Tag geht: "



„Termine auf Gebirge setzen → was ist morgen ?" (Augen zu)

# Appendix B

This appendix has a complete transcript of the interview with HS that was held on 5th July 2001. Parts of the interview were presented in chapter 6. I stands for interviewer, H for HS. The transcript is subdivided into 15 sections (001-015). Each section took 5 minutes.

# HS's number line

05.07.2001

**--001--**
00:40
I: Okay…! H..... (laughter) .. Aehm.. you want to describe your number line?
H: Yeah, okay. Ähm.. I'll start: it's..aeh.. subdivided into two parts.. negative and positive numbers. Ähm.. I'm normally staying at the .. at the origin at zero and looking forward into the positive direction ..Ähm.. – it's …when I am looking backwards on a negative number it's like a ..an waterfall just going down and..it's more..it's not a discrete..Ähm.way in its own it's more... ..Ähm...'nen verschwimmen, 'nen verschwimmendes, ..Ähm... en verschwimmender Wasserfall also keine diskrete Linie mehr („blurred waterfall, no discrete line anymore") and the positive numbers aehh and the positive numbers are discrete line ..Ähm..subdivided into into several parts ..Ähm...from 0 to10, from 10 to 20, from 20 to100, then to 1000, then to 10 000, then to 100 000 and then to one million ,
I: That's a lot!
H: ..then to one billion and then it's....Aehm..was heisst denn verschwimmen?
I: hmmmm..hmm..blurred.
H: And then after it's blurred it's not a discrete line anymore.
I: And you can see up.. to a billion?
H: A billion, yeah.
I: ….in your line if you stand on the zero point..?
H: – it's like a ..it's like … Ähm ..a motorway going up a very long hill. The thing is that several ..Ähm...parts ..Ähm. have different.... width and .... ..Ähm. ..the left and the aeh…right side have different em...yeah..let's say....em.. Umgebung?..
I: environments.
H: environments ...from..from 1 to 10 it's like ehmmm standing in in a flat plane, from 10 to 20 the .em...motorway itself is is a bit skipped to the left ..like this.. and aehm....from 100 to1000 ..Ähm.. it's falling straight down and it is very shadowed. So it's pretty hard for me to calculate in this region from 100 to1000
I: ehem
H: afterwards it gets clearer again and it's almost like a ... ..Ähm. ..always a left and right turn between this...these numbers..but not aehm....in a ..in a ... ..aehm
I: Did you enrich numbers?
H: Ähm.... algroritmic way..
I: like the steps...
H: After ....and from 0 to 10 it is a straight line..
I: aehem..and you can see it clearly?
H: I can always see it clearly
H: but.. ..then it makes a left turn to 20 and then another left turn to 100 then a right turn to 1000 then ...aehm..the problem is, you can't say left and right every time because it's three-dimensional so..
I: And you see it three-dimensional?
H: Yeah
H: And..aehmm..well..well..maybe ask more some more questions and then I can...
I: (laughter)…Do you have a colour?
H: Aehem..that depends ...I ...I won't say that I have have a distinct colour to every part or something like that but sometimes especially when I aehh..lay in bed at night and close my eyes..sometimes it it gets ..Ähm..coloured but ..I won't say that it .. actually I didn't pay too much attention on the on the colourscheme, but on the directional scheme on it, so.. I thought about ...and that's actually the question I ..I was not able to to answer for myself where does it come from this …Ähh.. threedimensional ..Ähm..structure
**--002—**
H: ..Ähm...the thing that appears to be the most approriate answers is that it in some parts looks like the way ..Ähm.. my parents and I drove when I when I was young to my grandma
I: Aha
H: That's a ..that's a way from about 15 km – it's like 10 miles, 9 miles and ..Ähm...that fits pretty good to some regions of it and also the dark part between 100 and 1000 seems to be the part in the in the woods
I: laughter
H: so ….but in some parts it doesn't fit so I am not sure, maybe in some parts it's related to this but I can't really prove it..so

I: When is your first memory of it ..I mean when did it start?
H: I'd say that I always calculated like this..Ähm... Of course the numb.. the higher numbers ..Ähm...were made up later, but I can remember that I already calculated like this maybe in the third class ..Äh..third grade
I: hm..and the negative numbers?
H: Well, they were introduced I don't know in the 8th class so I don't really know
I: so you didn't have them before?
H: that that but that's actually the reason why ..Ähm... why I have this .....Ähm..yeah..weird skim of it.. Äh....but actually if I really have to calculate in these numbers it's like I turn around and calculate in the positive direction..I mean that's normally
I: Okay, all right..
H: how people do it
I: So how do you calculate on your number line? I mean for people who don't have it that's very difficult to
H: for example addition or what?
I: yeah..yeah anything
H: Okay..
I: what do you use it for?
H: It's like
I: any, any calculation
H: ..Ähm...It's like you know the natural numbers like like..Ähm... you could say like ...was heisst..hm I don't even know the German words.so.....Ähm...
I: (laughter)
H: die Steigen einer Leiter?
I: steps
H: steps on a ladder ..so the discretes numbers are steps on a ladder ..and it's like yeah..climbing up a ladder
H: and ..Ähm...I can do that
I: so there are also non...?
H: Pretty fast
I: ..discrete numbers inbetween?
H: what do you mean?
I : so you can also imagine the non-discrete ones inbetween?
H: Ja..Ähm...for example $\pi$ is also a pretty clear line..it's maybe like a spectrum..you know
I: uehem
H: if you do an NMR spectrum or
I: ja
H: whatever, it's like ae ja, and the discrete numbers are all discrete lines like on a ladder
I: uehem
H: but I..for example if you use the ..rational numbers..especially like one third one fifth and stuff like that, they are also part of it and I can ...especially if you are like inbetween zero and five I can calculate with it pretty good
I: ehem
H: like climbing up a ladder
I: so you do addition wit them and and subtraction as well?
H: yeah, yeah of course, ..Ähm...it's it's like going up the ladder and climbing down again
I: aehem..and multiplication?
H: multiplication? Is like you have a ...let me describe it like this you have a for example ..Äh...five times seven you have a ..let..let's..Ähm... fold ..Ähm...a paper..five times and then I don't really have to think about it anymore it's just .. ..Ähm...pops up and it's like ..Ähm...you know if you have a folded ladder and then it's just bobo bobodoop
I: Ajah, okay
H: and it folds up and then I know that I am at 35.
I: and you see 35 as well ...then?
H: It' s there...then...I'd ...all these discrete lines there is no real number at all ...I don't I don't see
I: so there is no real number?
H: the numbers itself
I: okay..Ehem
H: I just know that I am at 35.
I: but how do you know?

H: there is ....I think that's my
I: that's your intuition? Okay yeah..
H: No that's my ..I have to give..that's sometimes a problem actually
I: ehem
H: I have to give this ..Ähm...this point in space I have to give it a number that everyone understands it for me it's not necessary.
I: okay. So ..yeah..
H: yeah..but yeah that's how it works I think
I: okay..ja. How often do you use it today?Like.. is it there every time you meet a number?
H: yeah..every time
I: but you are not always using it? Or you..
H: .....every time I calculate I use it.
I: Also for very complicated calculations? ...like higher mathematics..?
H: .....Ähm.....
**--003--**
H: No, I ....I I'm not actually able to do something like let's say 17 times 35 minus 275
I: Yeah
H: Whatever stuff like that I am not able to do it ..it's it's..Ähm...it works out pretty well in the range between zero and 100
H: and maybe to up to one thousand but I told you it's a bit shad..aeeh shadowed there .. ..Ähm...so that works out pretty well but I'm ..for that stuff I also use the calculator
I: it's quicker (laughter)
H: but ..Ähm...if I'm confronted with ..Ähm...new parts of mathematics I always have ..Äh...
..Ähm...picture of it
H: for example vectorspaces and ..ah.. subspaces of vectorspaces groups subgroups stuff like that I always have a picture but that then it gets pretty hard to describe
I: ja..yeahh
H: what is going on
I: ja..obviously..
H: what kind of picture I have in my mind
I: ja..ja...Do you do estimation with your number line?Like, what do you with the large... the very large numbers?
I: so they tell whatever the budget is a billion pounds or something..do you..
H: well I I used it actually in in every aspect in life
I: ahem.
H: so for example.. ..Ähm...for example in Germany ..ahhh..a roll costs let's say 50 Pfennig and in Italy it costs 500 Lire so it's like spreading up the numbers from one to ten to one to ..Ähm...10 000 and
H: then I know the relation between the different values of..of currencies ..Ähm...that's how I do it so I use it in every day life and for me I know that it's ..mnn...good to earn let's say 50 000 Euro per year
H: ..Ähm...and it's like .. it's like making a mark on my on my line
I: ehem
H: and then I know ..okay this one is higher and and lower
I: Ja
H: so I do put a mark on my line if someone tells me how much he earns per year –
I: Okay.Do you want to draw it? And while drawing you can
H: I can do that later and ....maybe the thing to ..you asked me before..my relation to the ..Ähm...to the calendar
I: Oh yeah..I wanted to ask you something else..did your number line... does it change over time..I mean the marks seem to change and perhaps the negative numbers came later but ..does it change for you kind of now and ten years later or a decade later, a day later, five days later, I mean is it like pretty stable or?
H: Aahh, I ...I...as long as I can remember it stayed the same... always!..
I: Aehem ...And it got longer?
H: the only thing ...yeah ..okay....it got longer but ..ahm...you know, tell me 10 to the eighty..it's not
I: it's not in it
H: it's far beyond it..my scope but..
I: yeah
H: but ..actually who can imagine 10 to the 80?
I: ja..I can't
H: ..Ähm...but going back...shall I I change to the calendar?
I: yeah..yeah definitely

H: aehhh..okay.. ..ahm...the last century are the numbers from 0 to one hundred
I: aehem
H: and right now…
I: so this is still on your number line?
H: What do you mean?
I: This is on your number line?
H:Yeah
I: okay, yeah
H: Right now..I'm after the right turn after 100 and 2001……when I'm …ahhh..when I am looking on the..on the timeline….I'm always at now and the timenumber to 19 hundred is exactly the same as the ..Äh.. numb..wait… the calendarline is exactly the same as the number line
H: from till 19 hundred..but then it doesn't go back into the negative numbers something like that then it makes a sharp left turn and it …well..then I have some..Ähm...then it goes completely different and I really have this different point of view I am not staying at the origin and calculating but I'm staying always at now and looking back and
I: forward..?
H: also forward..
I: yeah..okay.
H: but actually it's more..it's
**--004--**
H:…….more distinct in the past ..
H: so I have like..a very distinct mark at ..at the number line origin or 19 hundred on the calendar line and then at birth of Christ and ..Ähm...
I : so it goes back …
H: something like Bismarck
I: it goes back quite far..yeah..yeah
H: yeah …and then..and then..but then it goes actually back to the ..was is Urknall?
I: (laughter..) yeah..don't know..(laughter)
H: the big ..the big bang
I: yeah big bang
H: yeah..whatever ..Ähm...but then it also get shadowed again ..ahm..I'll try to ..I'll try to sketch it a bit later and then you maybe see better what I mean
I: so it's the same line it's just a different perspective?
H: No, actually ..it's..
I: it's parts of the same line
H: the..yeah..the time from 19 hundred to pfhhh whatever time in future is exactly as the .. ..Ähm...number line but …19 hundred and earlier it's just a part that doesn't exist in my number line ..and it's just like ..yeah..
H:…fit to it …or like glued to it
I: yeah, yeah..okay. ..and is it different in colour or shade?
H: not at all.
I: ja.
H: it's …..no..it just makes a sharp left turn at 19 hundred and
I: (giggle)…when do you use it…the… that timeline?
H: the timeline? Ah..pfffb
I: yeah..or for what do you use it?
H: …….hhhhhmm..pffff..Actually I am not that good in history so it's
I: (laughter)
H: it's not of a very good it's not
I: (laughter)
H: so it's not of good use..I just have it..
I: yeah..
H: it's aehm..it's
I: do you use it to keep track of birthdays or something?…Not really, hm…?
H: …No, there are some ..there are actually only….very few marks like ..beginning of first World War
H: end of first World War, beginning of Hitler's ..ahmm..and then end of second world war and beginning of Federal Republic of Germany ..and my birthday ..my father's birthday
H: my sister's birthday, ….and ….yeah…but..it's not really of use…so..it's just there..
I: yeah..
H: ..but for example if I plan the next year..

H: I ..mmm..it's .. ..Ähm...it's like a spiral going up
I: Äh?..around
H: a spiral.
I: around the number line or?
H: No, no..actually just separated from it. It doesn't ..it's not
I: so you just switch?
H: related..I just switch then and..
H: and it's…I can sketch it too..
H: maybe try to make my point of view today and
I: yeah, okay..
H: and ..for example..yesterday I realised…wow, it's beginning of July and it's seems to be like..that I am a bit delayed in my ..it's like 'n ..ellipsoidal spiral
I: aha
H: so..it's ..it seems that I ..I was a bit distracted the last weeks because it had free time I'm done with my seminar work and so I'm still in beginning of May, even if it's end of June
I: (laughter)
H: or beginning of July
I: ja..on this..on this line..
H: on this on this spiral
I: this spiral..ja..
H: so on this spiral it seems to be a bit delayed and ….the last two days..it..I went on pretty fast on the spiral again ..so I ..I had to keep track in my mind that ..wait..come on dude, ..get a bit faster
I:..yeah..
H: you have to ..you have to be in time..
I: So you plan events on it as well..?
H: totally.
I: so like what …..for your..like for your next few months?
H: Yeah, I ..for example..my..my ..ah...my holiday, my diploma thesis, my beginning of my PhD..
I: so how do they look on the spiral then..is it just a mark or…
H: no, I would say ..it ahm…it's like ..shaded areas I…I..
H: am..yeah, I can sketch it..
I: and you move on the spiral
H: yeah I totally move on it every day
I: yeah..
H: ja..and ..Ähm...
I: every day as well? It's not only years, and the year but it's every day as well, so you have
H: yeah, it's like
I : like a diary? so for today..?
H: and I also have..wait..
I: (laughter)
H: let me try to…
I: he is closing his eyes…(laughter)
H: ja..hhh…..I think that's typical that I can imagine it better
**--005--**
H:..Ähm... …. … well….I think ..it's like a spiral around the spiral..
H: but…..Ähm...interesting..interestingly, I'm looking back in the time in the timespiral..so..maybe I try to sketch it later..and
I: yeah..yeah..
H: it's pretty hard to describe now because I actually didn't think about it too deeply but..
I: yeah but..
H: but I will..hahah
I: hahaha..so for today you just have …a picture in your mind..like what..
H: for example..if I
H: mmm…you know the day today..it wasn't planned that well, but if I have a very well-planned day
H: amm..I have..like ah.. …..Ähm...a double cycle
H: where I have several marks okay, eight o'clock I have to get up, okay. Breakfast and it's not that I …..Äh... …..Ähm...it's not that I really …..Ähm...that there is a ..big ladder …..Ähm...laying there and that tells me to get up, it's just .. in my mind it' s more a ..intituively
I: yeah..and if you plan your future you say you see whateever your diplom Diplomarbeit..?
H: for example..

I: is is this a mark or..?
H: for example.. Äh.. once again where I use my timeline my life starts at the origin again and right now I'm at 27 of course and I'm..I'm at now again
H: so, my life itself…doesn't start at 75 on the timeline
I: obviously
H: but at the origin.
I: yeah, yeah..
H: and..that's how I
I: so you use it very flexible
H: …..Ähm...
I: yeah
H: I use it very flexible and I and I think I don't u…..Ähm...if I for example ..if I ..if I try to plan my future on the calendar line it's almost impossible because of this shaded area between 100 and 1000 where I'm in right now
I: ahem
H: or where we are in ..from my point of view
I: yeah..yeah
H: …..Ähm...I always plan my life on my timescale of course
H: where I start at the origin
H: and will die some day inbetween..hopefully
I: so how do you plan
H: what do you mean?
I: how do you plan then? I mean, do you have marks like this is my exam , and this is arggh
H: exactly, exam…
I: and how do you
H: PhD, diploma..
I: do you see it or is it kind of more visual..I mean
H: yeah, it's like….haaah..let me say it for example..if you have a sinusoidal longitudinal wave you have like .. …..Ähm...yeah it's like this,…but it's not sinusoidal but ..Äh...more
I:..ups and downs..?
H: more..as I planned it..
I: yeah
H: so contracted areas and more shaded areas ..for example .. …..Ähm...the timing between starting of my diploma thesis and the end of my diploma thesis is a very ..like …..Ähm...nicht..nicht-dicht..?
I: not …..Ähm... dense
H: not dense area. But the …..Ähm...the …..Äh...submit day submit date of my diploma thesis and then afterwards my …..Ähm...that are very dense areas
H: but actually .. …..Ähm...for me it's.. it's a very good …..Ähm...a very good orientation of planning my life..the problem is that …..Äh…….I'm ..I'm not living that conscious just ….that I can keep track of it every day
H: and every second
I: ahem, yeah
H: so sometimes it gets shaded and as I told you ..I'm a bit delayed on my …..Äh...year spiral
I: but you focus on it so two or three days later you think of it
I: and you refocus and you look where am I and compare
H: yeah ..exactly
I: and where should I be as well
H: exactly..exactly..
I: Okay, so…yeah..it's very interesting….okay..yahh
H: and for example……..Ähm...I told you it's an ellipsoidal …..Ähm.. ..Äh....spiral …..Ähm...the fall and the spring ..if you..if you look on it on a let's say neutral …..Äh.. point of view then the winter is at the bottom the summer is on the …..Äh...on the top
I: aeha
H: and it's
**--006--**
H: like …..Äh... I'll try to sketch it again I think it's better
I: yeah
H: …..Äh... It's hard to describe..so
I: do you want to sketch it and talk while you sketch
I: so timeline, lifeline

H: ja
I: whatever yearline
H: you keep track recording or
I: yeah..sure
H: Okay
H: Do you have just a pencil maybe?
I: a pencil? I am going to get you one
H: because
I: yeah, might be better actually with a pencil
H: okay, shall I

**--007--**
H: Okay I first sketch the timeline .....Äh...the number line..then..jae
I: okay, yeah, do you need some light?
H: okay, yeah..
I: Soll ich's Licht anmachen? (Shall I switch on the light?)
H: No, it's okay.
I: Okay.
H: I'll try to also sketch an .....Ähm...
I: please a title..(laughter)...
H: okay
I: timeline, numberline, whatever..
H: yeah, of course
I: because I don't know it..(laughter)
H: Okay, number line of Holger Schmid
I: (laughter) and a date..no
H: what is
I: fifth
H: fifth of July
H: Okay. .....Ähm..I'll try to ..use a coordinate system then you have a better idea
I: Okay, yeah..
H: and and because it's somehow oriented
H: in a in a threedimensional space....hmmmm..well it's pretty hard...
I: closing his eyes...(laughter)
H: Okay.....I will just sketch it at the... bottom .....I'll just explain to you in German what I mean
H: .....Ähm...Ich muss das jetzt hier nur so zeichnen. Die y-Achse ist aber eigentlich direkt nach hinten gerichtet..also ich kuck eigentlich
I: Okay..ja
H: so vorne drauf und kuck genau auf die x..xy- xz Ebene
I: Xy .. .....Äh...xz
H: ich kann das jetzt nicht dreidimensional malen - ja , okay?
I: okay....kannst ja denn beschreiben, was dann in der y
H: okay, so I look on the x that plane and all my numbers are in the positive halfspace of z greater than zero
I: are you going to explain the y – coordinates
H: the y coordinates is ..going into, going into into the plane
H: ...so....this is the original ...then it's going down like this....waterfall....
I: ich mach Dir mal das Licht an...ich kann so langsam auch nichts mehr sehen
H: I try to sketch it a bit perspectively but it will be hard...
I: it's not much better is it? .....Okay, and you are only writing the numbers for me because you don't really see them do you?
H: what do you mean..yeah, yeah ..of course I will ...I try to sketch it a bit perspectively
H: maybe I'll do several sketches..than it gets clearer whatever .....Ähm...I can everywhere on the line to sketch ho wit..how it looks like..
H: maybe that's ..the you get a better impression.....the problem now is..it...it gets
..it' s always ..okay the derivative is always positive so it's always getting up monotoniously..
I: okay.
H: .....Ähm...but it's now hard to say if it gets left or right..it's hard to sketch now..

I: ja
H: so maybe I should try to do my best on ahhhh sketching it projecting it on the planes?
I: okay..yeah
H: what do you think
I: yeah, yeah just do this and then just tell me if it goes left or right or whatever
H: I'm a null in drawing..okay
I: perhaps we'll find a very sophisticated computer programme where we can just..
H: well ..I
I: where you'll tell them and they'll they'll make it..
H: yeah..probably.....
I: closing his eyes again..we should get a video camera as well ohh
H: well.....maybe slightly to the right here
**--008--**
H: .....one more problem will be the dimensioning..
H: yeah, I mean ...it's not realistic
I: ahem
H: It's ..it's like... the numbers from 1 to one million..it' s it's like the numbers between 100 and 1000 is a longer line than from 0 to 10 but it's hard to draw
I: yeah..yeah..
H: I can.. I can't ...use the logaritmic scale right now...(laughter)
I: do you think you are thinking in logarithmic scale..?
H: no, not at all
I: no...okay..yeah, yeah
H: It's a...absolute scale..okay.....that is y and that is z so I am looking from the
I: and this stops at a hundred..or?
H: no, I will add it later
I: (laughter)..okay.
H: it's always a positive derivative
I: okay
H: it's never parallel to the xy plane
I: ehem
I: and obviously you don't see the .Ähm..coordinate systems..the axes...yeah
H: .....h..Ähm...I ...I do..but I haven't thought about projecting on planes actually
I: Aaah...okay..(giggle)
H: so I'll try to do my best
I: yeah. Do you rotate it as well? Can you rotate it?
H: yeah. Totally..
I: yeah
H: I can go whereever you want but it's just
I: yeah..okay
H: I mean you have to understand it and that's the problem
I : (laughter)
H: for me..it's clear but..
I: for you it's very obvious..yeah
H: Exactly. ....Okay...
I: so ..where is it shaded..you said..
H: here in between..I..maybe I try to really sketch the different parts later..
I: okay..ehem
H: I can start here right now maybe.. .....Ähm.....several parts in special sketches....okay, I'll start with the part I know best....
H:.....and also going back...
I: oh..that's a spiral..I can
H: no, no that's not a spiral at all
I: no?
H: It's like....the..it's like someone put a .....Ähm...an elastic.....ah...paper over it and is trying to pull it down..the numbers between 100 and 1000...
I: Okay so it's very
H: ...and it' s very dark
I: stretched...okay

H: it's very dark and there is there is a big there is a great tension if you can say something like that to numbers…(laughter) whatever…..Ähm...ja..1..does it get somewhat clearer or..?
I: yeah..yeah..
H: okay
I: yeah..yeah!
H: …..Ähm...even if it …..Äh..seems to be..seems to be..ahhh…….discontinuous..no, not discontinuous, but ahhh not a c1 curve?
I: aehem…ja
H: let me say like this. It is a c1 curve, it's always a c1 curve
**--009--**
H: mae…I think it's …man koennte es als Bobbahn benutzen..
I : Okay..
H: Man koennte da gemuetlich langfahren ohne sich was abzubrechen.
I: ehem
H: …..Ähm...but of course you would ……..Äh...drive it down the other direction
I: yeah..not upwards because it's very …
H: yeah ..okay I'll try to continue here……..Ähm...I ……Ähm...stop the scaling here and try to do my best again ..okay?
I: okay
H: …with another scaling it's just that you get a feeling for it how
I: yeah
H: …..Ähm...
I: this is back on page 2..ja,ja…
H: ja gut..okay
I: nur fuer mich dass ich weiss wo wir sind
H: ehem…..come on!…10 to the 4 ..okay…….here in it seems to be very small part but this part is scaling.. …..Äh..scaled..the same again..
I: ahem
H: so Äh let's consider you are in the dimensional space a the euclidi…
eucli..euclidean length would be …..Ähm... well-scaled
I: aehem..
H: but 1 just the projector right now and it's at 100 000 there is a sharp left turn again
I: aheme
H: so that's why it seems to be shorter here
I: okay..ehem
H: …..so..I cut the scale again here too..okay?
I: aehem
H: ..would be a hard job to do into a programme
I: (laughter)
H: and creating a satisfying picture
I: (laughter) obviously a future project
H: and the other part between one million is not that interesting anymore it's just there is a kind of a line between one million and one billion but
H: ah
I: it's very…
H: normally I don't calculate
I: it's very blurred…yeah
H: I do something like scaling down, cutting the last zeros and going back where I'm really familiar with ..so breaking it
I: okay..yeah..I see
H: so breaking it down from 1 to 10
I: yeah..yeah
H: because normally..in every day life it's not of interest if you have one million marks or one million two marks
I: hm…that's true..hm..yeah
H: you know?
I: yeah..yeah..
H: so that's why I break down and I hope that you have a feeling now and I'll try to sketch some more
I: okay, more details..and then the timeline..we need the timeline as well..
H: of course.Ja.

I: ya
H: wow!
I: (laughter) on page 3....
H: brrpf.....pf closing his eyes again..(giggle)
I: (laughter)...next time I'll bring a video tape
H: ja.....please not
I: (laughter)
H: I don't know why..but maybe interesting for you ..I have a problem on focusing now..it's lilke .....Ähm...because I I..
I: because I ask all these questions
H: no, it's because I did this projecting I have problems to switch into normal vision again that I can ah give you more the threedimensional of it..the shadowing
I: okay..
H: of it..the shading
I: okay I'll ask you different questions to divert you and we will come back to it. You said it might remind you, it might have started because you drove the way from your home to your parents
H: to my grandma
I: which way is this?
H: it's from Kelkheim through
I: where you are living today?
H: no, where my parents still live
I: yeah, yeha..I mean the Breslauer Strasse

**--010--**
I: Breslauer Strasse
H: Breslauer Strasse 37 .....Ähm...going.....ah...going to Fischbach
I: aha
H: then Fischbachtal..Eppstein..and then not.. .....Äh...then take it left in Eppstein ...not going over Bremtal and stuff like that but..
I: aeha
H: ..taking left..and.. then
I: to Lorsbach...or left before?
H: Lorsbach? Wait....Lorsbach, Lorsbach? No, no, no, .....ah...the second .....ah...the second crossing in in Eppstein
I: okay, beforeVockenhausen..?
H: you could take a right to Wildsachsen and then.
I: left..yeah, yeah.. okay....Richtung Idstein
H: Exactly and
I: okay direction to Idstein okay
H: then .....ah there is a small .. .....Äh...street going to Niederjosbach and Oberjosbach and that's were we drove
I: Okay, yeah..ja, I know this ..on the right
H: Exactly,
I: yeah, okay and you
H: a very
I: and your
H: a very curvy street
I: and your grandparents are..?
H: living in in Oberjosbach
I: Oberjosbach, okay, excellent.Yeah I know where this is.
H: But that's actually
I: And what's the shady ..the shady..the bit between Fischbach and Eppstein.. is..no.. which one is..?
H: No, the..wait ....phhhh....pfffffff....I'd say the part between Fischbach and Eppstein, ja.
I: Okay.
H: ja
I: and you drove from your house ...just through the main ...parts in ...Kelkheim? The normal one..Bahnhof..?
H: yeah, yeah, exactly
I: okay, great. Hey – we can tape this on video...(laughter) okay.
H: I don't know..I mean...

I: yeah, it's just..I mean it's nice
H: .....I think it won't remind you of it...I..
I: No, but it might be nice....
H: it was a
I: to get a feeling for it..yeah
H: it was one of my ae .....Ähm.....one of my..can you say tries yeah? ..one of my
tries to explain it
I: yeah
H: .....Ähm ..but it's but for me it's everything but satisfying so...if you would..ahh..if you if you would
videotape it the whole way long ..ahh..you would say is he crazy it doesn't relate to this at all ..
I: (laughter)
H: Ähm.
I: yeah, it just gives you a symbol or.....don't know ...yeah
H: I don't know ....I mean.....
I: ehhh...I mean that's interesting, because I know this...these routes as well.. so...
H: ja. (laughter)
I: ja,...okay....three-dimensional .....in plane....(laughter)
H: (laughter)
I: are you tired?
H: yeah..not..not tired but
I: it's very difficult, isn't it?
H: let's ...the most shaded region is the easiest one to draw
I: yeah.
H: and the rest..phhhh
I: what's with 1 to 10?
H: It's .....I was just thinking about if .....if the structure..the big structure..the
shaded region from 100 to 1000 ..
I: ehem
H: ..is found again in the scaling down between one and ten, I am not sure...
I: ahhh...aha!
H: .....I don't know, I can't give an answer right now
I: yeah..it's a shame that we can't just look into
H: Tja, well
I: go into your eyes and look what you see
H: I'd love to
I: might be a bit scary
H: to solve this
I: might be a bit scary
H: don't think so
I: okay, do you want to (Laughter) do you want to draw your timeline?
H: yeah, I think that's
I: ehem
H: a better approach now
I: page 4
H: ja, maybe I get back to it later
I: Yeah, no...I mean
H: maybe we should ...make a break and
I: have a beer?..
H: yeha, maybe that helps..
I: yeah..
H: .....Ähm...okay..calendarline ...okay
I: Is it the same line for calendars that you use for .....Ähm..for years in the back and your own plans..is it
the same line for history..like Bismarck and this and ..for planning you life..or is it...
H: No, as I told you ..

**--011--**
H: when I'm planning my life I use the .....Äh.....Äh..the part between .....Äh..zero
and one hundred..
I: Okay, yeah...but the history one is a different ..okay

H: .....ahhhh...tj...I ..it just came to my mind that that.....Ähm..that numbers you learned in school ....I think they were subdivided into this parts
I: Aha
H: I remember they were one..zero to ten ten to twenty then to 100 then to 1000 and then making bigger and bigger steps
I: ehem
H: So I think that's the reason why why I have these ...marks
I: ahe
H: and...pffffff..ahh
I: Hochleistung
H: I mean I would be happy to answer the question why it has this structure and it's it's a question that
I: yeah, I mean that's kind of the no..no solution question ..is it?
H: I don't know
I: yea, I mean people don't know, do they?
H: I mean
I: yeah
H: I'm always thinking about if it
I: You should be very happy you are having ..I mean
H: I am thinking about if it's somehow related to a way I drove to a dream I had to the ..to the class-room in .. in my boarding school and they also changed with the years so maybe it's related to that.. I mean... I don't know....
I: yeah
H: I thought about lot of it but ....it's not that it pops up and that it's (Fingerschnicksen) that's it
I: ahhh, it might be an influence of loads of things..yeah...yeah
H: ja, maybe...but normally it's not, normally it's like bingo that's it
H: that's how I found my answers in the past so..
I: (laughter)
H: it was not like ..accumulating different points of views - normally it was like the real the real answer popped up and then it was it
I: hmm
H: .....Ähm..ja, okay ...drawing the calendar line.....Ähm.....
.phhhhhhhhhh...huuuuuuu..pfhhhhhh...hchh....I have the problem that if I want to get into a position to draw it .....Ähm..then I somehow have this ....that my mind doesn't let me stop ..it always want to rotate
I: (Laughter)
H: know what I mean?
I: ja.
H: so. It's pretty hard to ...calm
I: just try...yeah
H: down and
I: just try to make it intuitively.. it mean it doesn't have to be perfect.. anything..
H: yeah
I: it should just give us..because I mean you want it to have it exactly like you are seeing it
H: ehem
I: but I just have no idea how you are seeing it anyway. So if it just gives me a rough idea about ..how large is it actually if you see it..I mean if you close your eyes ...the whole visual field? ..or is it something very small?
H: .....Ähm....ahhh...if I would..if I would ahhhh draw a picture like 10 cms away from my eyes...hhhhhh...it's it's always a matter of zooming
I: Okay, you could zoom, ehem
H: so, if I would concentrate on the calendar line now to specify it ... ahhhh..going back to 19 hundred that's the origin
I: aehem
H: and want to have an overlook over the century..ahh..the century would be of the size of maybe 5 to 7cm maybe
I: ehem
H: that's it
I: okay
H: and if I .....ahhh.. I just thought about why .....Äh.. why for me to draw from 0 to 10 is much easier .....Ähm..to go to 20 and look back and then I can describe it pretty easy
I: ah, yeah, okay..do this!yeah

H: okay, but

**--012--**
H: but first draw the calendar line....So that's 2001 and am
I: and this black one is .....Ähm..the future
H: this is the future, yeah
I: ehem
H: .....Ähm.....okay..that's 2000...1945.....and World War two oh not not three
I: (laughter)...oupps...
H: that's 19 hundred..the thing is ...now this is going sharply down
I: aha
H: so that's hard to draw now .....Äh..that's zero ja..zero before Christ after Christ ...
I: (laughter)
H: and that's mmm.....maybe minus 10000 and then is getting shady
I: minus 10000 – is it going so far back? ahhh
H: yeah, and then ..somewhere here...there are dinosaurs...
I: (laughter)...and where is the big bang?
H: the big bang...I don't know..it's const..it's accumulating again..it's
I: (laughter)
H: and it's something like that
I: okay, yeah...and this is.....this is part of your number line?
H: ...from here..
I: from there
H: ..to here ..
I: aha..so from 19 hundred
H: this is..this is maybe .....Ähm..this is
I: 19 hundred would be zero?
H: year ....right .....puhhhhhhh...I haven't thought about it....here it's a bit
.....Ähm..abgeflacht?
I: eha...shallow
H: so jetzt ...a more sharp line...this is year 10 000 and this is year 20 000, so and then it's ..it's getting..and it's going up again like this and like the..like the number line again
I: okay.
H: So that's pretty much like it, but here it's it's eee it's not like a solid line as in the number line
I: aha
H: more like a shady because .....Äh..the future
I: okay, yeah
H: hasn't been
I: obviously ja
H: ja
I: so this would be zero in the number line
H: Exactly
I: and 2001 would be ...a hundred
H: zero in ..yeah
I: and this ..oh no and 2000 would be a hundred? And threethousand?
H: like....
I: ah..okay I see I, okay...ehem..Excellent!..interesting..okay
H: so, some more drawing about the the spiral ..or?
I: oh yeah..your day..ja..your database day-plan
H: arhghhh, I know why I didn't study arts...
I : (laughter)
H: (laughter)
I: on page 5
H: yup
I: I think that will be the last thing we are going to do
H: so I'll try to sketch .....Ähm.....okay.....year spiral.. .....Ähm.....puhhhhh
I: so is this a different one from the calendar one again? Yeah, yeah,..okay
H: Wait, I'll try to .....ja, it's a it's like a tool of breaking down the timeline for easier imagination
I: (laughter) okay..
H: like I mean

I: ja..wow you have a real tool kit! (laughter)
H: (Laughter), but I .....Äh....for me actually the..the I mean I don't know if anyone does it like this but for me it's pretty obvious that I do it like this because of the.....Äh.a clock
I: ja
H: and I ..okay.. .....Ähm..year seen from a neutral position

**--013--**
H: like ...like god would see it..let's call it like this
I: (laughter) okay.
H: .....Ähm..summer, fall, ....that's actually supposed to be an ellipsoid
I: Okay. .....And that's kind of the same shade and all these things?
H: well, wait, I'll try to
I: okay, yeah
H: .....Ähm..spring..okay..here it's pretty dark
I: ehem
H: and .....Ähm.....puh.....wait..I'll try my best....hhhhhhhhhchhhh..
yeah..somehow .....this part is pretty dark and here it gets lighter..it's just because of ahh..I'd say sun and not sun
I: aha...okay..
H: and here...here it really...if I close my eyes it's ..it's really light here
I: ehem
H: and really bright
I: okay
H: and.....Ähm....and that's probably why I like the summer
I: (laughter)
H: okay. That's like the neutral ..way of seeing it...but that's .. .....Ähm..that seems be.....Äh..like..really it's..Äh. it's from a neutral positon. But here of course, there is a cut, beginning of the year ..and..this would be like a cut..and then it's going dow..going upward
I: okay. Around the timeline?
H: around the timeline somehow..yeah
I: okay..ehem
H: and I'm .. .....Ähm....yeah, I'll try to ..what I wanted to do now is..try to give you ahhh a view of how the past here is seen from now
I: okay, yeah..
H: and how the
I: future..
H: furture year is seen from right now
I: your..personal..?
H: my personal..jaja
I: yeah, okay
H: with all my stuff and so that you get a view...
I: okay, I am interested
H: ...of whole area shaded
I: yeah
H: I think I already told you. .....Ähm..so I 'm in the summer right now
I: ehe
H: and it's always that I'm going tangentially on the .....Ähm..on a
I: yeah..whatever
H: on the boundary
I: yeah
H: and .....Ähm..
I: Do you actually see yourself walking there or do you just see it how you would see it if you were walking
H: yeah that's the better
I: so, you don't see yourself?
H: no, no, not at all
I: okay. (Laughter)
H: no,no
I: okay
H: Okay, so ..... the problem again is now drawing three-dimensional ...that's

actually going up ..
I: ehem
H: so it's like. Äh....okay...this is llhh...to give you again how it's oriented in space..... x, z.....okay?
I: ehem
H: so if you look from the left that's z, that's y, okay?
I: okay. Ehem.
H: so this is..if you look from here..that's this point of view
I: ehem
H: if you look from the front it's this..okay?
I: okay.
H: okay? So it's this..like lifted a bit like sum..
I: yeeeeah
H: summer is better or higher than the winter
I: yeah, yeah..
H: .....Ähm....okay, the next .....Ähm..next two and a half weeks is like..free time so it's very..amm
I: aaahhh
H: what's up?
I: No, it's okay – free time ..that's nice
H: free time – that sounds great..me too

**--014--**
H: that's my holiday ....ohh..every time I've
I: Is this the holiday in Italy?
H: free ti...no, in Mallorca..sailing
I: oh, okay..em
H: I know I have a lot of holiday
I: (laughter)
H: then I have a short cut here in Frankfurt again and then I'm going to Zurich and here it starts..
I: so you see different colours or?
H: no, it's like ..this aehhh like this dense and not dense
I: okay, yeah...
H: like shaded areas..overlapping
I: and is it all on the same level or do
H: No, it's like..wait.. let me give you a good description....maybe you could considered it as a tube
I: ehem
H: being .....ah..being thick, being thin
I: Okay, ehem
H: and if it's thin I have free time and if it's thick I have a lot to do
I: ehem, okay.....
H: and I .....Ähm ...and I ..like for example .....Ähm..okay..let me first
I: yeah just write it here...okay
H: okay, free,..... Mallorca, .....Frankfurt, ....Zurich, ....Italy
I: How long are you going to Zurich?
H: for two days
I: oh, no
H: just to
I: only for two days..just to say hello?
H: and then..that's like ..okay..that's ....first of August
I: (laughter)
H: sorry for the German version
I: yeah
H: ahhh fifth of July...
I: aha
H: and then it's like ahh 15th of September...
H: that's like...how do you say..ahh..Zwischenjahrn?
I: bet...hmm..na..das sagt man nicht
H: in between years..yeah or whatever you mean
I: yeah..new year
H: between Christmas

I: Christmas and New Year..ja
H: Exactly. …Okay! Then it's …..Ähm..end of February…..end of March..there is my birthday…that's actually where I intend to …..ahhh..to stop
I: (laughter)
H: so here the tube is very thick
I: aha
H: and than it's going down like this again..and …..Ähm..that of course changes from …..Ähm.. …..Äh...from day to day because
I: there is ..yeah..
H: not subjective but
H: with the time I'm …I'm more able to to …..Äh..to foresee the future how it will be if it will be stressfull
H: or hectic or not
I: yeah
H: pfhhhhh
I: so stressfull is thick..and
H: yeah
I: yeah
H: Ähm..
I: or dense?
H: thick and very dark
I: ehem
H: and for example..Mallorca is pretty.. …..Ähm..
I: sunny..
H: that too but very light..
I: okay, yeah
H: so if it's fun it's light and thick
I: and why is it thick?
H: …..
I:…mmh (Laughter)
H: why is it a spiral?..I don't know!
I: I don't know either! Okay.
H: .Ähm..I think
I: aha
H: thick I ..I mean..just to give more and more explanation
I: ehem
H: thick because I will experience a lot
I: ja
H: but ..I don't know..maybe..it could be inverted..totally ..I don't know why
I: yeah, yeah…okay!
H: because the life is full…I mean..out of.. Ähm..Ähm.. how do you say .Ähm..mmm metaphors?
I: metaphors
H: metaphors! Well, explain so..yeah and this year is pretty ..this of course I'll be at home
I: ah
H: but this region here…is completely ..like very thin line because I don't have a clue what I will do during…I mean I know I'll…
I: so this is the time in Zurich?
H: Exactly.
I: ehem
H: I know that I will do my diploma thesis

**--015--**
H: …..Äh..so I know the topic and stuff like that
I: ehem
H: then I know how it works and how the experiment will be ..Äh..measured..stuff like that
I: ehem
H: but..I don't really have…ennn..like subdivided this six months of ..in different parts..what.. I will do ..when I will write when I will do experiments ..stuff like that.

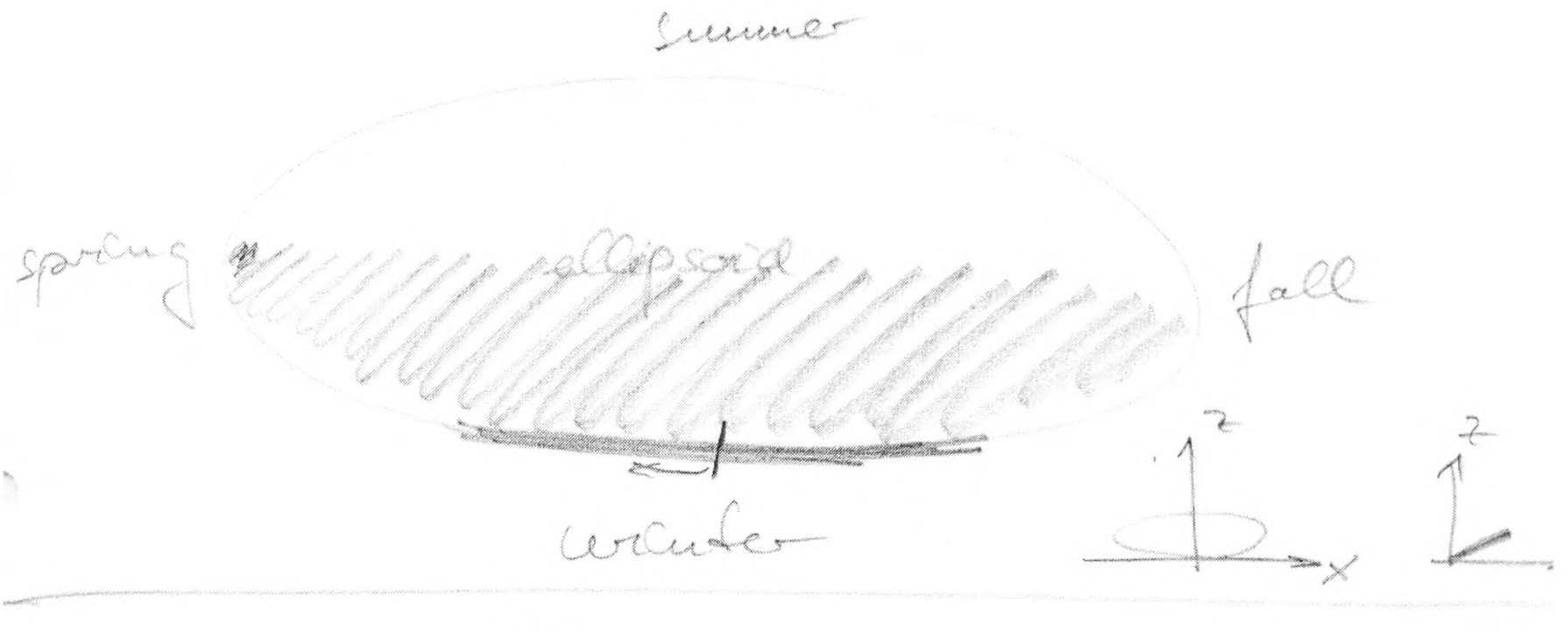
I: ehem
H: .....Ähm..but that will..that will get clearer in this time here
I: yeah
H: let's say this is planning time
I: ehem
H: and .....Ähm.. it's it's not aeh it's not a pity that it's not planned right now, it's just ...it's a bit unsatisfactory for me..and I do feel this somehow ..so for me it's the best if .....Ähm..if this tube is ..thick at very e..either it's .....Ähm..hectic or..or..fun..it doesn't matter but it.. I it..
I: it should be well-defined ...yeah
H: and it should be well-defined and thick
I: aha
H: then it's satisfying for me somehow
I: (laughter)...okay....yeah
H: so for example the last days were ..horrible .because it was just thin, I didn't know what to do
I: (laughter)
H:.Ähm..of course sometimes it's...sometimes I like it..but
I: ja
H: but if it's..if it's too long I don't like it, okay but that ..getting too much into the philosophical
I: (Laughter)
H: area..okay!
I: okay
H: Ähm..this is Ähm end of March, I will submit my.. I will be .. I will be done with my Ähmstuff..so that's Ähm...it's a spiral somehow going up, but from my point of view now it's like... Ähm.....it's a spiral.it's going like this....
I: ehem..okay..how far into the future do you see your own.. ? I mean ...obviously
H: right now?
I: yeah..like one year..obviously
H: not more than this because I don't know where I'll do my PhD
I: okay..
H: or if I'll do my PhD that's the things I will all
I: yeah..
H: I will all decide in the next few months..
I: okay, yeah, ehem
H: so. Ähm..but for example....going back on onto my personal Äh..life..line I know that I wanna be finished wish with my PhD with thirty
I: still have some time
H: yeah
I: if you go back..is it also memory? If you know say whatever..if you think of 19..98..let's say..can you still memorise your time..year..line..like this or is it kind of ...can you go back as well? And remember this..yeah?
H: you mean going back the spiral?
I: yeah, like
H: No.
I: go back from 2001 to 1998 and see..I mean obviously it changed but..can you kind of see it?
H: wait.....
I: Or go to 94...haha
H: Ähm...for some days..for some years it's possible..it's very easy for the year I went to Berkeley
I: aha
H: ahh..the year before I went to Berkeley...hmm..for some years yeah but...the more it gets in the past it's almost impossible
I: the more difficult? ....yeah...okay
H: ja.
I: do you want to add something?
H: well
I: oder wollen wir hier Schluss machen?
H: I hope I could help you
I: Ohh, we thank you very much. (Laughter)
H: We or you?
I: I thank you very much. (Laughter)

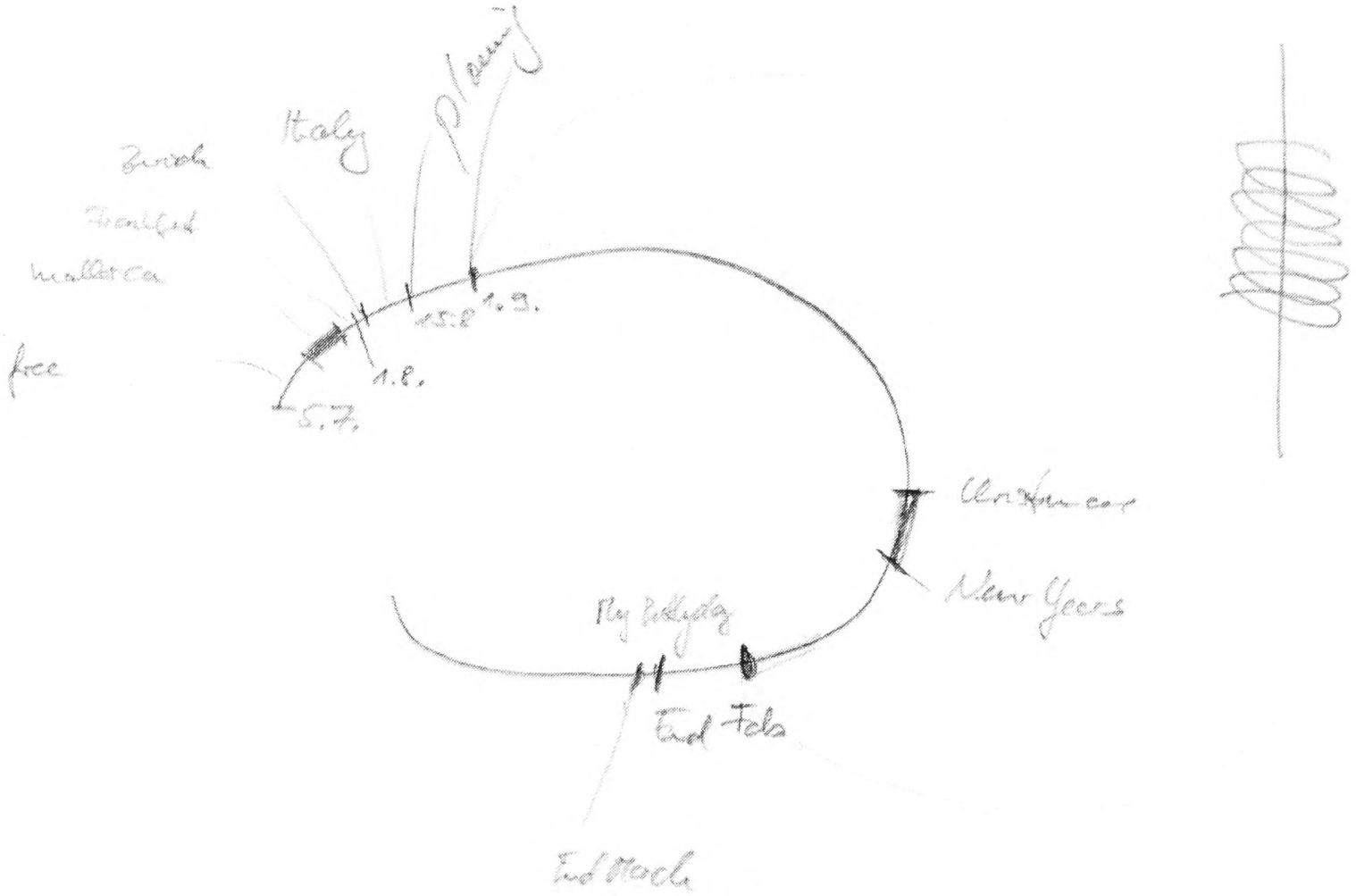
# Appendix C

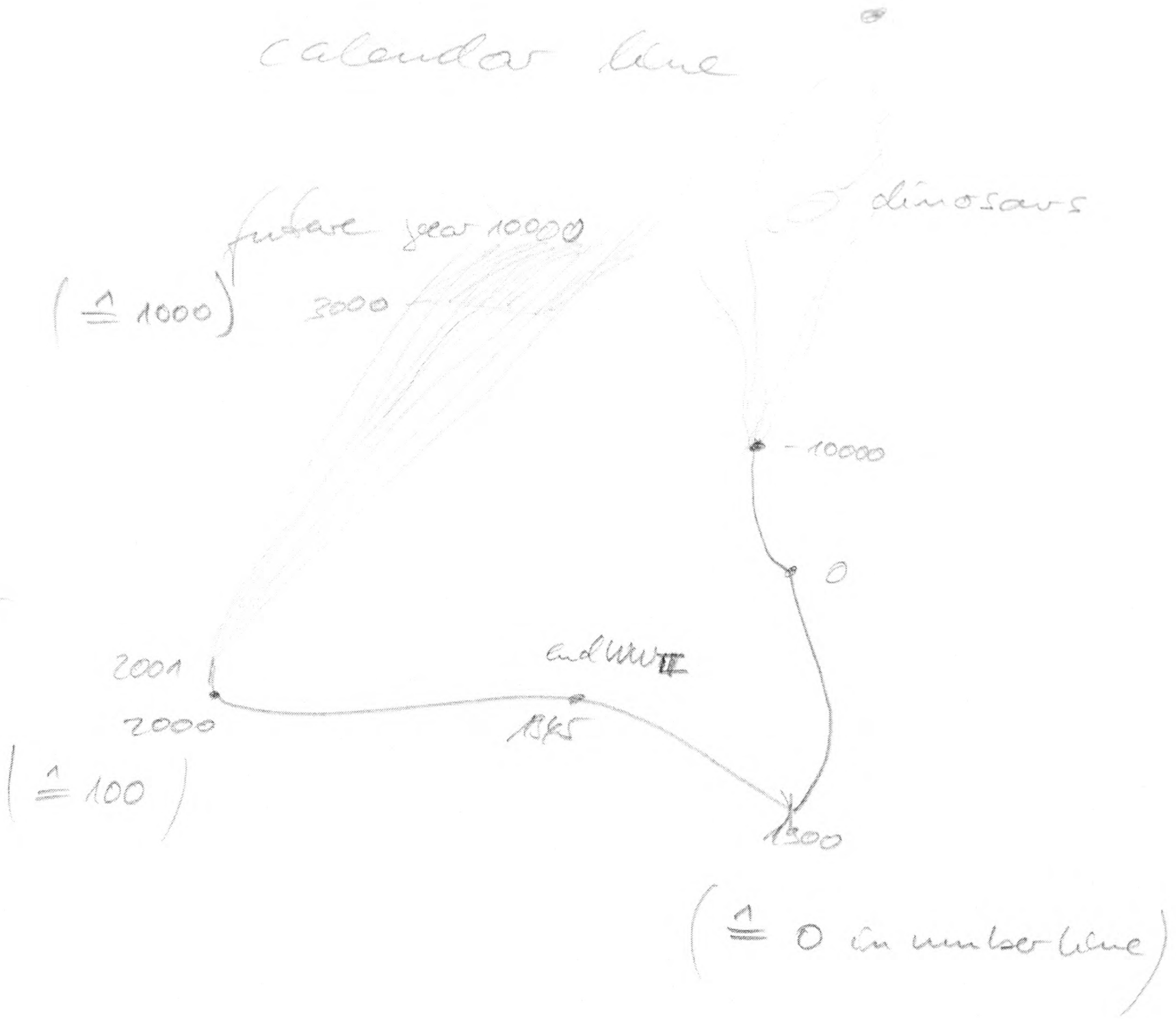
This appendix has drawings of HS's year spiral and calendar line. Both were briefly mentioned in chapter 6.

year spiral

year seen from ventral position




calendar line
dinosaurs
future year 10000
(≙ 1000)
3000
10000
0
2001
2000
end WW II
1945
(≙ 100)
1500
(≙ 0 on number line)

# Appendix D

This appendix has an English version of Seron et al.'s (1992) short questionnaire on number representation. This questionnaire was used as described in chapter 7.

***UNIVERSITY OF OXFORD***
DEPARTMENT OF EXPERIMENTAL PSYCHOLOGY

## A FEW WORDS BEFORE YOU FILL OUT THE QUESTIONAIRE:

Our research group at the Department of Experimental Psychology, Oxford, is interested in the way numbers are represented in memory.

Beyond doubt each of you has already done mental calculation by thinking of numbers as if they were written on a sheet of paper. Except for most people's ability to visualise calculations and numbers in a written format numbers are abstract concepts that don't have precise representations.

In contrast, a few people develop a personal way of representing numbers. In every-day life or in an arithmetic context, these people can't think of a number without this number appearing in a very particular form, with a place on a line, with a well-defined colour, or associated with an image or an impression. Additionally, this representation stays the same over time (numbers are always visualised in the same way). Obviously, these representations differ between individuals and they can be of various types, e.g. graded lines with ordered numbers, a succession of numbers "in space", associations of numbers with colours or with images, dots…and much more.

**It is this type of representation we are especially interested in.**

(We are not interested in people who when doing mental calculation can mentally represent the calculations and numbers like they would appear in written calculation.)

Thank you very much for participating. If you have any further question, please don't hesitate to ask us.

year of course: ..... sex: **M** ❑ **F** ❑

subject: .....

age: .....years Are you: **left handed** ❑ **right handed** ❑

(1) Do you think you have a way of representing numbers as described above (spatial organisation, association with colours, images, sensations, dots....)?

**YES** ❑ **NO** ❑

If you answered **NO** please answer question 2.
If you answered **YES** please go directly to question 3.

(2) Only for those who answered **NO** to question 1:

In which way do you represent numbers when you encounter them?
To help you answering this question, close your eyes and imagine the numbers 8 or 17. What do these numbers evoke in you?

(You can choose several answers.)

---

❑ - nothing.

---

❑ - a visual representation of numbers as they are written in digits (8,17).

---

❑ - a visual representation of numbers as they are written in number words (eight, seventeen).

---

❑ - an auditory representation of numbers as they are repeated mentally.

---

❑ - other.

---

❑ - I don't know.

---

In case you answered "other", please go to question 3.

For everybody who didn't answer "other" the questionnaire ends here.

- Thank you very much for participating –

(3) Only for people who answered **"Yes"** to question 1 or **"other"** to question 3:

Could you please give us a description of your representation as exactly as possible: what is it, what does it serve you for, when and for what do you use it, since when have you used it, in your opinion what's the origin of this representation...etc.

We ask you, if possible, to help us with a drawing. If you need more space, please use the back of this page.

(4) Are you interested in taking part in more studies on the same topic? Essentially, you would be asked to fill out some more detailed questionnaires.

**YES** ❑ **NO** ❑

If you answered **YES** please leave us your mail address here:

SURNAME:.....

FIRST NAME:.....

ADDRESS:.....

PHONE:.....E-MAIL ADDRESS: .....

- ***Thank you very much for participating –***

# Appendix E

This appendix has an English version of Seron et al.'s (1992) extended questionnaire on aspects of the number representation. This questionnaire was used as described in chapter 7.

## *Concerning number representations...*

Some time ago you filled out a short questionnaire in which you described your type of number representation. Thanks again for your participation.

After receiving this information from you we would now like to ask you to answer several additonal questions.

Most of these questions can be answered by just ticking the box next to the most suitable answer; for some, however, we will ask you to give a more detailed response. In the latter case if the space provided for the detailed response isn't enough, please continue your answer on the back of the previous page.

Some questions might appear redundant, because you already answered very similar questions. Others could be more or less difficult to answer or might even seem not very pertinent to your number representation. We ask you to try nevertheless to answer each question.

If you have any further questions, please don't hesitate to ask us.

*Thank you very much for participating!*

1. Do you remember when your number representation first appeared?

- ☐ Yes, I was roughly …….. years old.
- ☐ No, I don't remember it.

2. Is your representation related to a way in which numbers or calculations were presented to you (e.g. at school or at home)?

- ☐ Yes.
- ☐ No.
- ☐ I don't know.

If yes, please describe:

……

……

……

3. Do you remember the conditions under which your representation first took place?

- ☐ Yes.
- ☐ No.

If yes, please describe the conditions:

……

……

……

4. When did you first become aware of your number representation?

- ☐ During my children, around: ……years
- ☐ During my adolescence, around: ……years
- ☐ Later, around: ……years
- ☐ Only this study made me aware of it.
- ☐ I can't remember.

5. Do you have relatives who use number representations?

- ☐ Yes.
- ☐ No.
- ☐ I don't know.

If yes, who (please indicate how you are related to this person)?……

If you can, please describe their number representation briefly:

……

6. How do you see numbers in your number representation?

- ❑ - written in digits.
- ❑ - written in letters.
- ❑ - in form of lines.
- ❑ - in form of sounds.
- ❑ - in form of dots.
- ❑ - in form of colours.
- ❑ - in another form

  which ? .....
- ❑ - I don't know.

7. When you visualise a number with the help of your number representation, does it always have the same attributes?

| | Yes | No | I don't know. |
|---|---|---|---|
| - same shape | ❑ | ❑ | ❑ |
| - same size | ❑ | ❑ | ❑ |
| - same colour | ❑ | ❑ | ❑ |
| - same position | ❑ | ❑ | ❑ |

8. Do numbers in your number representation appear as if:

- ❑ - they were typed.
- ❑ - they were hand-written.
- ❑ - they were written in a different way  How ? .....
- ❑ - they don't appear written.
- ❑ - I don't know.

*For the following questions, please answer by ticking one of the five boxes that stand for different frequencies:* 1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always

9. Is your number representation present when you:

- **add:**
  - ◆ simple (result below 20)

| | *never* 1 2 3 4 5 *always* |
|---|---|
| ★ orally | ❑❑❑❑❑ |
| ★ written | ❑❑❑❑❑ |

  - ◆ complex (result above 20)

| | |
|---|---|
| ★ orally | ❑❑❑❑❑ |
| ★ written | ❑❑❑❑❑ |

- **multiply:**
  - ◆ simple (tables 1 to 9)

| | *never* *always* |
|---|---|
| ★ orally | ❑❑❑❑❑ |
| ★ written | ❑❑❑❑❑ |

  - ◆ complex

| | |
|---|---|
| ★ orally | ❑❑❑❑❑ |
| ★ written | ❑❑❑❑❑ |

- **subtract:** ◆ simple

| | *never* | *always* |
|---|---|---|
| ★ orally | ❑❑❑❑❑ | |
| ★ written | ❑❑❑❑❑ | |

◆ complex

| | | |
|---|---|---|
| ★ orally | ❑❑❑❑❑ | |
| ★ written | ❑❑❑❑❑ | |

- **divide:** ◆ simple

| | *never* | *always* |
|---|---|---|
| ★ orally | ❑❑❑❑❑ | |
| ★ written | ❑❑❑❑❑ | |

◆ complex

| | | |
|---|---|---|
| ★ orally | ❑❑❑❑❑ | |
| ★ written | ❑❑❑❑❑ | |

10. It is possible that your representation is not present for each type of calculation. Please indicate by ticking the appropriate boxes when it plays a role:

| | while you are calculating | | to visualise the result | |
|---|---|---|---|---|
| | *never* | *always* | *never* | *always* |
| addition | ❑❑❑❑❑ | | ❑❑❑❑❑ | |
| multiplication | ❑❑❑❑❑ | | ❑❑❑❑❑ | |
| subtraction | ❑❑❑❑❑ | | ❑❑❑❑❑ | |
| division | ❑❑❑❑❑ | | ❑❑❑❑❑ | |

If this is the case, please describe the role your representation plays for each type of calculation:

ADDITION: .....

.....

MULTIPLICATION: .....

.....

SUBTRACTION: .....

.....

DIVISION: .....

.....

11. Please describe how you usually procede to solve an addition like "13+8=":

.....

.....

.....

.....

12. Please indicate for each of the following situations how often your representation plays a role:
*(1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always)*

| | ***never*** | | | | ***always*** |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| - when you count (objects, persons, events)..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you see a written number ..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you hear a number..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you say a number..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you think of a number..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you write a number..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - when you read a number (during any reading)..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - during every day life when you hear words like *the first, third, on second floor...*? | ❑ | ❑ | ❑ | ❑ | ❑ |

Do you visualise numbers in the same way as you do with:

| | ***never*** | | | | ***always*** |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| - prices (e.g. something for £53 )..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - addresses..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - phone numbers..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - bus numbers, tube lines..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - passcodes (for bank cards, padlocks, safe...)..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - games (dice, cards, board games)..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - car brands..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - TV channels, radio channels..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - historical dates..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - day and time of appointments..... | ❑ | ❑ | ❑ | ❑ | ❑ |
| - age of persons you know..... | ❑ | ❑ | ❑ | ❑ | ❑ |

13. Do you also have specific visual representations for :

| | Yes | No |
|---|---|---|
| - the time..... | ❑ | ❑ |
| - weekdays..... | ❑ | ❑ |
| - months..... | ❑ | ❑ |
| - letters of the alphabet..... | ❑ | ❑ |

If yes, please describe of what they consist (if you like, you are very welcome to make a drawing on the back of this page):

.....

.....

.....

14. When you are confronted with a number, does this automatically activate your represenation?

❑ Yes.

❑ No.

❑ It depends (on the context, the situation ...).

Please describe here:.....

.....

15. Can you voluntarily decide to make your representation disappear?

☐ Yes.

☐ No.

☐ It depends.

If yes, could you please describe how you do it:.....

.....

16. Once your representation appeared, can you decide not to occupy yourself with it?

☐ Yes.

☐ No.

☐ It depends.

If yes, how to you procede to not occupy yourself with it?.....

.....

17. Does your representation entail parts that vary in their precision, clarity or elaboration?

☐ Yes, my representation entails parts with different clarity.

☐ No, every number is represented equally precise.

If yes, which parts of your representation are

- very clear:.....

- less clear:.....

Above which number does your representation definitively loose its precision?

.....

.....

What do you do to visualise a number that at first only appears blurred?

.....

.....

18. How are you situated in relation to your representation?

☐ - you remain "exterior" to it (it presents itself as something that you can consult as if it were a drawing on a piece of paper)

☐ - you mentally penetrate your representation (as if you were in the representation yourself and you could walk on it).

☐ - your representation passes you (as if it were passing in front of your eyes).

☐ - it depends on the situation.

Please explain in more detail:.....

.....

.....

19. If your representation has a spatial character or a character of distance to it (e.g. lines, grids, steps...), could you please describe, how you procede in order to visualise a certain number (or how your representation enfolds itself)? Do you position yourself directly on that number (e.g. 13) or do you start at 0 or any other starting point, to move up to the number from there?

.....

.....

.....

20. Do you have trouble using your representation if you engage in other activities at the same time like:

| | *yes* | *no* | *I don't know.* |
|---|---|---|---|
| - reading | ❑ | ❑ | ❑ |
| - watching TV | ❑ | ❑ | ❑ |
| - driving a vehicle | ❑ | ❑ | ❑ |
| - listening to music | ❑ | ❑ | ❑ |
| - discussing with somebody else | ❑ | ❑ | ❑ |
| - other (please name): ..... | ❑ | ❑ | ❑ |

20. Do you find it more or less difficult to acess your representation when you

| | *more difficult* | *less difficult* | *without effect* | *I don't know* |
|---|---|---|---|---|
| - close your eyes..... | ❑ | ❑ | ❑ | ❑ |
| - are in complete darkness..... | ❑ | ❑ | ❑ | ❑ |
| - are wide awake ..... | ❑ | ❑ | ❑ | ❑ |
| - are at a noisy place..... | ❑ | ❑ | ❑ | ❑ |
| - are tired..... | ❑ | ❑ | ❑ | ❑ |
| - are depressed..... | ❑ | ❑ | ❑ | ❑ |
| - have a headache..... | ❑ | ❑ | ❑ | ❑ |

If this is the case what are the problems caused by these circumstances?.....

.....

.....

.....

.....

.....

***Thank you very much for participating***