Temporal orienting in the human brain: neural mechanisms of control and modulation

Gustavo Rohenkohl - DPhil Thesis - Trinity Term 2010

New College

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Abstract

The main aim of the experiments reported in this thesis was to explore the neural mechanisms underlying the temporal orienting of attention. In Chapter 3, I explored the possible dissociation between exogenous and endogenous temporal orienting by comparing reaction times to targets appearing after rhythmic or symbolic cues. Behavioural results provided evidence for the existence of dissociable exogenous and endogenous types of temporal orienting of attention. The experiment in Chapter 4 combined spatiotemporal expectations using rhythmic moving cues to test the modulatory effect of exogenous temporal orienting in the brain. Specifically, I used EEG to test the effect of temporal orienting on perceptual and motor stages of target analysis, as well as on anticipatory oscillatory brain activity. The time-frequency analysis revealed that rhythmic cues can entrain slow brains oscillations, providing a putative mechanism for enhancing the perceptual processing of expected events. Spatiotemporal expectations also modulated the amplitude of visual responses and the timing and amount of preparatory motor activity. In Chapter 5, I used a novel task to explore the neural modulatory effects of spatial and temporal expectations acting in isolation or in coordination. For the first time, the analysis of early visual responses demonstrated that temporal expectations alone, independently of spatial orienting, can enhance early visual perceptual processes. The time-frequency analysis in this experiment showed a desynchronisation of alpha oscillations focused over central-parietal electrodes induced by rhythmic cues that were independent of spatial expectations. When rhythmic cues carried spatiotemporal information, the alpha desynchronisation also spread over contralateral occipital electrodes. In Chapter 6, fMRI was used to test the possible neural dissociation between motor and temporal orienting. The results confirmed the large overlap between these two processes, but also indicated independent behavioural and neural effects of temporal orienting. Temporal orienting activated the left IPS across motor conditions, further implicating the left IPS in temporal orienting. Based on the results of these experiments, directions for future studies are discussed.

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Chapter 1

1. Introduction

1.1. Attentional orienting

The first scientific evidence that it was possible to focus attention voluntarily to a spatial location in the absence of eye movements was provided by Helmholtz nearly 150 years ago (1867/2000). At the time, Helmholtz had as one of his most enthusiastic students Wilhelm Wundt, who later became known as the father of Experimental Psychology.

Over a century later, Posner (1980) established a new paradigm for the study of attention that changed permanently the field of Cognitive Sciences. Posner developed a simple experimental task with which it was possible to chart the time course of orienting attention to spatial locations, either voluntarily or reflexively; and to characterise and quantify the behavioural advantages conferred (Posner, 1980). The experiments developed by Posner were fundamental for the understanding of how we select a relevant stimulus from a complex environment to optimise our perception and action (Itti, Rees, & Tsotsos, 2005). Tremendous strides have been made in understanding the mechanisms of attention ever since, from the behavioural biases to neural systems and cellular

mechanisms (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Nobre, 2001b; Yantis & Serences, 2003). These studies enabled the development of increasingly sophisticated theoretical and computational models (Desimone & Duncan, 1995; Lee, Maunsell, & Lauwereyns, 2009; Reynolds & Heeger, 2009).

Posner (1980) proposed that there are two modes of control over spatial visual orienting: endogenous and exogenous orienting. Endogenous orienting is understood as a voluntary focus on a location, where the allocation of the attentional resources is made intentionally (goal directed, cognitive control, top-down) by the participant. Exogenous attention, on the other hand, is an involuntary (i.e. stimulus driven, transient, automatic, bottom-up) focus on a location (Corbetta & Shulman, 2002; Giordano, McElree, & Carrasco, 2009). In practice, a classical endogenous spatial orienting task uses a central cue (e.g. arrow) to indicate where a target is more likely to occur. In the exogenous orienting manipulation, a cue is presented (usually transiently) in the same location that the target will be presented. Behavioural results have demonstrated that exogenous orienting elicited stronger effects than endogenous cues (Laubrock, Engbert, & Kliegl, 2005). Studies have also suggested that exogenous cues are less susceptive to interference (Giordano, et al., 2009), and harder to ignore than endogenous cues (Muller & Rabbitt, 1989). Another common finding is that exogenous cues induce faster and more transient effects than endogenous orienting (Busse, Katzner, & Treue, 2008; Nakayama & Mackeben, 1989).

Recently, the field of attention has broadened immensely to show that, in addition to being able to orient attention within space (Carrasco, Eck-

stein, Verghese, Boynton, & Treue, 2009; Corbetta & Shulman, 2002; Posner, Snyder, & Davidson, 1980), attention can be oriented to other attributes such as visual features (Martinez-Trujillo & Treue, 2004; Maunsell & Treue, 2006), objects (Abrams & Law, 2000; Duncan, 1984; Goldsmith & Yeari, 2003), semantic categories (Cristescu, Devlin, & Nobre, 2006; Cristescu & Nobre, 2008), motor actions (Rushworth, Ellison, & Walsh, 2001a; Rushworth, Johansen-Berg, Göbel, & Devlin, 2003), and instants in time (Doherty, Rao, Mesulam, & Nobre, 2005; Lange & Roder, 2006; Nobre, Correa, & Coull, 2007; Nobre & Coull, 2010).

1.1.1. Neural mechanisms

1.1.1.1. Non-human primate studies and the biased competition model

The modulatory influences of attention affect visual processing in a number of ways. Single-cell recording in monkeys showed that when two stimuli are presented within the receptive field a visual neuron, there is a selective enhancement of neural responses to the attended stimulus. This effect has been demonstrated throughout extrastriate visual areas mainly in the ventral stream in which the effect has been investigated (e.g. V2, V4, inferior (IT) temporal areas (Luck, Chelazzi, Hillyard, & Desimone, 1997; Motter, 1993; Treue & Maunsell, 1996).

One of the main functions of attention is to select the relevant stimulus or stimulus attribute and to filter out the irrelevant ones. Moran and Desimone (1985) were the first to demonstrate this by recording activity from V4

and IT neurones while monkeys performed a discrimination task on a target stimulus at one specific location while ignoring a distractor stimulus at another location in their receptive field. The relevant target location was indicated to the monkey by an explicit instruction at the beginning of each block of trials (i.e. top-down). Their results showed that when two competing stimuli are contained within the receptive field (RF) of an extrastriate neuron, and one of them is attended, the neuron responds as though only the attended stimulus is present. When the distracter was presented outside the neuron's receptive field, attention had no effect on the recorded cell responses as the two stimuli were not competing anymore for processing. These results became some of the most influential findings in the neuroscience of attention, and have now been extensively confirmed (Chelazzi, Miller, Duncan, & Desimone, 1993; Luck, et al., 1997; Reynolds, Chelazzi, & Desimone, 1999; Treue & Maunsell, 1996).

The results from Moran and Desimone (1985) study suggested that top-down mechanisms of attention enhance the processing of stimuli presented at attended locations by effectively filtering out the influence of nearby distracting stimuli. These findings were fundamental for the development of a theoretical model known as the "biased competition" model (Desimone & Duncan, 1995). The main assumption of this model is that several stimuli that appear together in a neuron's receptive field compete for its processing resources. This means that stimuli are not processed independently but rather interact with one another in a mutually suppressive way. The model states that attention biases the competition in favour of the relevant stimulus. This assumption was vali-

dated empirically and modelled formally by subsequent work (Reynolds & Desimone, 1999).

1.1.1.2. Electrophysiological studies in humans

Studies of spatial attention in which visual event-related potentials (ERP) for attended versus unattended stimuli are compared, have mainly focused on the visual C1, P1 and N1 components. The first visual component (C1) is detected approximately 50 ms after target onset, and is thought to be related to the initial cortical processing of visual stimuli in V1 (Clark, Fan, & Hillyard, 1995; Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002). Due to the layout of the topographical representation of primary visual cortex along the calcarine, the C1 component reverses polarity when the upper versus lower visual field is stimulated. Its polarity reversal and distribution over contralateral posterior electrodes suggests this potential reflect initial processing in V1, in which the upper and lower retinotopic representations of the visual field tend to be located below and above the calcarine sulcus respectively. Similarly to studies in monkeys (Luck, et al., 1997), the C1 does not seem to be modulated by attention (Clark, et al., 1995; Di Russo, et al., 2002; Martinez, et al., 1999). However, studies have reported a consistent modulation in P1 and N1 by manipulations of spatial attention. The P1 is a positive deflection observed in the visual ERP, typically peaking around 100-120 ms. Spatial orienting studies have found an increase in amplitude when a target appears at an attended compared to non-attended spatial locations (Hopfinger & West, 2006; Mangun & Hillyard, 1987; Van Voorhis & Hillyard, 1977; Woldorff, et al., 1997; Woldorff, et al., 2002).

Similar effects have been found in the first negative component (i.e. N1). The N1 is a negative deflection that follows the P1, usually peaking around 160-200 ms after stimulus onset. Attentional effects in N1 are commonly conveyed by an increase in negativity of this component. Even though both P1 and N1 are measured by electrodes placed over lateral occipital scalp regions, some studies have suggested that their activity originates from different neural sources. Miniussi, Nobre and Rao (2002) have suggested that the N1 generators and therefore functional attributes may partly be task dependent. For example, specific proposals for the function of N1 include spatial orienting toward a relevant stimulus (Luck, Heinze, Mangun, & Hillyard, 1990; Nobre, Sebestyen, & Miniussi, 2000b), discrimination processes within an attended location (Vogel & Luck, 2000), and automatic recognition related to sensory traces (Doniger, et al., 2001).

1.1.2. Functional neuroanatomy of attention

1.1.2.1. Lesion and transcranial magnetic stimulation studies

Based on data gathered from different methodologies in humans and monkeys, Mesulam (1990; 1981) was one of the first scientists to propose a neural model for spatial attention, called the large-scale neural network. Mesulam noticed that visuospatial deficits occur most frequently and are more enduring following lesions to the right cerebral hemisphere (Heilman & Van Den Abell, 1980; Mesulam, 1981). More specifically, the right hemisphere seems to regulate the distribution of spatial orientation across the entire extrapersonal landscape

whereas the left hemisphere's influence is confined predominantly to the contralateral hemispace (Heilman, Watson, & Valenstein, 1985; Mesulam, 1981). Further evidence from neglect patients has identified several brain regions involved in spatial attention implicating mainly the posterior parietal cortex but also the frontal cortex and subcortical structures such as the thalamus and striatum (Husain & Rorden, 2003; Karnath, Himmelbach, & Rorden, 2002; Mesulam, 1990, 1999; Mesulam, 1981). This network involve mainly three cortical regions: a dorsolateral posterior parietal region, the frontal eye fields and the cingulate cortex.

More recently, the advent of transcranial magnetic stimulation (TMS) has enabled the examination of behavioural effects after transient cortical virtual lesions in healthy humans (for reviews see Chambers & Mattingley, 2005; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Walsh & Cowey, 2000). TMS is a non-invasive technique in which a brief magnetic field is applied on the scalp while the participant performs a behavioural task. TMS induces a "virtual lesion" in the underlying stimulated cortical region because the magnetic field briefly disrupts the normal pattern of neuronal activity in the area. If the cortical area is essential for the behaviour of interest, then performance in the behavioural task is disrupted. TMS has extended the findings based on research on patients with brain lesions, by providing high spatial resolution and greater control over the affected area, and by circumventing issues related to possible neural reorganisation in patients with lesions. Studies with TMS have refined our knowledge of the localisation and lateralisation of brain areas involved in the control of spatial attention. Using repetitive TMS (rTMS) applied over parietal

areas, Pascual-Leone and colleagues (1994) have confirmed the 'extinction' phenomena following a disruption of the right parietal cortex. Rushworth and colleagues (2001a) also found impairments in visual spatial attention induced by rTMS applied over the right parietal lobe (angular gyrus). In their experiment, subjects performed a simple visual spatial orienting task, in which cues predicted the likely spatial location of a target that required simple detection. Rushworth and colleagues (2001a) also had a motor orienting version of the task, which will be discussed later in this chapter.

1.1.2.2. Neuroimaging studies

Over the years, non-invasive imaging methods have been widely used to expose brain areas at work in the healthy human brain (Logothetis, 2008). Positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI) quickly emerged to the mainstream in the study of human brain function. In the attentional literature these tools revealed an extensive cortical network underlying spatial orienting (Corbetta & Shulman, 2002; Gitelman, et al., 1999; Kastner & Ungerleider, 2000; Nobre, 2001b; Yantis, et al., 2002). Soon, researchers realised that there was a convergence in the pattern of activation across laboratories, focused mainly in the frontal and parietal cortices (Figure 1). In the frontal cortex, activations are usually centred along the frontal (FEF) and supplementary (SEF) eye fields. Depending on the task, the anterior cingulate is also activated. Parietal-cortex activity occurs in the intraparietal sulcus (IPS) and often extends into the superior (SPL) and inferior (IPL) parietal lobe. Animal studies have shown that within IPS, the lateral in-

traparietal cortex (area LIP) seem to be particularly involved in visual attention processes (for a review see Colby & Goldberg, 1999). This pattern is known as the frontoparietal network, and has been consistently replicated by many functional imaging (for review see Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Nobre, 2001b; Yantis & Serences, 2003) The network activation is usually more pronounced in the right hemisphere (Gitelman, et al., 1999).

The frontoparietal network involved in orienting spatial attention has been shown to overlap significantly with brain areas that are involved in controlling eye movements (oculomotor control) (Corbetta, et al., 1998; Nobre, Gitelman, Dias, & Mesulam, 2000a; Petit, et al., 1996). This overlap suggests a strong functional link between the attentional and oculomotor systems. The de-

gree of association and overlap between eye movements and spatial attention has long been debated (Kliegl, Rolfs, Laubrock, & Engbert, 2009; Laubrock, et al., 2005; Laubrock, Engbert, Rolfs, & Kliegl, 2007; Laubrock, Kliegl, Rolfs, & Engbert, 2010). Typically, saccades are preceded by covert shifts of visual attention to the target location (Deubel & Schneider, 1996; Hoffman & Subramaniam, 1995; Walker, Deubel, Schneider, & Findlay, 1997). On the other hand, shifts of covert attention are often linked to saccade preparation but do not necessarily initiate saccades (Kustov & Robinson, 1996; Rizzolatti, Riggio, Dascola, & Umilta, 1987). Gersch and colleagues (2004) examined the pattern of attentional allocation during a sequence of saccades to predetermined locations. They found increased sensitivity primarily at the goal of the next saccade and decreased sensitivity for points between the current fixation and the location of the next saccade. Microsaccades (smaller than 1° of visual angle), the fastest components of miniature eye movements involuntarily altering eye position during fixation, have also recently been shown to be influenced by covert shifts of attention. Engbert and Kliegl (2003) reported an alteration of microsaccade rates by the onset of central visual spatial cues. Interestingly, their results also showed that the direction of the microsaccades followed the direction of the attentional shift. These findings were confirmed by Laubrock and colleagues (2010), who observed that in a classic Posner cueing paradigm using saccades as responses, microsaccades follows the direction of the cue in at least 75% of cases. During manual responses, however, the direction of microsaccades drops to chance level. Thus, the overlap between attention and oculomotor mechanisms is an intricate issue, not only for its neural anatomical identification, but also its behavioural dissociation.

More recently, neuroimaging studies have examined the possible dissociation between brain regions involved in endogenous and exogenous orienting. Neuroimaging studies indicate a strong cortical overlap between endogenous and exogenous attention, with both subsystems affecting early visual processing (Gandhi, Heeger, & Boynton, 1999; Kim, et al., 1999; Liu, Pestilli, & Carrasco, 2005; Peelen, Heslenfeld, & Theeuwes, 2004; Pinsk, Doniger, & Kastner, 2004). However, fMRI evidence suggests that exogenous attention induces a more pronounced rightward asymmetry of parietal activation, while posterior parietal and temporo-occipital activations are more pronounced in endogenous orienting tasks (Kim, et al., 1999).

1.1.2.3. Linking the mechanisms of control and modulation

Recently, studies investigating the neural mechanisms of spatial attention have been interested in the causal mechanisms underpinning neural control. Studies combining stimulation and brain imaging/recording of brain regions in humans (O'Shea, Taylor, & Rushworth, 2008; Ruff, et al., 2006; Taylor, Nobre, & Rushworth, 2007b) and non-human primates (Awh, Armstrong, & Moore, 2006; Moore & Armstrong, 2003; Moore & Fallah, 2004) have supported the idea that top-down signals originating in FEF can have a causal impact on activity in the visual cortex.

The first studies to investigate the impact of FEF stimulation on visual perception were performed using microstimulation of FEF in non-human primates (Moore & Fallah, 2001, 2004). In two similar studies, Moore and Fallah (2001, 2004) used microelectrodes to stimulate FEF neurons, identifying the lo-

cations at which a saccade would land upon a threshold level of stimulation (known as the response field). They tested whether a subthreshold FEF stimulation would modulated the detection of change in luminance in targets placed within but not outside the response field of the neurons. Taken together, their results indicate that monkeys could detect smaller changes in target luminance when the target was preceded by a subthreshold microstimulation (i.e. currents that did not evoke saccades) of FEF sites.

Moore and Armstrong (2003) performed follow-up experiments involving simultaneous stimulation of FEF and recording of V4 neurons with receptive fields aligned to the FEF response fields. Throughout the experiment, visual stimuli were presented inside (target) and outside (distracter) the RF of a V4 neuron. The results indicated that visual responses in area V4 were enhanced after brief stimulation of retinotopically corresponding sites, within the FEF, using currents below that needed to evoke saccades. The authors also found that responses to stimuli presented at other locations were suppressed. Interestingly, both the enhancement and suppression effects depended on the presence of additional 'distracter' stimuli outside the V4 neuron's receptive field. According to Moore and Armstrong (2003), these results demonstrated that the effect of subthreshold stimulation on responses in visual cortex is to change the gain of visual responses in a spatially selective manner. These results were also confirmed by other studies (Armstrong, Fitzgerald, & Moore, 2006; Moore & Fallah, 2004).

In humans, studies have combined imaging techniques (i.e. fMRI or EEG) with TMS in order to investigate the effect of right FEF stimulation on visual processes. Ruff and colleagues (2006) investigated the effect of stimulation in FEF on retinotopically organised visual areas (V1-V4). They measured brain activity using fMRI while the participants had their right FEF stimulated with TMS. In two different conditions, participants were asked to fixate either on a blank display or on a display with bilateral moving and changing visual stimuli, designed to activate the visual regions. Their findings indicated that stimulation of the right FEF produced a characteristic topographic pattern of activity changes in retinotopic extrastriate areas. FEF TMS led to increases in activity for retinotopic representations of the peripheral visual field, but to decreases in activity for the central field. This finding was supported by a psychophysical experiment, in which the authors manipulated the contrast of the visual gratings. TMS to the right FEF increased the perceived luminance of a peripheral grating relative to a comparison grating that was presented centrally (Ruff, et al., 2006).

Another study that investigated the causal relationship between the right FEF and visual areas was performed by Taylor and colleagues (2007b). In an endogenous visual spatial attention manipulation, Taylor and colleagues (2007b) stimulated the right FEF using TMS whilst recording the modulation of ERPs at electrodes placed over visual areas. The FEF TMS was applied during the delay between the central cue and target onset. The results indicated that the right FEF stimulation caused a change in the neural activity evoked by visual stimuli at the contralateral location. Importantly, this effect was not observed with stimulation of a control site (sensorimotor cortex). This effect

seemed to occur at the same time as ERPs were shown to be modulated by visuospatial attention. The EEG analysis also revealed a modulation of ongoing neural activity recorded during earlier anticipation of the visual stimuli (Taylor, et al., 2007b). The findings reported by Taylor and colleagues (2007b) give support to the idea that the activity in anticipation to an event is a central mechanism by which attention enhances the perceptual processing of stimuli.

1.1.2.4. Anticipatory changes in baseline activation

It is interesting to observe that evidence gathered from experiments on humans and non-human primates indicates that the period of anticipation of the target seems to be crucial for the enhancement of visual processing. Accordingly, many different models of attention have proposed that attentional biases are coded directly within the baseline activation profile of behaviourally relevant perceptual representations (Desimone & Duncan, 1995; Driver & Frith, 2000; Kastner & Ungerleider, 2000; Reynolds & Heeger, 2009). As suggested by Driver and Frith (2000), "generating an image of the target property in the mind's eye may serve as the 'target template'".

According to the biased competition model of attention, top-down control mechanisms increase spontaneous firing within neural populations that code task-relevant perceptual information (Desimone & Duncan, 1995). Studies using single-unit neurophysiology in non-human primates have suggested that an attentional cue for a specific target stimulus modulates baseline activity in neurons that preferentially respond to that stimulus (Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, et al., 1993). For example, Chelazzi and colleagues

(1998; 1993) recorded from single neurons within area IT during the delay period of a cued visual search task. In this task, the monkeys were cued by an object to be selected from an upcoming array. Their findings indicated that neurons that responded optimally to a particular cue stimulus maintained an above-baseline firing rate until the onset of the target array. Similar modulations have also been observed in response to spatial cueing within retinotopically organised extrastriate visual areas (Luck, et al., 1997).

In humans, fMRI studies of attention have also shown differential increases in baseline activity across retinotopically specific regions of visual cortex during spatial attention (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Ress, Backus, & Heeger, 2000; Silver, Ress, & Heeger, 2007; Stokes, Thompson, Nobre, & Duncan, 2009). Stokes and colleagues (2009) explored this preparatory activation of task-relevant perceptual representations in visual cortex using multivoxel pattern analysis (MVPA) of functional neuroimaging data. The MVPA is a type of analysis that enables the comparison of the pattern of activation across populations of neurons (for reviews see Haynes & Rees, 2006; Norman, Polyn, Detre, & Haxby, 2006). In order to determine whether top-down attentional biases pre-activate the target template, the experimenters first characterised the pattern of neuronal activations to viewing an X or an O stimulus using a separate, pattern-localizer task. In an object-based attention manipulation, participants were cued, via an auditory tone, to attend for a specific target in preparation to detect faint stimuli that were embedded within visual noise. This experimental design allowed the authors to investigate the extent to which the same population codes that were activated in the pattern-localizer task would be

present in the activation elicited by the auditory cues (i.e. in absence of any visual input). Their findings indicated that presentation of the auditory cue was followed by a selective activation of target-specific neuronal subpopulations within lateral occipital complex (a shape-processing visual area), even before the onset of the visual target. The activation persisted until a target appeared or throughout trials in which no target was presented, and correlated with behavioural measures of perceptual discrimination of the target. This result supports the idea that an elevated baseline activity could potentiate (or prime) subsequent neural processing.

Recently, new evidence has given further support to the idea that anticipatory neural activity is a central mechanism for the attentional enhancement of stimuli processing. Studies investigating oscillatory activity preceding an event onset have found that attention also modulates visual processing by changing the frequency pattern of this activity (for reviews see Fries, 2009a; Palva & Palva, 2007; Schroeder & Lakatos, 2008, 2009). In the next section, I will discuss these new findings, and consider how these modulations might occur.

1.2. Oscillatory activity as a mechanism for controlling neural excitability

When Hans Berger first recorded electrical activity coming from the brain, developing what we now know as the electroencephalogram (EEG), one of

his first observations was on a specific frequency of the brain waves that was clearly enhanced when participants had their eyes shut (Berger, 1929). Berger described these waves as a "rhythmic oscillation of potential at a frequency of 10 cycles per second ... detected in the human subject by electrodes applied to the head ... present when the subject lies quietly with eyes closed and disappearing when attention is fully occupied" (1929). The years that were to follow Berger's discovery were accompanied by a mixture of extreme interest and suspicion as to whether the signal recorded by Berger was actually deriving from brain activity. Adrian and Matthews (1934a), two of the most prominent neuroscientists at the time were immediately excited about Berger's findings, however, they were not completely convinced that the then called 'Berger Rhythm' was not purely an artefact related to muscles or eye movements. In their own words:

> We found it difficult to accept the view that such uniform activity could occur throughout the brain in a conscious subject, and as this seemed to us to be Berger's conclusion we decided to repeat his experiments. The result has been to satisfy us, after an initial period of hesitation, that potential waves which he describes do arise in the cortex, and to show that they can be explained in a way which does not conflict with the results from animals. (p. 356)

It was only after a series of studies in the beginning of the 1930's conducted in the University of Cambridge by Adrian and Matthews - including measurements taken directly from the brain in trephined patients (i.e. with a hole in their

skull) (1934b) - that Berger's findings were confirmed and started to be widely accepted. At the time, the findings from trephined patients were fundamental, mainly because the signal recorded from these patients was not distorted by the skull. Therefore, Adrian and Matthews were confident that the Berger oscillations were coming from the brain, and were not just an artefact from muscles of the face and neck.

Unfortunately, the enthusiasm for Berger's findings did not seem to last for long, and in the ensuing decades there was a decline in the investigation of the brain rhythms in humans (Buzsáki, 2006). Part of this indifference is due to the notion that the 'Berger rhythm' - currently more commonly known as alpha rhythm - was just something that appears when you close your eyes, and disappears when the eyes are open.

It was not until researchers started to associate these oscillations with brain function, that the field really started to grow. Over the last two decades there has been increasing evidence associating neuronal oscillations in defined frequency bands with a variety of cognitive functions (for reviews see Fries, 2009a; Palva & Palva, 2007; Schroeder & Lakatos, 2008, 2009) and mental states (Sarma, et al., 2010; Uhlhaas, Haenschel, Nikolic, & Singer, 2008; Uhlhaas & Singer, 2006, 2007, 2010) (see Table 1).

Even though there is still some controversy in the field (see Shadlen & Movshon, 1999), there is an increasing consensus that neuronal oscillations play a functional role in brain operations (Buzsaki & Draguhn, 2004). In support of this idea, there have been some recent methodological studies showing a reliable correlation between brain oscillations and intra-cortical local field potentials, multi-unit activity (Whittingstall & Logothetis, 2009) and BOLD signal (Goldman, Stern, Engel, & Cohen, 2002; Laufs, et al., 2003; Mayhew, Dirckx, Niazy, Iannetti, & Wise, 2010; Yuan, et al., 2010).

1.2.1. Physiological bases of oscillatory activity

The neuronal mechanisms responsible for generating oscillatory activity and its synchronisation have been extensively studied. However, the exact

mechanisms by which such oscillations are generated are still not fully understood. It is largely accepted that local field potentials (LFPs) and electroencephalogram (EEG) are mainly generated by transmembrane currents occurring synchronously in ensembles of neurons (see Chapter 2 for more details on EEG). Schroeder and Lakatos have shown that the regular 'oscillation' in LFP voltage measured across cortical layers reflects the rhythmic (and synchronous) alternation of inward and outward transmembrane current flow in the local neuronal ensemble (Lakatos, et al., 2005). By analysing concomitant local neuronal firing using multiunit activity (MUA), Lakatos and colleagues (2005) showed that brain oscillations reflect shifting between net depolarised and hyperpolarised states in the local neuronal ensemble. These findings are in agreement with a hypothesis proposed by Bishop nearly eighty year ago. Bishop (1933) was one of the first scientists to suggest that the neuro-electric oscillations reflect cyclical variations in neuronal excitability.

No one knows exactly how many oscillators there are in the brain. The most accepted classification proposes five major oscillatory bands: *delta*, 0.5 - 4 hertz; *theta*, 4 - 8 hertz; *alpha*, 8 - 12 hertz; *beta*, 12 - 30 hertz; *gamma*, >30 hertz. However, such division is somewhat arbitrary, since oscillations generated by the same physiological machinery in different species often fall into different bands with different names (Buzsáki, 2006).

The alpha-band rhythm has been the most strongly associated with visual attention studies in humans, and therefore is the focus of this thesis. The work done by Lopes da Silva and colleagues in the 1970's has suggested an ac-

tive interaction between the thalamus and cortex as the basis of alpha rhythm generation (for reviews see Hughes & Crunelli, 2005; Lopes da Silva, 1991). Isolated thalamic alpha rhythms can also be observed (Lopes da Silva, van Lierop, Schrijer, & van Leeuwen, 1973a, 1973b). However, this activity is unlikely to be visible in non-invasive EEG recordings in humans.

1.2.2. Oscillations and attention

Recently, there has been and increasing interest in the role of slow brain oscillations in attention. It is interesting to point Berger's (1929) intuition that the alpha waves disappear because "attention is fully occupied" was surprisingly close to our current understanding, even though it was based on insufficient, anecdotal evidence (i.e. eye opening). This phenomenon is now referred to as alpha desynchronisation (or suppression), and is believed to be intrinsically related to attentional processing (Fries, Reynolds, Rorie, & Desimone, 2001; Muller & Keil, 2004; Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Womelsdorf & Fries, 2007; Worden, Foxe, Wang, & Simpson, 2000).

Using a technique to isolate and quantify the amount of activity within the alpha-band frequency over time, known as the temporal spectral evolution (TSE) technique, Worden and colleagues (2000) provided one of the first pieces of evidence linking anticipatory alpha modulation to the spatial allocation of attention. In an endogenous spatial orienting task, central cues indicated to which hemifield the participants should direct their attention. Time-frequency analysis was performed during the interval between cues and targets. The

authors found that the power in the alpha-band activity increased (reflecting increased synchronisation) over the hemisphere that was contralateral to the distractor (i.e. ipsilateral to the cued direction of attention). This finding indicates that the anticipatory alpha activity is likely to be enhancing visual processing for relevant events and/or suppressing visual processing for irrelevant events.

Thut and colleagues (2006) performed another study that has been fundamental for enhancing the understanding of the linkage between attention and slow brain oscillations. In this task, symbolic auditory cues indicated the hemifield in which a visual target was more likely to appear. The use of auditory cues helps to dissociate between cue and target related brain activity. The authors reported a lateralised alpha-band desynchronisation preceding the onset of a visual target. These effects over occipital sites were dominated over the hemisphere contralateral to the attended position. Interestingly, a comparison between alpha activity and behavioural data revealed that reaction times were faster to targets that were preceded by these changes in alpha activity. These results were recently confirmed in a MEG experiment (Wyart & Tallon-Baudry, 2009). Using an endogenous orienting manipulation, Wyart and Tallon-Baudry (2009) recorded MEG from participants who were required to discriminate a low-contrast grating presented at a cued or non-cued location. The results indicated that spatial attention suppresses alpha-band signal in lateral occipital visual areas.

The studies described so far suggest two possible different functions for the alpha oscillations: inhibition of distracting, competing stimulation or fa-

cilitation of task-relevant, target stimuli. The increase in alpha power contralaterally to distractors found by Worden and colleagues (2000) suggests that the main function of alpha is to inhibit (or suppress) irrelevant events. On the other hand, Thut's and Wyart's findings favour a facilitatory function, as alpha activity was suppressed contralaterally to the target (Thut, et al., 2006; Wyart & Tallon-Baudry, 2009).

Recently, Rihs and colleagues (2009) attempted to arbitrate between the inconsistent findings about alpha-band oscillations in spatial attention. In their experiment, EEG was recorded whilst participants were required to respond as quickly as possible to a target that could appear after an interval 700 or 1900 ms (randomised across trials). Central cues indicated the location to which the participants should direct their attention. The time-frequency analysis was focused on the last 200 ms before target onset (i.e. 500 to 700 ms in the short and 1700 to 1900 ms in the long intervals). The results revealed that alpha activity was diminished in the early phase of the orienting task. However, analysing the time-course of alpha activation during the long cue-target delay, the authors found that this early facilitatory process was followed by a spatially-specific sustained increase in alpha-band power directed towards to-be-ignored positions. The authors speculated that these differences in the time-course of alpha activity were due to an increased need for suppressing input from to-be-ignored locations in the long interval condition to prevent reflexive reorienting to this position (Rihs, et al., 2009). However, this study contains some considerable limitations that hinder any major generalisation of their findings. For example, previous studies found that increase in posterior alpha activity is associated with

holding items in working memory (Jensen, Gelfand, Kounios, & Lisman, 2002). Therefore, the alpha synchronisation found only during the long cue-target delay could be more associated with working memory, than attentional processes. Also, as I will describe later, their data are potentially confound by temporal expectations.

Another study that has been fundamental for enhancing our understanding of slow brain oscillations and visual perception was performed by Capotosto and colleagues (2009). These authors combined EEG and rTMS in a classical endogenous spatial orienting task. The stimulus-onset asynchrony between a central cue and the target was fixed at 2s. rTMS was delivered to the frontal eye field (FEF) or intraparietal sulcus (IPS) at cue onset for 150 ms. EEG recordings were used to monitor the effect of rTMS disruption on occipital alpha-band activity in anticipation to the target. Behavioural results showed an impairment of target identification when rTMS was applied to right IPS or right FEF while subjects attended to a spatial location. Time-frequency analysis performed on the EEG data indicated that the behavioural effect was associated with the disruption of anticipatory alpha desynchronisation.

Studies investigating changes in oscillatory activity related to attention have also been carried out in non-human primates, in which it is possible to examine the cellular bases of these effects. Using an endogenous spatial attention design, Fries and colleagues (2001) recorded simultaneously local field potentials (LFPs) and action potentials from a small population of neurons (multiunit activity) in visual area V4, with overlapping receptive fields (RFs). The monkey's

attention was directed by a line next to the fixation spot, pointing to the location of the target. After a brief fixation period, two stimuli were presented at equal eccentricity, one inside and one outside the RF. On separate trials, the monkey's attention was directed to either stimulus location. The authors then compared neuronal activity between attending to the stimulus inside versus outside the RFs. Their results indicated a lowering of power of activity in lower frequency bands, including alpha, and less temporal correlation between the multi-unit recordings of action potentials and the lower frequency bands of the LFP. Interestingly, spatial attention reduced this low-frequency synchronisation both during the delay and stimulus period.

In the study performed by Fries and colleagues (2001), they also found that attention modulates higher frequency bands (gamma). The involvement of gamma oscillations in perceptual and attentional processes has been widely studied (for reviews see Fries, 2009b; Fries, Nikolic, & Singer, 2007; Fries, Scheeringa, & Oostenveld, 2008; Schroeder & Lakatos, 2009; Uhlhaas, et al., 2009). Contrary to what is found in lower frequency oscillations, gamma activity is enhanced by attentional orienting (Bichot, Rossi, & Desimone, 2005; Fries, et al., 2001; Taylor, Mandon, Freiwald, & Kreiter, 2005; Womelsdorf, Fries, Mitra, & Desimone, 2006). More specifically, animal studies have shown that selective attention to a visual stimulus enhances the gamma-band synchronisation within neurons in extrastriate visual cortex driven by that specific stimulus.

Similar to the neuroanatomical studies previously discussed, anticipatory changes in neural oscillations also indicate that one of the mechanisms by

which attention enhances perceptual processing is by shifting the baseline patterns of oscillation in visual areas. Attentional modulation in oscillatory activity across different bands could be priming the neural processing of forthcoming events, as proposed by the biased competition model. In line with this proposal, Fries (2009a) suggests the gamma-band synchronisation could be the underlying mechanisms by which attention influences visual processing. The basic idea is that synchronisation of action potentials at a high frequency (gamma-band) indicates that their activity tends to hit receiving (efferent) neurons together in a way to enhance temporal summation of their signal and thus help ensure that their message gets through.

A recent study recording MEG in human participants gave further support to the idea that top-down preparatory states of attention are accompanied by increases in gamma-band activity in visual areal (Siegel, Donner, Oostenveld, Fries, & Engel, 2008). In this study, participants performed a spatially cued motion-discrimination task. The study used a novel source-reconstruction technique to investigate the sources of oscillatory activity within, and between, several cortical regions simultaneously. The results indicated that visuospatial attention modulated gamma oscillatory synchronisation between the frontoparietal networks and visual areas in a spatially selective fashion. Strikingly, the authors found that specific oscillatory synchronisation at most stages of the human dorsal visual pathway may enhance the processing of attended visual stimuli. This study provided some of the most convincing evidence that frequency-specific synchronisation between frontal (FEF), parietal (IPS), and visual (V1/V2/MT) cortex is a central mechanism for attentional selection.

One might be asking why the brain would rely on frequency bands to influence the pattern of spiking? Buzsáki (2006), and others (see Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008; Schroeder & Lakatos, 2008), have proposed that one of the main functions of neural oscillations is to prepare the brain machinery to the *timing* of events. More specifically, having different oscillatory bands (from *fast* to *slow*) enables the brain to prepare for motor responses and prepare the sensory system in anticipation of environmental events. All these functions are clearly involved in attentional processes. In the next section I will explore specifically how the brain 'prepares the sensory system in anticipation of environmental events' in order to optimise perception and action.

1.3. Directing attention to instants in time

Over the years cognitive psychologists and neuroscientists have been trying to tackle the problem of how temporal information about events can bias our behaviour (see Nobre & Coull, 2010). Some of the first evidence of how temporal information can improve behavioural performance was found by Herbert Woodrow (1914). Woodrow described a set of experiments in which he found that the temporal interval between a warning cue and a target (foreperiod) had a significant effect on reaction time tasks. Woodrow found that reaction times were longest after the shortest foreperiod and became faster as the foreperiod increased (Woodrow, 1914). The foreperiod effect became one of the most well studied effects in the temporal attention literature, and Woodrow's

findings were consistently confirmed (Los, 2004; Los, Knol, & Boers, 2001; Los & Schut, 2008; Los & van den Heuvel, 2001; Niemi & Naatanen, 1981; Vallesi, et al., 2007a; Vallesi, Shallice, & Walsh, 2006, 2007b)

Another landmark in the temporal expectation literature happened in the late 1990's, when Nobre and Coull published a series of papers providing the first evidence of voluntary orienting of attention in time (Coull & Nobre, 1998b; Miniussi, Wilding, Coull, & Nobre, 1999; Nobre, Coull, Frith, & Mesulam, 1999). In a temporal version of Posner's (1980) endogenous attention task, symbolic central cues predicted the appearance of a central target stimulus after a short or long interval. The task required simple speeded detection of the target stimulus. The results indicated that temporal orienting cues shortened reaction times only to targets appearing at the first, short interval. After passage of a short interval, it became highly predictable that the target would occur at the longer interval independently of the cue information, enabling participants to reorient their attention to this next relevant time point (Coull, Frith, Büchel, & Nobre, 2000). This effect is compatible with improved performance at the longer foreperiods in variable foreperiod tasks (Correa, Lupianez, & Tudela, 2006b). These findings were the first demonstration of our ability to orient attention flexibly and voluntarily to the anticipated timing of task-relevant events. Importantly, different from the previous foreperiods tasks, the paradigm developed by Nobre and Coull allowed manipulation of temporal orienting on a trial-by-trial basis.

1.3.1. Exogenous Temporal Orienting and the Entrainment Model of Attention

In an extensive review paper published in 1976 entitled "Time, our lost dimension: Toward a new theory of perception, attention, and memory", Mari R. Jones established the first steps of what it would later become known as the Entrainment Model of Attention (Jones, 1976). According to Jones, attentional resources 'pulse' in an oscillatory manner, distributed in time by a simple phase oscillator. Importantly, these attentional oscillations can be entrained by external rhythmical stimuli. When not entrained, the phase and period drift around the focus widens (Figure 2). In the presence of external rhythmical stimuli, however, period and phase become entrained to the rhythm, and the focus narrows to the emphasised points in time. The consequence of this focus on specific time points is that stimuli that occur when expected are processed more effectively, whereas those that occur at unexpected times suffer processing deficits (Barnes & Jones, 2000; Large & Jones, 1999).

A major support for the Entrainment Model of Attention was found by Jones and colleagues (2002). In this study, a target tone was presented at the beginning of a trial, followed by a series of tones with an embedded rhythmicity. Participants were then asked to respond to a probe tone presented at variable intervals following the end of the rhythmic sequence. Task performance was enhanced on trials when the probe tones were presented in-phase with the rhythmic sequence, compared to those presented out-of-phase. According to the authors, this result indicates that temporal attention was tuned by predictable events. In other words, periodic tones entrained attention and had the effect of narrowing the temporal selection window of attention, and increased the attentional gain (better signal-to-noise ratio) for stimuli that occurred at the in phase with the entrained period.

Recent studies have also supported the idea of the "entrainment of attention" in the visual domain (Ariga & Yokosawa, 2008; Mathewson, Fabiani,

Gratton, Beck, & Lleras, 2010). Mathewson and colleagues (2010) presented a backward-masked target at near-threshold, preceded by a series of rhythmic rapid visual stimuli (SOA = 82 ms), as temporal cues. Temporal orienting was manipulated both by changing the number of cues preceding target presentation (none, 2, 4 and 8 cues), as well as the interval between the last cue and target onset (32, 59, 82, 107 and 130 ms). It is important to notice that a target presented at 82 ms was in-phase with the rhythmic sequence. Accuracy and perceptual sensitivity (d') for target detection were both improved when the target was presented in-phase with the rhythmic cues. According to the authors, this result indicates that awareness of near-threshold stimuli can be enhanced by entrainment to rhythmic events.

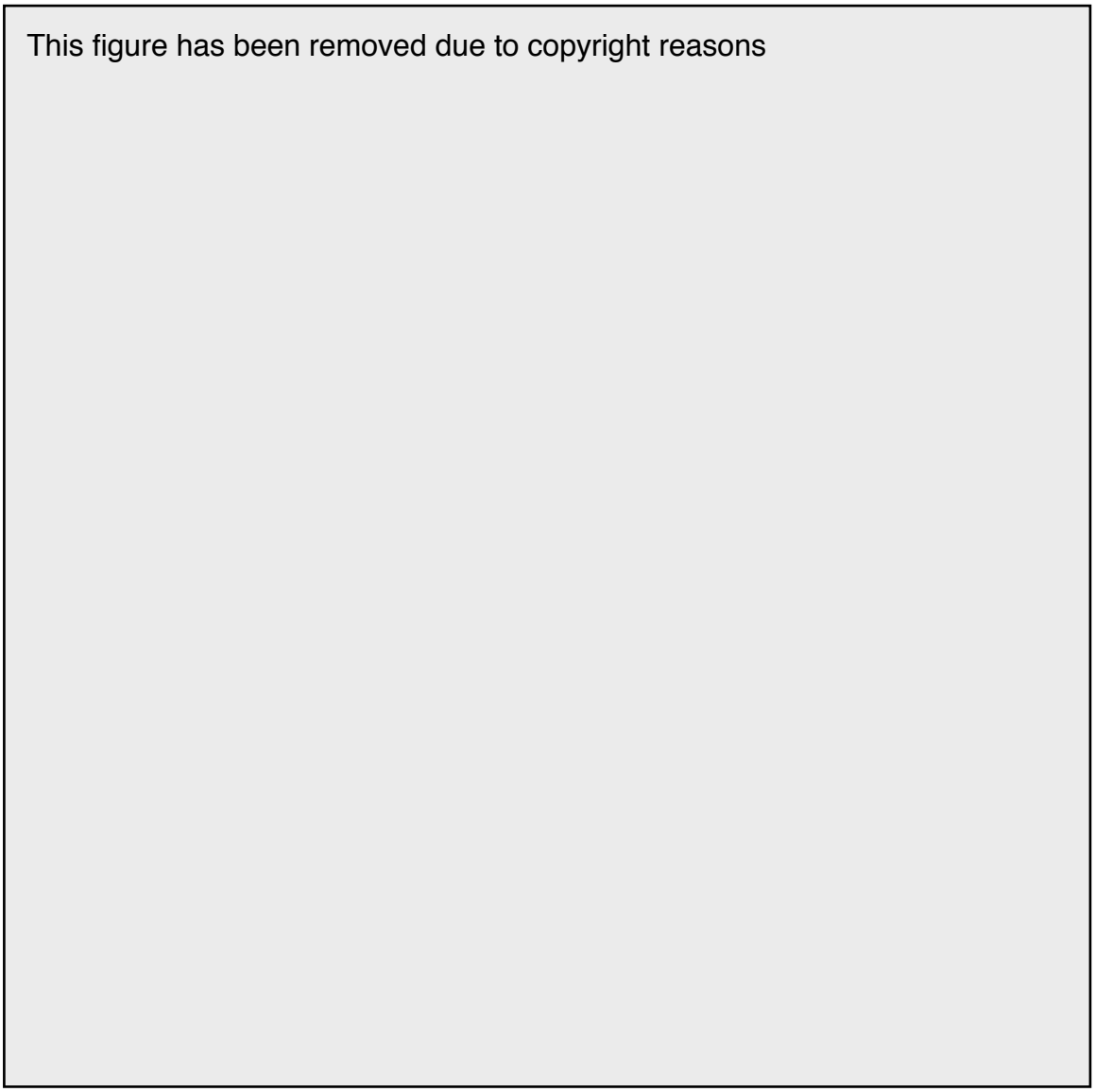
Doherty and colleagues (2005) manipulated temporal and spatial expectations about perceptual events using the trajectory of a moving stimulus. In this task, a stimulus (ball) appeared at the side of a display monitor and moved across to the other side of the monitor in discrete steps, passing 'under' an occluding band along its way (Figure 3). The participants' goal was to monitor the moving ball covertly, and to discriminate a small shape embedded within the ball upon its reappearance after occlusion. Temporal and/or spatial expectations were derived from the inherent dynamics with which the ball moved across the screen. In different conditions, the ball appeared at regular intervals (550 ms, temporal expectation) or at irregular intervals (200–900 ms, no temporal expectation), and following a linear spatial trajectory (spatial expectation) or erratic spatial trajectory (no spatial expectation). The ball remained occluded for two motion steps (1100 ms). Temporal and spatial expectations were manipulated in

a factorial fashion, to yield four possible types of expectation about when and/ or where the ball would reappear. In the condition of combined temporal and spatial expectations (TS), participants could predict the exact moment and location for the re-appearance of the ball after occlusion. In the condition of isolated temporal expectation (T), the participants could anticipate the exact moment but could not anticipate where along the vertical occlusion band the target would reappear. In the condition of isolated spatial expectation (S) the participants could anticipate the exact location but could not anticipate when the target would reappear after occlusion. In the no-expectation condition (N), the participants could anticipate neither the exact moment nor the location of target reappearance. Behavioural results confirmed the ability of both temporal and spatial expectations derived from the motion properties of the ball to shorten reaction times (additive main effects). This effect was replicated by Correa and Nobre (2008) using a variable occlusion period (short: 400–867 ms, medium: 868–1,333 ms, long: 1,334– 1,800 ms) on a trial-by-trial basis providing an important validation about the generality of the effects described by Doherty and colleagues (2005).

1.3.2. Dissociation between exogenous and endogenous temporal orienting

Coull and Nobre (2008b) recently proposed a taxonomy for the literatures on timing and temporal orienting of attention. Within temporal orienting, they propose a dissociation between voluntary (endogenous) and automatic (exogenous) temporal attention (Figure 4). Similar to the spatial attention counter-

part (Busse, et al., 2008; Corbetta & Shulman, 2002; Goldsmith & Yeari, 2003; Posner, 1980; Rosen, et al., 1999), endogenous temporal orienting (or Endogenous temporal expectations) is when attention is directed to a moment deliberately via informative pre-cues. This was the main type of manipulation used in early Nobre and Coull studies, in which the symbolic cue informed participants about the interval at which a target stimulus could appear (for a review see Griffin & Nobre, 2005). Exogenous temporal orienting (or exogenous temporal expectation), on the other hand, is established incidentally via a temporally regular stimulus structure (exogenous temporal expectation). In exogenous temporal orienting tasks, the structure of rhythmic cues directs attention. Studies using isochronous rhythmic presentation of events is presumed to tap into exogenous temporal orienting mechanisms, which proceed in a largely automatic fashion (Doherty, et al., 2005; Jones, et al., 2002). However, contrary to spatial attention studies, in the temporal domain there is no evidence of studies comparing the effects of endogenous and exogenous temporal orienting directly. The experiment presented in Chapter 3 of this thesis specifically tests for the existence and separability of these two forms of temporal orienting.



1.3.3. Neural mechanisms of temporal orienting

The study of the neural mechanisms underlying temporal orienting has proven particularly challenging. Contrary to other types of attention, where our basic understanding about the neural organisation of perceptual and motor systems has provided valuable guidance, in the temporal domain, this guidance was almost absent. When it comes to how temporal expectations are coded and

how they can influence information processing, insights from basic neuroscience are sorely lacking.

One possible guidance for the study of the neural mechanisms of temporal attention would be based on the neural system underlying the coding of temporal intervals on the scale that is relevant to organise cognition (see Nobre, 2010). However, very little is known about the *timing* system, and the very existence of a dedicated timing system in the brain is hotly debated. Some propose that temporal intervals are computed by a centralised neural system, possibly organised around thalamo-cortical-striatal motor circuits (Coull, Vidal, Nazarian, & Macar, 2004; Matell, Meck, & Nicolelis, 2003), the cerebellum (Ivry, 1996; Ivry & Schlerf, 2008) or their combination (O'Reilly, Mesulam, & Nobre, 2008). Others propose that the computation of temporal parameters occurs in a distributed fashion, across many or all neural systems (Karmarkar & Buonomano, 2007; Mauk & Buonomano, 2004; Nobre & O'Reilly, 2004). Within distributed models, temporal estimations have often been linked to circuits involved in processing spatial representations and spatially guided actions (Burr, Tozzi, & Morrone, 2007; Leon & Shadlen, 2003). Given this state of affairs, there is no clear theoretically motivated favourite starting point for identifying the system(s) that control the orienting of attention to relevant temporal intervals. Nevertheless, in the past 10 years, there has been an increase in the quest of how the brain uses temporal information to optimise our perception and behaviour.

1.3.3.1. Studies in the human brain

Due to their high temporal resolution, electrophysiological studies offer the possibility of assessing the modulatory effects of temporal attention on stimuli processing. Miniussi and colleagues (1999) showed that endogenous temporal orienting of attention in speeded target-detection tasks modulated late ERPs (P300) but had no effect on early visual potentials (P1, N1). Their results showed that temporal attention elicited a specific pattern of modulation affecting later, non-perceptual stages of stimulus processing. Similarly, a follow-up study by Griffin and colleagues (2002) contrasted temporal and spatial attention directly. Spatial attention enhanced the amplitude of early visual potentials (P1 and N1) while temporal attention modulated only the later N2 and P300 components. These findings suggested that endogenous temporal orienting has distinct modulatory effects upon stimuli processing. At least in simple speeded target-detection tasks, visual temporal orienting appeared to act mainly by modulating later, non-perceptual stages of processing, unlike spatial attention, which affected early, perceptual stages of stimulus processing.

Doherty and colleagues (2005) published a study challenging this notion that temporal expectations do not modulate early perceptual processing. As described previously, Doherty and colleagues (2005) used exogenous spatiotemporal cues (rhythmic) to induce temporal and spatial expectations orthogonally. The results replicated the characteristic amplitude enhancement of the contralateral visual P1 induced by spatial orienting. In the case of isolated temporal expectation there was no modulation of the early visual P1 potential, but again

later post-perceptual potentials showed the characteristic effects including the earlier latency of the late P300 potential. However, this experiment also revealed that, whereas temporal expectations in isolation exerted no effect upon the early visual P1 potential, when temporal expectations were combined with spatial expectations, they greatly boosted the effect of spatial expectation in enhancing the P1. These new findings suggest a sensible and ecologically valid way in which temporal expectations can selectively bias visual perceptual functions. The authors refer to this interaction as a "Synergistic Effect" of space and time. An interpretation of this effect is that exogenous temporal expectations for visual stimuli exert the strongest effects when coupled with predictions about other features that can be clearly mapped onto neuronal receptive-field properties.

1.3.3.1. Evidence from non-human primates studies

Single-unit studies have shown a modulation of spatial-attention effects by the evolving temporal probability of target appearance in areas V4 (Ghose & Maunsell, 2002), LIP (Janssen & Shadlen, 2005), IT (Anderson & Sheinberg, 2008) and, more recently, MT (Ghose & Bearl, 2010). In the majority of these studies, the temporal probability of target appearance was manipulated using hazard functions (i.e. the conditional probability of an event occurring at a given time given that it has not yet occurred) (for reviews see Luce, 1986; Nobre, et al., 2007).

Ghose and Maunsell (2002) recorded the spiking activity from the area V4 of the visual cortex while monkeys had to respond to a stimulus change. The probability of target occurrence changed over time. Their results indicated

that the activity in visual area V4 by spatial attention co-varied with the hazard function. This was the first study to demonstrate the effects of temporal expectations within perceptual areas. Using a similar manipulation, Janssen and Shadlen (2005) showed that the lateral intraparietal area (LIP) was also modulated by temporal expectations.

Recently, Ghose and Bearl (2010) investigated the changes in visual representations in the motion-sensitive middle temporal area (MT). Monkeys were trained to detect a brief motion pulse embedded in noise. The likely location of pulse appearance varied systematically in time so that during the first second, if a pulse appeared, it was more likely to appear within the receptive field (RF), whereas during the following second, the likely location was opposite to the RF. The authors then compared the neuronal activity in the receptive fields during periods when the animals were expecting the motion pulse with periods of time when they were not. The results indicated that activity within the receptive field changed consistently with an increased temporal likelihood of pulse occurrence.

The only single-unit study to investigate the effect of voluntary temporal orienting using endogenous cues was performed by Anderson and Sheinberg (2008). In this task, a set of 100 objects was used as both cues and targets. Each picture had two different meanings depending on whether it was the first (cue) or second image (target) in a trial. Macaque monkeys learned to associate each object to a button-press response (left and right) and to a cue-target delay interval (short or long). Then, if the object appeared as the first stimulus in the

trial it would cue the animals to the delay and the button that they should respond. Whereas if the object appeared after the cue it just indicated the motor response. Temporal cues were valid in 80% of the trials, in the remaining 20% the cues were invalid (i.e. the target would appear at the wrong cue-target interval). Neural responses were recorded from the inferior temporal cortex (IT): an extrastriate visual area known to be involved in object perception (Kriegeskorte, et al., 2008; McAdams & Maunsell, 1999; Tsao, Freiwald, Knutsen, Mandeville, & Tootell, 2003). The results indicated that the magnitude of the evoked local field potential (LFP) was reduced and delayed, and neuronal spiking was attenuated, when targets appeared unexpectedly early (invalid trials). This result restricted to the invalid trials is analogous to the effects on behavioural performance and late ERPs in human studies. These effects are concentrated at early interval because it is only at the short interval that the conditional probabilities are manipulated (i.e. after the short interval, the probability of target appearance is always 100%)

1.3.3.1. Might oscillations provide a natural way through which temporal regularity of events can organise neural excitability?

The entrainment of brain activity to sensory input has been observed in different levels, from the optic tectum in the larvae of zebrafish (Sumbre, Muto, Baier, & Poo, 2008) to the human auditory (Snyder & Large, 2005; Zanto, Snyder, & Large, 2006) and visual (Herrmann, 2001; Williams, Mechler, Gordon, Shapley, & Hawken, 2004) cortices. Using repetitive visual sensory stimuli for up to 20 s, Sumbre and colleagues (2008) observed rhythmic post-stimulation activity among specific neuronal ensembles of zebrafish larvae, with

a regular interval matching previous visual stimulation. This finding suggests that the entrainment of neural oscillations to visual stimulation can occur at very low levels of the perceptual system. Similarly, Williams and colleagues (2004) reported an entrainment of primary visual cortex of macaque monkey and humans to the refresh rate of video displays.

Recent studies have shown that slower rhythmic stimuli can also induce comparable neural oscillations (Herrmann, 2001; Snyder & Large, 2005; Will & Berg, 2007; Zanto, et al., 2006). In an EEG study, Will and Berg (2007) examined the activity over the auditory cortex in response to rhythmic auditory stimulations (i.e. drum sounds and clicks with repetition rates of 1–8 Hz) compared to silence and random-noise conditions, during a passive hearing task. Time-frequency analysis indicated an increase in synchronisation of brain oscillations following the periodic stimulation, peaking in the delta range (2 Hz). Using a similar paradigm, Snyder and Large (2005) found bursts of gamma oscillations (20 - 60 Hz) entrained to the rhythmicity of previously presented tones. Participants were asked to listen to the stimuli passively, while their EEG activity was being recorded. The tones were presented in an isochronous rhythmic manner (fixed SOA of 390 ms), but in 30% of the trials some tones were omitted. Interestingly, the results indicated that induced gamma activity predicted tone onsets, even when expected tones were omitted.

Lakatos and colleagues (2008) provided some of the first evidence that the entrainment of neuronal activity to external events in early sensory areas can be modulated by attention. In their study, interdigitated auditory and

visual stimuli (beeps and flashes) were rhythmically delivered to two macaque monkeys, while multi-electrode arrays were positioned to straddle the layers of V1 to record brain activity. The interval between events within modality was jittered in a Gaussian distribution around a mean of 650 ms, therefore, the intervals between modalities was around 300 ms on average. In different blocks, the animals had to attend to either the visual or the auditory stimulus stream and make a manual response to an infrequently presented deviant stimulus (i.e. differed slightly in intensity). The results revealed that delta-band oscillations became entrained to the rhythm of the attended stimuli, within which burst of gamma-band activity became nested. As a consequence of their coupling to delta oscillations, gamma activity displayed an increase in amplitude near the visual stimulus onset when monkeys were required to attend to the visual stimuli, but a decrease in amplitude near visual stimulus onset in the 'attend to auditory' condition. This coupling between the phase of delta to power of gamma activity resulted in increased response gain for task-relevant events and decreased reaction times. Accordingly, Schroeder and Lakatos propose that alignment of low-frequency oscillations (in the delta range) to the timing of rhythmic or regular events, and the nesting of gamma oscillations to these low-frequency carrier rhythms, provide a central mechanism for regulating cortical excitability by temporal expectations (Lakatos, et al., 2008; Schroeder & Lakatos, 2008).

The experiments presented in chapter 4 and 5 investigated whether there is an entrainment of rhythms relevant to spatial attention when temporal expectations were added. Additionally, the experiment in Chapter 5 also tests whether this entrainment can also occur in the absence of spatial expectations.

1.3.3.2. Functional neuroimaging of temporal orienting

The first imaging study to examine the neuroanatomical correlates of temporal orienting was done by Coull and Nobre (1998b). In this study, they used PET and fMRI to identify brain areas activated by attentional orienting to temporal intervals and drew a comparison between the cortical substrates of temporal and spatial orienting. To separate brain activations that were specific to temporal versus spatial orienting, this study used four conditions in a factorial design (Space, Time, Spatiotemporal and Neutral) – plus a basic rest condition. Endogenous central cues oriented attention to temporal intervals or spatial locations in turn. They found a common pattern of activation in frontal and parietal regions when temporal and spatial attentional orienting were contrasted against a simple visual-fixation task. This result indicated that both spatial and temporal orienting engaged a similar network of parietal and frontal areas which serves attentional orienting regardless of the particular context of expectations. When temporal and spatial attentional orienting were contrasted directly, temporal orienting preferentially activated the left IPS and left inferior premotor cortex, while spatial orienting activated the right IPS, revealing some degree of separation in the pattern of activation according to the type of expectations required in the task. In a similar paradigm, Coull and colleagues (2000) used event-related fMRI and foveal stimuli to investigate temporal orienting independent of spatial expectation. They showed that temporal orienting activated inferior parietal, inferior premotor and prefrontal areas in the left hemisphere predominantly. The authors noted that the pattern of activation was similar to that seen during motor preparation (Krams, Rushworth, Deiber, Frackowiak, &

Passingham, 1998) and motor attention tasks (Rushworth, et al., 2001a; Rushworth, et al., 2003) and suggestive of a close link between orienting attention to time and to motor acts.

1.3.3.3. Control of temporal orienting

Despite growing acknowledgement of the importance of temporal orienting of attention, little is known about its neural control mechanisms. It remains unclear whether there exists a core control network responsible for coding temporal regularities and signalling these in a top-down fashion to perceptual and/or motor areas engaged in ongoing tasks; or whether temporal expectation is coded locally within brain areas engaged by a given task (for reviews see Coull, 2010; Coull & Nobre, 2008b; Nobre, 2010).

As previously mentioned, an initial set of experiments investigating temporal attention implicated a common network that largely overlapped with the motor preparation system. Areas such as the IPS and preSMA have consistently been associated with temporal predictability, whether of a motor or perceptual nature. Studies of both simple (Sakai, et al., 2000) and choice RT (Dreher, Koechlin, Ali, & Grafman, 2002; Praamstra, 2006) have identified increased activity in left premotor and inferior parietal cortices when targets are presented after temporally predictable rather than random intervals, or when subjects use informative temporal pre-cues to predict target onset (Coull & Nobre, 1998b). These same regions are also activated by temporal prediction of a more perceptual nature, when subjects use temporal information inherent in the velocity of a dynamic visual stimulus to predict its final position (Assmus, Marshall, Noth,

Zilles, & Fink, 2005; Assmus, et al., 2003; Coull, Vidal, Goulon, Nazarian, & Craig, 2008; Field & Wann, 2005). These areas provide a good hypothesis for studies investigating the possible dissociation between motor and temporal orienting.

The inferior parietal cortex has also been implicated in motor orienting of attention (or "motor intention") (Rushworth, et al., 2001a), in which subjects are cued to respond to a target with a particular motor effector. Such neuroanatomical overlap may indicate that activation of left inferior parietal cortex by temporal orienting is simply a consequence of motor intention mechanisms being recruited incidentally. However, not much further work has been done on this because of extreme difficulties in teasing apart cue-related and target-related brain activity using fMRI. One common problem is that most temporal orienting tasks require systematic temporal correlations between stimuli, which bundle the hemodynamic response function. Therefore, it still unclear whether the overlap between temporal and motor orienting is bound to the specific experimental parameters. Therefore, in chapter 6 I present an experiment that approaches this issue directly by comparing and contrasting temporal and motor orienting using fMRI.

Chapter 2

2. Methods

2.1. Electroencephalography

The first study to record electrical signals coming from the human brain was done by Hanz Berger (1929). At the time of his discovery, Berger was trying to study if humans could communicate by sending brain waves through the air (i.e. telepathy). Even though his studies failed to confirm his hypothesis, Berger discovered one of the most important tools in human neuroscience - the Electroencephalogram (EEG).

The main advantage of the EEG compared to fMRI or PET, is its temporal resolution. The EEG is also the only method (with its counterpart MEG) that provides a direct measure of brain activity non-invasively in humans. In this chapter, I will briefly describe the basic principles of EEG, and the processes involved in running and analysing EEG experiments.

2.1.1. The neuronal origin of the EEG signals

The EEG provides a direct measure of the ongoing electrical activity in the brain, recorded at the scalp in the form of small voltage fluctuations. These fluctuations are a product of changes in the electrical current mainly caused by postsynaptic activity. In more detail, when a neuron is depolarised, capacitative currents flow inwards over the dendritic membranes. To complete the circuit, this is counterbalanced by outward capacitative currents across the cell membrane of the more basal dendrites. Together, the negativity at the apical dendrites and the positivity at the cell body create a dipole. However, the dipoles produced by single neurons are relatively weak and cannot be measured at the scalp. The voltage changes can only be recorded at the scalp when a large number of parallel-oriented neurons that are well aligned and similarly oriented depolarise in a synchronous fashion, producing a summation of dipoles from many different cells, which together form a much stronger dipole. Lorente de Nó (1947) referred to this as an *open-field* (Figure 5). Therefore, field potentials can only be recorded as EEG from the scalp if the open-field potentials are strong enough, and have the right orientation (Gray, Konig, Engel, & Singer, 1989; Luck, 2005). In the brain, the main source of these open fields comes from pyramidal neurons within the cortex. Therefore, the EEG signal is believed to be derived from excitatory synaptic potentials in the nearby and well oriented pyramidal cortical cells (Allison, Wood, & McCarthy, 1986). It is fundamental for anyone using EEG to understand that the signal detected at the scalp is a selective measure of neural activity, typically biased towards postsynaptic potentials in cortical pyramidal neurons.

There are two main challenges researchers face when attempting to trace back the localisation of a signal based on EEG data: the "inverse problem" and the volume conduction (Plonsey, 1963).

The "inverse problem" emerges when one tries to back estimate a specific dipole location based on data recorded from the scalp. One way to understand the "inverse problem" is by tracing a comparison to a simpler type of problem: "the forward problem". The "forward problem" involves computing the distribution of voltage that would be observed at the scalp for dipole(s) in known location(s) and orientation(s). However, when there is no initial information about the dipole location or orientation this problem becomes mathematically intractable (underdetermined). The "inverse problem" denotes that the signal detected by the EEG could reflect an infinite number of potential configurations and pathways from which it could originate, and therefore, it is insoluble (Helmholtz, 1867/2000; Luck, 2005).

The problem of volume conduction relates to the propagation of voltage through the different tissues in the head. The spread of electrical activity generated by populations of neurons is differentially influenced by the various elements of the head, such as the skull and the scalp, which have different conduction properties. Electrical activity follows the path of least resistance and, therefore, may be distorted or blurred by the configuration of different tissues. For example, since electricity tends to follow the path of least resistance, electrical signals coming from the field potentials tend to spread laterally when they encounter the high resistance of the skull. The spread of electricity greatly blurs the surface distribution of voltage.

2.1.2. The EEG recording and the myth of the 'perfect reference'

Arguably, the most important stage in an EEG experiment is the recording. As pointed out by Luck (2005) in his book: 'there is no substitute for good data'. Ideally, any researcher using EEG is aiming for 'artefact free' data, and, even though 'artefact free' data do not really exist, there are ways to minimise the amount of noise in the EEG signal. Small details, such as making sure that the participant is comfortable and checking the impedance level for each electrode (preferentially $< 5K\Omega$), can make a big difference in the quality of the EEG signal.

EEG is typically recorded from electrodes arranged on the scalp according to the 10-20 system (AEEGS, 1991). This system is so called because it

places electrodes at 10-percent and 20-percent points along lines of latitude and longitude. The first step in this system is to define an equator, which passes through the nasion (the depression between the eyes at the top of the nose, labelled Nz), the inion (the bump at the back of the head, labelled Iz), and the left and right pre-aurical points (depressions just anterior to the middle of the pinnae, labelled A1 and A2). A longitude line is then drawn between Iz and Nz, and this line is then divided into equal sections that are each 10 percent of the length of the line. Additional latitude lines, concentric with the equator, are then placed at these 10 percent points.

The potential from each electrode site is compared with that at a selected reference site (Nunez, 1981). Ideally, the reference electrodes should be placed at sites that are presumed to be unaffected by task-dependent electrical activity, enabling the removal of common background noise from the waveforms. In the search for this 'neutral spot', neuroscientists have tried a vast number of different parts in the human body, such as nose, chin, earlobe, mastoids (the bony protrusion behind each ear), neck and big toe (Luck, 2005). However, there are no completely electrical neutral sites, and the voltage recorded between an active site and a reference site will always reflect activity at both of the sites. The most important factor involved in choosing a reference is that sites which are biased toward one hemisphere should be avoided. A common solution is to combine mathematically the left and right mastoids by using an average reference derivation. Average mastoids is a relatively safe reference to use because potentials at the mastoids are greatly attenuated due to the distance of this site to the brain, and by the thick bone plate underneath. In addition, the risk of

muscle artefacts at this site is minimal, and since this reference is used across many laboratories it enables comparison to data from other laboratories (Nunez, 1981).

2.1.3. Processing and filtering the data

The procedures of choice for processing and filtering of EEG data depend on how the researcher wants to analyse the data. For example, the same EEG data can be used to run time-frequency analysis or to calculate event-related potentials (ERPs).

The first step of processing EEG data is to remove, or to correct, trials contaminated by artefacts. Artefacts may lead to erroneous conclusions about the effects of an experimental manipulation. There are several types of artefact that can contaminate EEG recordings. This artefacts can be due to electrical noise in the environment (e.g. related to the monitor, power or lights), or due to physiological factors, such as blinks (most common), eye movements, muscle activity, subject movements, and skin potentials. The eye-blink response consists primarily of a monophasic deflection of 50-100μV with a typical duration of 200-400 ms. Therefore, one possible approach would be to set a threshold above these values, so that these artefacts would be automatically rejected. Other types of artefact might also involve drifts in the EEG signal in one or more channels. *Focused voltage drifts* can be caused by movement of the subject during the experiment. *Spread voltage drifts* are usually caused by a change in the impedance of the skin or the electrodes. Whilst *focused drifts* are easily de-

tectable, and therefore can be simply rejected, *spread voltage drifts* are hard to identify, and almost always the safer way to control for its distortions is to apply a very low frequency filter. Filtering the EEG signal is often necessary in order to reduce the excess of noise in the data (e.g. artefact induced by the displays refresh rate, slow drifts). There are three main types of filters: *High-pass filters* - attenuate low and pass high frequencies; *Low-pass filters* - attenuate high and pass low frequencies; and *Bandpass filters* - attenuate both high and low frequencies. It is important to point out that filters should be used with caution and only in ranges that are well outside frequencies of physiological interest, in order to avoid distortions in the shape or time course of event-related potentials. The use of filtering should also be minimised or kept safely outside the range of frequencies used for time-frequency analyses of brain oscillations. The Nyquist sampling theorem, which broadly states that the accurate measurement of an analog process requires sampling at least twice the rate of this process, provides a safe guideline for setting maximal filter values.

2.1.4. Interpreting the EEG data

2.1.4.1. Event-related potentials

After artefact removal, the EEG signal can be time-locked and averaged to the onset of sensory, motor, or cognitive processes of interest. This procedure averages together all the consistent neural signals related to the processing of the even of interest whilst removing or minimising all the variable sources of signal related to the various sources of artefact and noise. Deflections in the

ERP waveforms are usually referred to as components, or potentials, that can be described in terms of their polarity, latency and amplitude. An ERP component is usually described in terms of whether the peak is a positive or negative inflection, followed by a number to indicate either the latency or the ordinal position of the peak (e.g. P100 describes a positive going peak occurring around 100 ms after the stimulus onset). In terms of its interpretation, the latency of an ERP helps us to understand which stage of the neural process that component reflects (e.g. perceptual, decision making, or motor). However, the polarity of the peak is not believed to hold any particular significance (e.g. a negative peak does not mean underlying inhibitory processes), but instead depends on the particular position of the active electrode reference electrodes relative to the neuronal population(s) generating the signal (Allison, et al., 1986; Clark, et al., 1995).

Analysis of ERPs in terms of polarity and time latency alone does not allow clear inferences regarding the cognitive processes. Activity recorded at a particular scalp site represents the summation of activity generated by several different sources in the brain, which may have different time-courses. This is because the brain acts as a volume conductor, so the activity generated in one location may propagate through the brain tissue and be detectable at other locations. This effect is called “spatial summation”. Voltage signals also interact over time, resulting in “temporal summation”. Thus, the timing of the ERP waveform features need not correspond directly with the temporal characteristics of individual neural generators whose activity is reflected in the waveform. Therefore, ERP components do not necessarily represent activity in a single neuronal en-

semble or coordinated network of ensembles; not necessarily a well bounded single stage of information processing.

C1, P1 and N1 are the first ERP components associated with visual perception. The C1 component typically onsets over central parieto–occipital scalp between 45 and 60 ms post-stimulus and peaks between 70 and 90 ms. The C1 is believed to reflect activity in early primary visual cortex. Interestingly, because of the layout of the topographical representation of primary visual cortex along the calcarine sulcus, the C1 component reversal in polarity when the upper versus lower visual field is stimulated. Due to this reverse polarity, the C1 can easily be missed when using stimuli placed along the horizontal meridian. The P1 is a positive component that emerges between 70 and 90 ms, normally peaking around 80-130 ms. Following P1, the N1 is a negative component that peaks around 130-180 ms. Although the P1 and N1 component are also measured over the parieto-occipital regions, their distributions are more lateralised if compared to that of the C1.

Due to the EEG limitations previously mentioned, it is difficult to be sure about the generators of these components in the brain. However, experiments using different techniques, such as fMRI, PET or intracranial recordings have helped clarify the sources of these early visual components. Nowadays, it is believed that the C1 component reflects primarily activity from the earliest retinotopic cortical regions of the visual processing hierarchy, particularly from V1, organised around the calcarine fissure, but likely also from V2 (Foxe, et al., 2008; Im, Gururajan, Zhang, Chen, & He, 2007). Usually, the C1 component

does not show any modulation by attentional manipulations (Clark, et al., 1995; Gomez Gonzalez, Clark, Fan, Luck, & Hillyard, 1994). The P1 and N1 components have been associated with activity in extrastriate visual areas along both ventral and dorsal visual pathways. Contrary to C1, the P1 and N1 have been shown to be modulated by attentional processes (Luck & Hillyard, 1995; Mangun & Hillyard, 1987). Moreover, modulation of the two components can be functionally dissociable (Heinze, Luck, Mangun, & Hillyard, 1990; Hillyard & Hansen, 1986; Luck, et al., 1990), suggesting that spatial attention can affect multiple levels of perceptual analysis with relative independence.

The P300 is known as the prominent positive peak of event-related potentials with an amplitude maximum over the centro-parietal area of the scalp and a latency of 300–500 ms (Fabiani, Gratton, Karis, & Donchin, 1987). The P300 has been suggested to reflect a number of cognitive processes related to the detection of a target or an omitted stimulus (Sutton, Tueting, Zubin, & John, 1967), such as the assessment of stimulus relevance, decision making, and updating process (Polich, 2007).

2.1.4.2. Lateralised readiness potential

The first observation of changes in activity over the motor cortex in anticipation to a planned muscle movement was described by Kornhuber and Deecke (1965). The authors named this component as the *Bereitschaftspotential,* which translates as the *readiness potential*. Later, Vaughan, Costa, and Ritter (1968) realised that this potential was larger at the hemisphere that was contralateral to the side of the muscle movement. Nowadays, the *lateralised readiness*

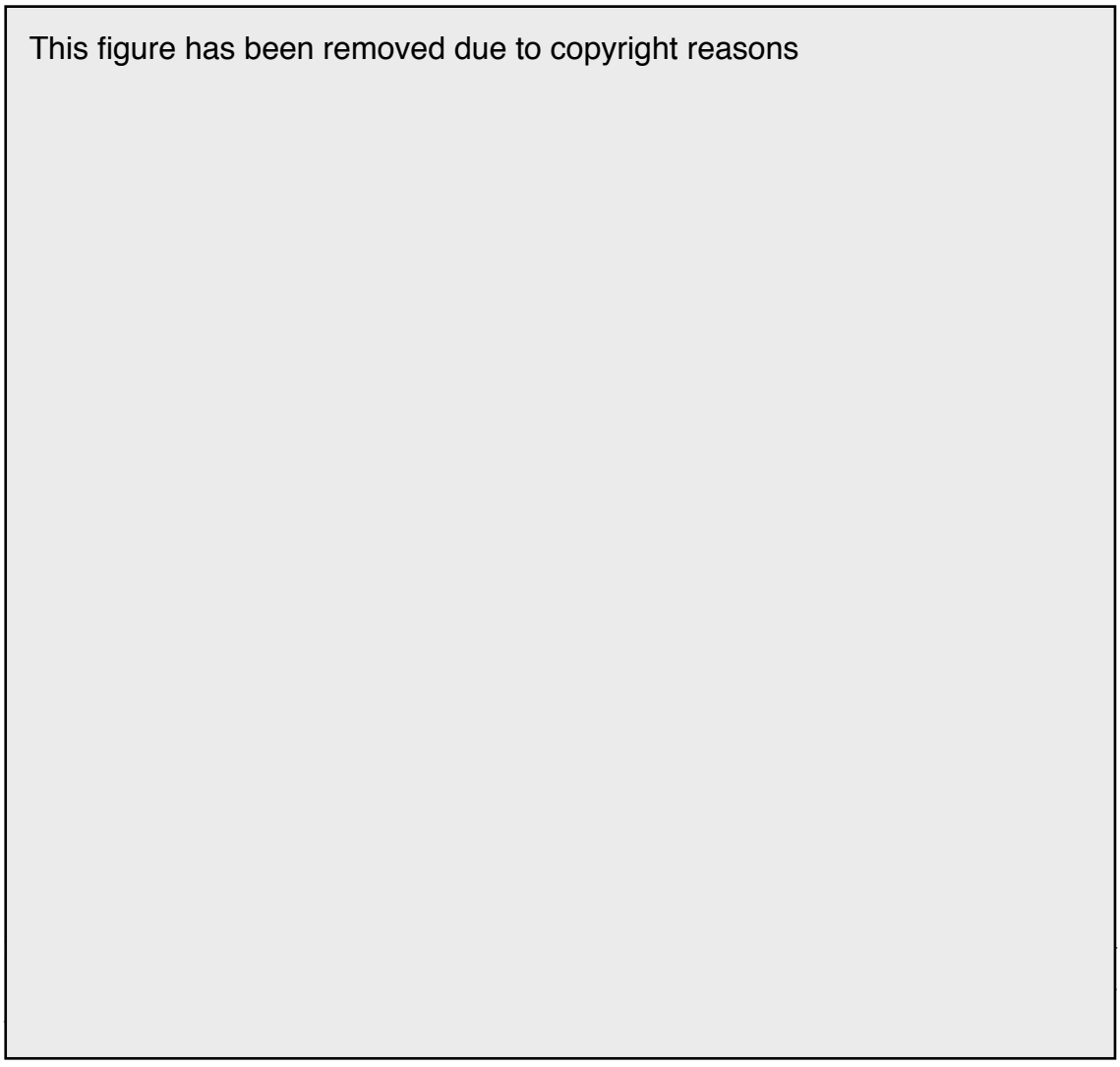
potential (LRP) is a widely used measurement of effector specific motor preparation (Coles, 1989; Masaki, Wild-Wall, Sangals, & Sommer, 2004; Miller, Patterson, & Ulrich, 1998; Taylor, Nobre, & Rushworth, 2007a; Ulrich & Miller, 2001). The LRP compares activity over contralateral versus ipsilateral motor cortex by using the following formula: LRP = [mean (C4 - C3)$_{\text{left-hand movement}}$ + mean (C3 - C4)$_{\text{right- hand movement}}$]/2. C3 and C4 are the electrode positions that are, on average, above the left and the right lateral motor cortex respectively. Typical LRP results show that response selection and preparation are accompanied by a negative potential, reflecting greater activation contralateral to the moved hand.

2.1.4.3. Time-frequency analysis

The rhythmic characteristics of the EEG were noted from its earliest descriptions (Berger, 1929). These oscillations are mainly generated by transmembrane currents occurring synchronously in ensembles of neurons (see Introduction, section 1.2.1 for more details) (Schroeder & Lakatos, 2008). Using time-frequency analysis it is possible to detect changes in the oscillatory activity in the brain that is associated with changes in behaviour or cognitive functions.

Importantly, time-frequency analysis opened the possibility to investigate induced, and not just evoked brain activity. An evoked response, oscillatory or not, is characterised by precise phase-locking to the stimulus onset. Therefore, this response can be detected by averaging single trials responses (e.g. ERPs and LRPs). In contrast, induced responses consist of oscillatory bursts whose latency may jitter from trial to trial (Figure 6, green boxes). Due to small temporal differences, this induced activity would not be captured by the averag-

ing procedure used to derive ERPs (Figure 6). Indeed, many EEG signals are not necessarily phase-locked to an event and therefore are not represented in event-related potentials. It is important note that its likely that most event-related EEG dynamics have both induced and evoked aspects (Makeig, et al., 2004), although the precise relationship between induced and evoked activity is not yet clearly understood. Measuring induced neural activity is particularly suitable for tracking anticipatory brain activity linked to developing expectations in attention tasks, since it is often impossible to define the precise temporal onsets of these 'events' in the first place (e.g., changes in baseline firing rates or oscillatory activity describe in the Introduction, section 1.2.2).



Oscillatory components contained in the ongoing EEG signal often show amplitude[1] changes relative to experimental events. The time-frequency analysis performed in this thesis is focused on these amplitude changes in anticipation to an event. As described previously (see Introduction), the first studies investigating brain oscillations relied on visual inspection of the EEG signal (Adrian & Matthews, 1934a; Berger, 1929). However, with the advent of computers, researchers were able to quantify oscillatory activity using spectral analysis methods (van Vugt, Sederberg, & Kahana, 2007). Time-frequency analysis is based on *Fourier analysis*. In brief, the *Fourier* analysis decomposes any complex signal (e.g EEG) into sine waves, transforming the signal that was defined in time domain, into the frequency domain (Buzsáki, 2006). These sine waves can then be analysed in terms of changes in *amplitude* and *phase*. Calculating time-frequency representations of power is done using a sliding time window. This can be done according to two principles: either the time window has a fixed length independent of frequency, or the time window decreases in length with increasing frequency. Power is calculated for each time window the power is calculated. Two main methods, based in the *Fourier* analysis, have been widely used in the recent years, namely *wavelets* and *multitapers*.

In wavelets analysis, the signal is decomposed into scaled and shifted versions of the oscillating waveform of interest. Since the wavelet functions are shifted and scaled versions of one another, the proportion between temporal width and frequency bandwidth remains the same for all frequencies, leading to

[1] Amplitude differences are also commonly referred to as Power changes. Power is a value of the amplitude squared. For convenience, here the terms amplitude and power are used as synonyms

more precision in estimates of neural activity at higher frequencies (Sinkkonen, Tiitinen, & Naatanen, 1995). A more recent method of analysis is known as *multitapers.* Before explaining how *multitapers* analysis works, it is important to define what a '*taper'* is in the context of this method. *Tapers* are functions that smooth the data by having a value of one in the centre and then slowly scaling down to zero at the edges. The aim of the tapers is to reduce spectral leakage and control the frequency smoothing. Using the *multitapers* method, the signal is calculated by averaging multiple convolved orthogonal tapers. This type of procedure is used to reduce contamination between frequencies, rendering them well suited for non-stationary processes with high dynamic ranges and/or rapid variations (Walden, Percival, & McCoy, 1998). The time-frequency analysis performed in this thesis used the *multitapers* procedure, which allows a better control of time and frequency smoothing.

As mentioned previously, there are two orthogonal measurements that can be used in time-frequency analysis: *amplitude* and *phase*. Whilst *amplitude* values can be simply analysed in terms of their increase or decrease in any frequency of interest, *phase* values can be used to provide a number of measurements. Among the most commonly used phase measurements are: *phase coherence*, *phase-locking*, and *phase reset* (Buzsáki, 2006). *Phase coherence* is a measure of the state in which two signals maintain a fixed relationship. *Phase-locking* value (PLV) is a measurement of interaction between oscillators that have a fixed phase difference. The PLV is computed by normalising the lengths of amplitude and phase to 1 for all trials and then computing their complex average. Thus, only the information about the phase of the spectral estimate of each trial

is taken into account. *Phase reset* occurs when an event leads to an oscillation in one or more frequencies restarting at the same phase (Figure 7).

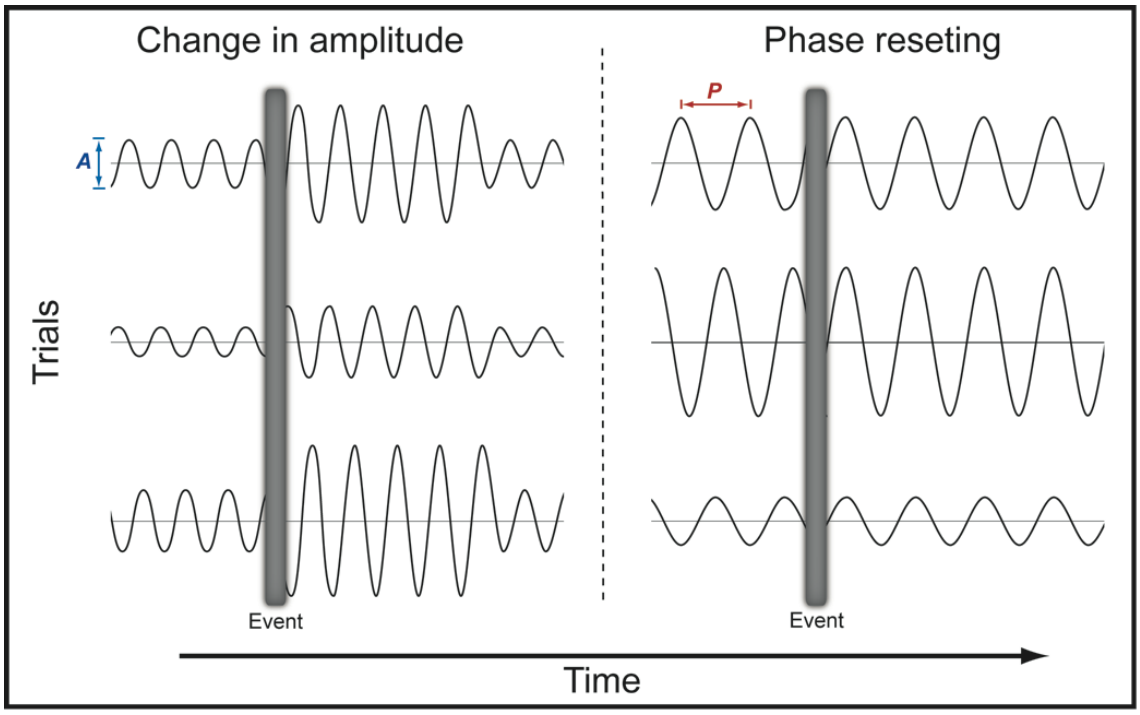


Figure 7. Schematic example of change in Amplitude and Phase reset after an event onset.

Another measurement extracted from time-frequency analysis is the coupling of power to the phase of any certain frequency (Figure 8). Usually, the power changes in higher frequencies are nested to a preferred phase in lower oscillations. Figure 8 shows that the typical oscillations recorded in the brain are normally complex mixtures of components at different frequencies (green line). The blue lines illustrate the decomposition of individual oscillatory components in the delta (1.5 Hz), theta (7 Hz) and gamma (40 Hz). Notice how the gamma oscillatory *amplitude* varies with the *phase* of the underlying theta oscillation, and how theta oscillatory amplitude varies with the phase of the underlying delta oscillation.

Recently, phase-power coupling effects have been reliably associated with a number of cognitive functions both in human (Axmacher, et al., 2010; Canolty, et al., 2006; Palva, Palva, & Kaila, 2005; Schack, Vath, Petsche, Geissler, & Moller, 2002; Shils, Litt, Skolnick, & Stecker, 1996) and non-human primates (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007; Lakatos, et al., 2008; Lakatos, et al., 2009; Lee, Simpson, Logothetis, & Rainer, 2005). Schroeder, Lakatos and colleagues (2008; 2008; 2010) have suggested that attention can operate in a *rhythmic mode*, enforcing the entrainment of low frequency neuronal oscillations to sensory events. This entrainment then aligns the high excitability phase of oscillations with relevant events in the perceptual stream, amplifying their neural representation (see Introduction 1.2).

2.1.5. Advantages and disadvantages of EEG

Arguably, the main advantage of the EEG method is its temporal resolution (e.g. compared to fMRI or PET). The EEG is a direct measurement

of actual brain activity occurring in real time. Additionally, EEG is relatively inexpensive and non-invasive (e.g. compared to single-unit or field-potential recordings in epileptic patients). However, there are also several limitations which need to be taken into account when designing and conducting experiments. First, since EEG is a correlational technique, one cannot interpret its results in terms of a simple cause-effect process. Second, since the EEG method is blind to many forms of neural activity, it is not possible to infer much from the absence of effects. As previously mentioned, another problem is that its poor spatial resolution precludes strong inferences about the underlying neuronal sources of effects. Furthermore, though there are ways to minimise the noise in the signal, the EEG still has a fairly poor signal-to-noise ratio (due to the size of the response of individual neurons compared to background activity). This relatively large signal-to-noise ratio means that a large number of trials are necessary to measure the waveforms accurately. It is important to note that even though techniques, such as fMRI, are better equipped to deal with some of these problems, they are still susceptible to many of the same limitations.

However, the EEG has been one of the main tools in human neuroscience for almost a century now. Therefore, there are many positive aspects to the EEG technique which makes it very useful for studying cognitive processing within the human brain (Luck, 2005; Rugg & Coles, 1995). As previously mentioned, the main advantage with EEG compared to other imaging methods (e.g. fMRI, PET) is its excellent temporal resolution (in the order of ms). Since the EEG is a real-time measurement, it is a very efficient tool to study stimulus processing, even for very fast or subliminal events (Astle, Nobre, & Scerif, 2010).

Also, due to its temporal resolution, the EEG is a better tool to study the modulations of neural activity over the different stages of stimuli processing, from early perceptual processing and decision making to action preparation and execution. It is important to remember that even though the EEG has a poor spatial resolution, its signal provides a macroscopic measure of cortical brain activity in large populations of neurons, especially cortical excitatory pyramidal cells. Due to the growing interest in the role of brain oscillations in cognitive functions, the EEG provides an efficient and inexpensive technique in the study of human neuroscience.

2.2. Functional Magnetic Resonance Imaging

With the advent of functional magnetic resonance imaging (fMRI) in the early 1990's (Ogawa, Lee, Kay, & Tank, 1990), neuroscientists were able to visualise neural activity in specific cortical and subcortical brain regions that underlie human behaviour. The method provides an indirect measure of neuronal activity, relying on using magnetic-resonance imaging to capture changes in hemodynamic parameters (mainly blood flow) that are coupled to increases in metabolic demands triggered by certain aspects of neuronal activity. It has a complementary profile of spatial versus temporal resolution when compared to EEG. In practise, its spatial resolution can reach around $1mm^3$, though in most studies the resolution used is $3mm^3$. Its temporal resolution, however, is bounded by the slow hemodynamic dynamics and, consequently, is in the order

of seconds. In this chapter, I will briefly describe the principles of fMRI, its applications and limitations.

2.2.1. Principles of Magnetic Resonance Imaging

Magnetic-resonance imaging (MRI), also known as nuclear magnetic resonance (NMR), is an imaging technique based on the behaviour of some atomic nuclei within a stable magnetic field (B_0). In the absence of a strong external magnetic field, atomic nuclei spin at different orientations. When placed in a static magnetic field, the spins align along the axis determined by the direction of the magnetic field. In this case, protons can assume two energy states: parallel (low-energy level, the proton is aligned with the magnetic field) and antiparallel (high-energy level, the proton is aligned in an opposite direction to the magnetic field) (Figure 9) (Huettel, Song, & McCarthy, 2009). Since the distribution of water differs considerably among grey matter, white matter, cerebral spinal fluid, bone, skin, etc., it is possible to obtain a structural image of the brain based on the density distribution of hydrogen nuclei (protons). The abundance of hydrogen protons makes them easier to measure than other atoms. Another important point is that because MRI relies on net magnetisation (the difference between aligned versus anti-aligned nuclei) it demands a very concentrated atom to get a good signal.

When a radio-frequency (RF) pulse is applied to atoms within B_0, a separate magnetic field (B_1) is produced. This RF pulse is delivered at a certain frequency (Larmor frequency), which excites a number of hydrogen protons into the high-excitation state and thereby changes the net magnetisation in the tissue. Consequently, the net magnetisation is rotated to a certain angle away from the B_o axis. This angle is referred to as the flip angle, and is proportional to the duration and amplitude of the RF pulse. When the pulse is switched off the spins start returning to equilibrium (spin relaxation), emitting electromagnetic energy. At this time, a receiver coil can detect a signal, known as Free Induction Decay. This complex signal is analysed along its different frequency components using Fourier transforms and its distribution can be plotted, yielding information about the concentration of protons in the tissue (Haacke, Brown, Thomp-

son, & Venkatesan, 1999). The time constants for different aspects of relaxation are influenced by multiple mechanisms, known as 'spin-lattice' relaxation and 'spin-spin' relaxation. 'Spin-lattice' relaxation occurs as the spinning nuclei give away their energy as they return to their original state. This translates into the longitudinal (i.e. - along the z-axis) component returning to its equilibrium value at a rate T1. 'Spin-spin' relaxation happens along the transverse (i.e., on the x-y plane) component of the magnetisation vector. It is due to the ensemble of spins falling out of phase with each other and thereby adding destructively to the net magnetisation vector. These two mechanisms are often referred to as T1 and T2 relaxation, respectively. Changing the measurement parameters to emphasise T1 or T2 relaxation (i.e., T1- or T2-weighted images) can be very useful in differentiating brain structures or lesions, since some structures will be more apparent in some kind of images but not in others. Another kind of relaxation is caused by inhomogeneities in the magnetic field at the microscopic level. If there are variations in the magnetic field, there will also be variations in precession frequency of the individual protons, which causes the ensemble to lose phase coherence faster than expected due simply to T2 relaxation. This change is referred to as T2* (Jezzard & Clare, 2001). Physiological factors, like blood flow, can cause variations in the magnetic field, which in turn modulate the amount of T2* relaxation. Haemoglobin within the blood has magnetic qualities: in an oxygenated form haemoglobin bears diamagnetic (no overall magnetic field) properties, while in a deoxygenated form it is in a paramagnetic state (Pauling & Coryell, 1936). The inhomogeneous magnetic field induced by deoxygenated haemoglobin can modulate or reduce the coherence of protons (i.e. dephasing in the trans-

verse plane) and decrease the T2* recovery time of protons within water molecules as they move through this magnetic field.

2.2.2. Imaging brain activity: the BOLD signal

The principle of Blood-Oxygen-Level-Dependent (BOLD) contrast (Ogawa, et al., 1990), by far the most commonly used fMRI signal, is based on two premises. The first is that the deoxygenated form of the haemoglobin molecule in blood is paramagnetic (i.e. a positive magnetic susceptibility) and therefore causes distortions in the surrounding magnetic field (Pauling & Coryell, 1936). The second premise is that neuronal activity and blood flow are closely linked. This observation dates at least back to the end of the 19th century (Angelo Mosso, described in James, 1890; Roy & Sherrington, 1890), and by now is well validated, even though the intermediary steps coupling neuronal activity to blood flow are not completely understood (Raichle, 1998).

Ogawa and colleagues (1990) suggested that manipulating the proportion of oxygenated blood would affect the MRI signal due to T2* changes. They confirmed these predictions empirically, and proposed that T2*-weighted images might, therefore, provide a measure of neuronal activity. The imaging method developed to be sensitive to T2* changes caused by deoxygenated haemoglobin was named BOLD, and reflects mainly changes in blood flow and blood oxygenation associated with neuronal activity (Belliveau, et al., 1991; Ogawa, et al., 1990). Increases in the ratio of deoxygenated-to-oxygenated haemoglobin lead to dynamic increases in distortions, or inhomogeneities in the lo-

cal magnetic field. This, in turn, leads to an overall loss in the signal generated by local protons in hydrogen (e.g. water molecules). The strength of the BOLD signal, therefore, is proportional to relative changes in oxygenation of haemoglobin in blood (Bartels, Logothetis, & Moutoussis, 2008; Heeger & Ress, 2002; Logothetis, 2007, 2008).

The BOLD signal is typically observed to increase in areas of increased neuronal activity, suggesting a surplus of oxygenated blood being delivered to the site. Neuronal activity results in high metabolic demand, which in turn is coupled to increased blood flow to the region. This net increased blood flow leads to a transient increase in the ratio of oxygenated: deoxygenated haemoglobin, as the amount of oxygen supplied typically supersedes the amount of oxygen actually extracted. The inflow of oxygenated blood during neural activity, displaces the deoxygenated haemoglobin (which suppresses/reduces the BOLD signal) thus leading to a net increase in BOLD signal during neuronal activity. fMRI measures based on the BOLD effect have one severe shortcoming: there is a time lag of 3-6 seconds until the BOLD response in a brain region reaches its peak. The haemodynamic signal therefore lags orders of magnitude behind the underlying neuronal event of interest, which occurs within the milliseconds timescale.

Although the BOLD signal is not a direct measurement of neuronal activity, there has been increasing evidence that both are tightly coupled. One of the most important pieces of evidence for the neuronal origins of the BOLD signal was obtained by Logothetis and colleagues (2001). They recorded neural ac-

tivity with intracortical electrodes at the same time as recording the BOLD signal in an fMRI scanner while awake monkeys viewed visual stimuli. The results showed that the BOLD signal was more strongly correlated with local field potentials (LFP), reflecting synchronous postsynaptic activity from dendrites, compared to multi-unit activity responses (MUA), reflecting action potentials. Further, they data showed that the BOLD signal reflects a summation of excitatory and inhibitory postsynaptic potential (Logothetis, et al., 2001). The BOLD signal therefore reflects an increase in the input activity to a given brain region and/or local signal integration within that region, rather than its spiking outputs. More recently, Lee and colleagues (2010), combined optogenetic (for a review of the technique see Zhang, Aravanis, Adamantidis, de Lecea, & Deisseroth, 2007) control of inputs with high-field fMRI in rats. Their findings provide further evidence that nerve cell activity is indeed responsible for the BOLD signal (Lee, et al., 2010). It is interesting to observe that FP and MUA are often correlated, so BOLD can often also provide a good surrogate measure of the spiking output of a region. However, there are exceptions, such as when synaptic input leads to inhibition of neurons as in the cerebellum purkinje cell system (Mathiesen, Caesar, Akgoren, & Lauritzen, 1998; Mathiesen, Caesar, & Lauritzen, 2000). Taken together, these studies, and others, provide an empirical foundation for the widely-used fMRI BOLD signal (Heeger & Ress, 2002; Logothetis, 2008).

2.2.3. fMRI analysis

2.2.3.1. Image pre-processing

Pre-processing raw data is the first step of fMRI analysis. The aim is to prepare data for statistical analysis. At this stage, unwanted variability due to uncontrolled physical or physiological factors is removed, increasing the signal-to-noise ratio. Pre-processing usually consists of realignment, slice-timing correction, normalisation and smoothing.

One of the most common problems in fMRI data is the movement of the head while acquiring data. Since most fMRI experiments require participants to stay inside the scanner for a considerable amount of time (>1hr in Experiment of Chapters 6), it is inevitable that participants will move their head during the session. Some simple precautions can be taken in order to minimise head movements, such as ensuring that the participant is comfortable before starting the experiment and using head-immobilisation systems, such as MRI compatible cushions, to restrain head motion. However, even small head movements (of a few millimetres) can have serious deleterious effects on the pattern of activation. Therefore, motion correction can be used to realign all the volumes collected in an experiment so that a voxel is always in the same position in every volume. Motion-correction algorithms co-register successive volumes to a single reference volume, such as the first image acquired in an experiment (Ashburner & Friston, 1999; Friston, et al., 1995). The first step of this process is to determine the realignment parameters representing the translation and rotation values for each volume relative to the reference volume. After the realignment parameters are

computed, the original data are resampled to determine the spatial values that would have been obtained without head motion.

During the experiment, brain volumes are acquired by sampling the constituent slices in a particular order: typically either ascending or descending, though sometimes in an interleaved manner (e.g., the scanner collects the odd slices first in an ascending or descending order, and then it collects the even slices). Correcting for slice-timing differences is important because slices acquired early versus late in the volume sequence could be measuring different phases of the haemodynamic response function. To correct for slice-timing differences, most analysis packages use temporal interpolation. Temporal interpolation algorithms use information from a nearby time point to estimate the amplitude of the MR signal at the onset of each time between images (TR). The accuracy of interpolation depends on the variability of the experimental data and the rate of sampling. Temporal interpolation is more effective for less variable data and for data collected at short TRs than for data collected at longer TRs (more than 3s).

The T2* image focuses on the dynamic artefacts and, consequently, its anatomical resolution is inherently low and insufficient for localising accurately functional activations. Therefore, a high resolution structural image is also collected, and later coregistered with the low-resolution functional volumes (Friston, et al., 1995). In order to average or compare activation patterns across individual participants, it is also necessary to place the structural and functional

images across participants into a common reference space. However, individual brains show a varied morphology. In order to be able to generalise the pattern of functional activations observed in an fMRI experiment, it is necessary to remove this individual variability by placing the individuals' brains into a common spatial framework. This is achieved using structural normalisation. During normalisation, the high-resolution structural image for each participant is warped to match a template brain such as the template brain from the Montreal Neurological Institute (MNI) (Collins, Neelin, Peters, & Evans, 1994). This common brain template is based on the average of many individual brains, which have all been registered into a widely used standard coordinate system developed by Talairach and Tournoux (Talairach & Tournoux, 1988). Once a mapping has been established between the individual neuroanatomy and the standard template, the functional images are then re-sliced accordingly, bringing the measures of activity into a common space.

Functional data are also spatially smoothed using a Gaussian filter during pre-processing. The most important reason for smoothing is to increase the signal-to-noise ratio (noise values from neighbouring voxels will cancel out) and to remove effects due to residual functional anatomical differences between participants. Gaussian smoothing is also necessary to meet assumptions of random field theory, which is used for subsequent data analysis (Brett, Penny, & Kiebel, 2004; Poline, Worsley, Holmes, Frackowiak, & Friston, 1995). Smoothing allows for cluster-based thresholding, and therefore it is used to reduce the number of potential false positives.

2.2.3.2. Statistical Analysis: the General linear model

After pre-processing, the data can be analysed according to a general linear model (GLM) (Friston, et al., 1995). The GLM tests the degree to which a specific model fits the time-course data from each individual voxel. The onsets of the events within a task are modelled through a series of basic functions that simulate the hemodynamic response. The model can then be estimated using standard least-squares techniques (Friston, Harrison, & Penny, 2003; Penny, Stephan, Mechelli, & Friston, 2004), and used to produce statistical parametric maps (SPMs) that consist of z values corresponding to the activation at each voxel for a particular experimental condition.

Typically, fMRI analyses are performed using a two-stage procedure. Initially, a first-level analysis is performed to estimate within-subject effects; the results for each subject are then passed onto a second-level analysis to assess effects over the whole group of subjects (Friston, Holmes, & Worsley, 1999). SPM images produced by the second-level analysis are comprised of t, or F, statistics corresponding to a specific experimental comparison for each voxel. The statistical maps can then be interrogated at a chosen statistical threshold, corrected for multiple comparisons. When strong hypotheses are in place, the data can also be examined by interrogating activity in smaller predefined regions-of-interest (Friston, 2005).

2.2.4. Advantages and disadvantages o fMRI

Clearly, the main advantage to fMRI when compared to other imaging techniques is its spatial resolution. fMRI allows the mapping of neuronal activation in the healthy human brain, with a high degree of spatial resolution, during cognitive functions, for a range of different behaviours. However, it is important to point out that although the spatial resolution of fMRI is superior to that offered by EEG, spatial information offered by a typical voxel (3 x 3 x 3 mm) still carries information from many neurons. In fact, a recent estimate of neural density in human neocortex suggests that a typical 3-mm^3 voxel reflects the mean response of approximately 2.5 million neurons (Sherwood, et al., 2006).

The most obvious fMRI disadvantage is its poor temporal resolution. Contrary to EEG measurements, with fMRI it becomes difficult to determine whether a modulation of activity in a perceptual processing region reflects an early or late, re-entrant response. Another limitation of this technique is that even though fMRI has a good spatial resolution, it can be very hard to obtain good quality images from some regions, resulting in limitations when examining cognitive activity in these regions. This is usually due to their proximity to air cavities, such as around the orbitofrontal cortex and anterior medial temporal lobe. Finally, it is always important to remember that, even though empirical evidence links the BOLD response with neuronal activity, many other factors may influence the BOLD response that are yet to be determined (Bandettini & Ungerleider, 2001; Heeger & Ress, 2002; Logothetis, 2008).

In this thesis a multi-methodological approach was used to investigate the neural basis temporal attention. This approach was taken to benefit from the relative strengths of different methods. In chapters 4 and 5, EEG was used to measure event-related potentials, as well as brain oscillations associated with spatial and temporal expectations. Since my interest was in understanding how temporal and spatial orienting can bias visual perception, the ERP analysis focused on the P1 component. I also used the lateralised readiness potential to investigate if temporal/spatial orienting can enhance motor preparation. The time-frequency analysis was focused on the low-frequency changes in anticipation to an expected event. In chapter 6, fMRI was used to compare and contrast the neural systems that control of temporal and motor orienting to test for their degree of functional neuroanatomical overlap.

Chapter 3

3. Behavioural dissociation between exogenous and endogenous temporal orienting of attention

Our behaviour is adapted flexibly to meet our task goals. Selective attention research has revealed that predictions about the locations or other features of relevant events can bias neural activity starting from early stages of perceptual analysis (Chalk, et al., 2010; Gandhi, et al., 1999; Ito & Gilbert, 1999; Luck, et al., 1997; McAdams & Reid, 2005; Posner & Gilbert, 1999). It has become increasingly evident that predictions about the timing of events also play a major role in organising and optimising behaviour (Nobre, et al., 2007; Nobre & Coull, 2010). However, compared to spatial attention, relatively little is known about the functional mechanisms by which temporal expectations alter performance.

Like spatial orienting of attention, temporal orienting has been proposed to occur in an endogenous or exogenous fashion (Coull & Nobre, 2008b). In spatial attention, exogenous orienting is an involuntary focus of attention driven by an inherently salient or transient cue (also referred to as stimulus driven, automatic, bottom-up). Endogenous orienting, on the other hand, is un-

derstood as a voluntary, intentional focus of attention to a specific location, usually guided by a symbolic cue (also referred to a goal directed, controlled, top-down) (Egeth & Yantis, 1997; Muller & Rabbitt, 1989).

In spatial attention studies, the properties of exogenous and endogenous orienting are well established. Behavioural results have demonstrated that exogenous orienting elicits stronger validity effects than endogenous cues (Laubrock, et al., 2005). Studies have also suggested that exogenous cues are less susceptible to interference (Giordano, et al., 2009), and harder to ignore than endogenous cues (Muller & Rabbitt, 1989). Another common finding is that exogenous cues induce faster and more transient effects than endogenous orienting (Busse, et al., 2008; Nakayama & Mackeben, 1989). Taken together, these findings suggest that while endogenous attention is more flexible and susceptible to interference, exogenous orienting is a fast, automatic and robust process.

In a recent review, Coull and Nobre (2008b) have suggested a distinction between endogenous and exogenous attention in the temporal domain. Exogenous temporal orienting is proposed to be generated automatically by exposure to stimuli with rhythmic or predictable temporal structure (Coull & Nobre, 2008b; Doherty, et al., 2005; O'Reilly, et al., 2008). On the other hand, endogenous temporal orienting is proposed to be engaged in tasks that use informative, symbolic cues to direct attention in time (Coull & Nobre, 1998b; Miniussi, et al., 1999; Nobre, et al., 1999).

In this experiment, we adapted the task from Doherty and colleagues (Doherty, et al., 2005) to test for the existence of separable effects of endogenous versus exogenous temporal expectations. In this task, a ball moves across the computer monitor in discrete steps and passes 'under' an occluding band (see Figure 10). The participants' task is to make a speeded discrimination of a shape contained within the ball when it reappears from under the occluder. We used a factorial design to test for the existence of separable effects of exogenous versus endogenous temporal expectations, formed on the basis of the rhythmic temporal structure of dynamic events versus explicit symbolic cues respectively. The temporal structure of the events was either rhythmic or arrhythmic. In rhythmic trials, each ball and intervening interval had a constant duration. These parameters provided precise temporal predictions for the duration of the occlusion period, and were always valid. In arrhythmic, neutral trials, intervals between balls varied randomly, providing no prediction for the duration of the occlusion period. The presence or absence of the isochronous rhythm was crossed with the presence or absence of symbolic cues to predict the duration of the occlusion period. The colour of the ball acted as a symbolic cue. In valid trials, it predicted the duration of the occlusion interval with 100% validity; in neutral trials the colour provided no information about the duration of the occlusion period.

In order to test whether expectations built from the temporal structure of events versus from symbolic cues were under cognitive control, we also manipulated task instructions. Participants were told to use the information provided by rhythm of the events ("attend to speed") or the colour of the ball

("attend to colour") in different blocks. If, as we predict, temporal expectations induced by the temporal rhythm of the events are 'exogenous', they should be automatic and not contingent upon or greatly affected by participants focusing on this source of information. On the other hand, if, as we predict, temporal expectations induced by predictive cues are 'endogenous', they should come under cognitive control and be significantly influenced by instruction to use this source of information. Having established two separable forms of temporal orienting, we were also interested in testing whether these two sources of bias show strong interactions or whether they operate mainly independently, resulting in additive effects.

3.1. Materials and Methods

3.1.1. Participants

Eighteen right-handed participants took part voluntarily in this experiment (mean age = 30.8ys, 10 females). All participants had normal or corrected-to-normal vision. This study was approved by the Central University Research Ethics Committee of the University of Oxford and all subjects provided written informed consent.

3.1.2. Apparatus

The stimuli were created and presented using Presentation version 12.2 (Neurobehavioral Systems, Albany, NY). Images were displayed on a 21-inch CRT (CTX ultra screen) with a spatial resolution of 1024 by 768 pixels and a vertical refresh rate of 60 Hz, placed at 100 cm in front of the participant. Eye movements were monitored using a monocular remote video-based infrared eye tracker (ISCAN, ETL-400 system, 60 Hz). A chin rest was used to maintain a constant viewing distance and head position.

3.1.3.Stimuli and Task

A schematic of the task is provided in Figure 10. The display consisted of a grey background, with a small white rectangle as the fixation point (0.29°) placed at the centre of the screen, and a white vertical occluding band (width: 3.5°) placed on the right (11.4-14.7° eccentricity). A stimulus (coloured ball - diameter:0.86°) appeared in the left hemifield (50% upper and 50% lower visual field), and moved diagonally across a computer screen in seven steps (200 ms duration) until reaching an occluding band. After a short (600 ms) or long (1400 ms) occlusion period, the target stimulus reappeared containing an upright (50%) or tilted (50%) cross, which participants were required to discriminate. Forced-choice responses were delivered using a button-press response with their right or left hand accordingly, as quickly as possible. The task was performed in the absence of eye movements. Eye tracking was performed to ensure

that participant maintained central fixation throughout the active periods of the task.

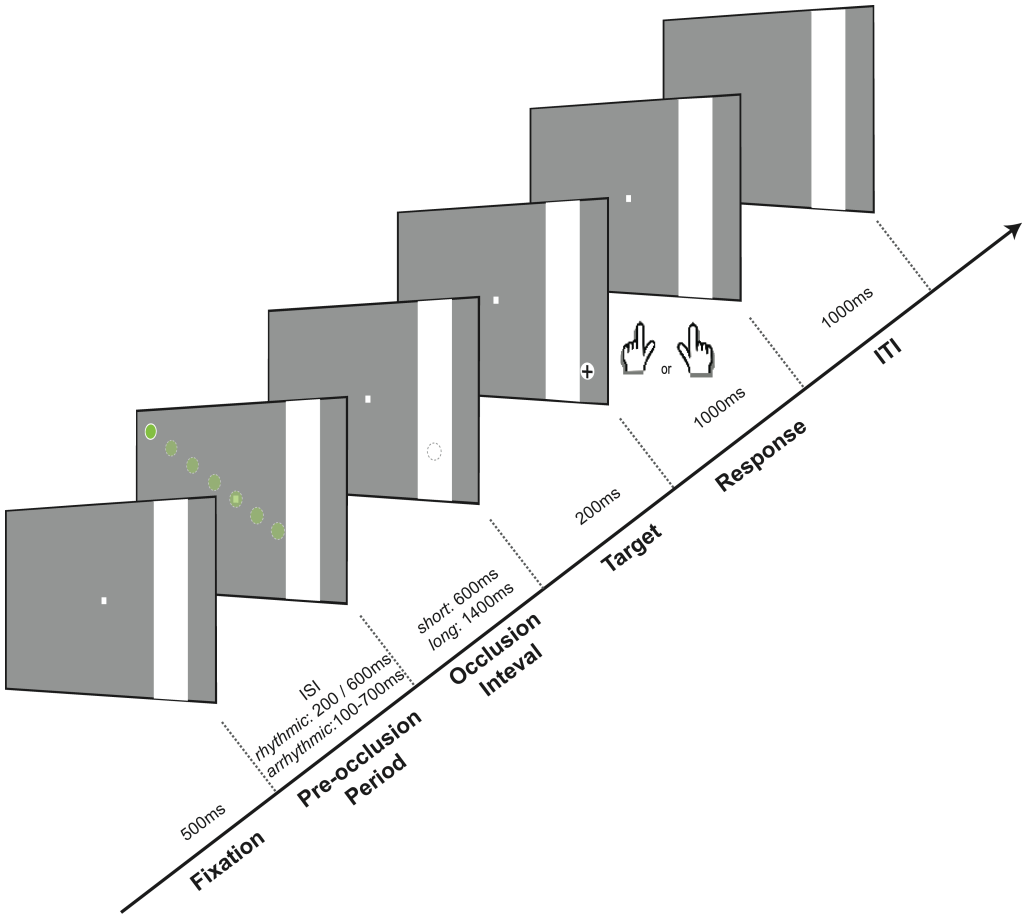


Figure 10. Schematic of the task. A coloured ball appears at the left side of a grey screen and moves across the screen in seven steps. After reaching the occluding band, the ball disappears behind for a single step. When the ball reappears it contains either an upright (50%) or a tilted (50%) cross. Temporal expectations could be induced by the rhythm and/or the colour of the balls preceding the occlusion.

In rhythmic trials, the duration of the inter-stimulus interval (ISI) between successive balls was either 200 ms (fast condition) or 600 ms (slow condition), predicting the reappearance of the target after the short or long occlusion period respectively with 100% validity. In arrhythmic, neutral trials, the

inter-stimulus interval varied randomly between 100-700 ms, providing no temporal prediction.

In the steps leading up to the occluding band, the ball could be yellow, green or blue. The colour acted as a symbolic cue. Two colours predicted the duration of the occlusion with 100% validity, each signifying the short or the long occlusion period. The third colour acted as a neutral cue, providing no specific information (50% short or long occlusion). Assignment of colour to the three cue types (valid short, valid long, neutral) was counterbalanced across participants.

The instructions given to the participants were also manipulated. Each block started with a screen instructing participant to "attend to *speed*" (temporal expectations established by *rhythmic* cues) or to "attend to *colour*" (temporal expectations established by *symbolic* cues).

All participants performed a training session with 72 trials to learn the association between the cues and the occlusion period. They then proceeded to complete 10 blocks of 48 trials each. At the beginning of each trial, six additional trials acted as a brief practise period to facilitate participants' engagement with the instructed condition. In total, there were 30 trials in each of the experimental conditions of interest available for analysis, based on the factors of instruction (speed, colour), rhythm (valid, neutral), symbolic cues (valid, neutral), and occlusion period (short, long). Trials with errors were eliminated from the analysis of reaction times (RTs).

3.2. Results

To analyse the behavioural consequences of expectations driven by temporal rhythms versus symbolic cues under different task instructions, RTs from correct responses were submitted to a repeated-measures analysis of variance (ANOVA), testing the three factors of instruction (speed vs. colour) *rhythm* (valid vs. neutral) and *cue* (valid vs. neutral). Based on previous findings (Correa & Nobre, 2008; Coull, et al., 2000; Coull & Nobre, 1998b; Nobre, 2010), and due to differences in conditional probabilities of target appearance as function of occlusion interval, the analyses of primary interest focused on correct trials after the short occlusion interval.

Performance accuracy was high (average 90.4%) and did not differentiate between conditions (lines in Figure 11) [Fs(1, 17) < 4,08, ps>.05]. In line with previous temporal orienting studies, RT values provided a sensitive measurement of the effects of temporal expectations (Nobre, 2010). The analysis revealed main effects of *rhythm* [F (1, 17) = 36.23, p<.001] as well as of *symbolic* cues [F(1, 17) = 8.80, p=.009] (Figure 11A). For both cue types, valid temporal predictions speeded reaction times when compared to neutral conditions. However, whilst the effect of the temporal *rhythm* was independent of instruction (main effect of rhythm), there was an interaction between *symbolic* cues and instruction [F(1, 17) = 7.03, p=.017] (Figure 11B). *Post hoc* subsidiary analyses with *Bonferroni* adjustment for multiple comparisons demonstrated that the effect of the *symbolic* cues was only observed if associated with the "*attend-to-colour*" instruction [F(1, 17) = 10.50, p=.005]. There were no significant effects

involving the interaction between temporal expectations driven by rhythms and by symbolic cues [Fs(1, 17) < .36, ps>.55]. As expected, no differences were observed after the long occlusion period [Fs (1, 17) < 2.23, p's>.10].

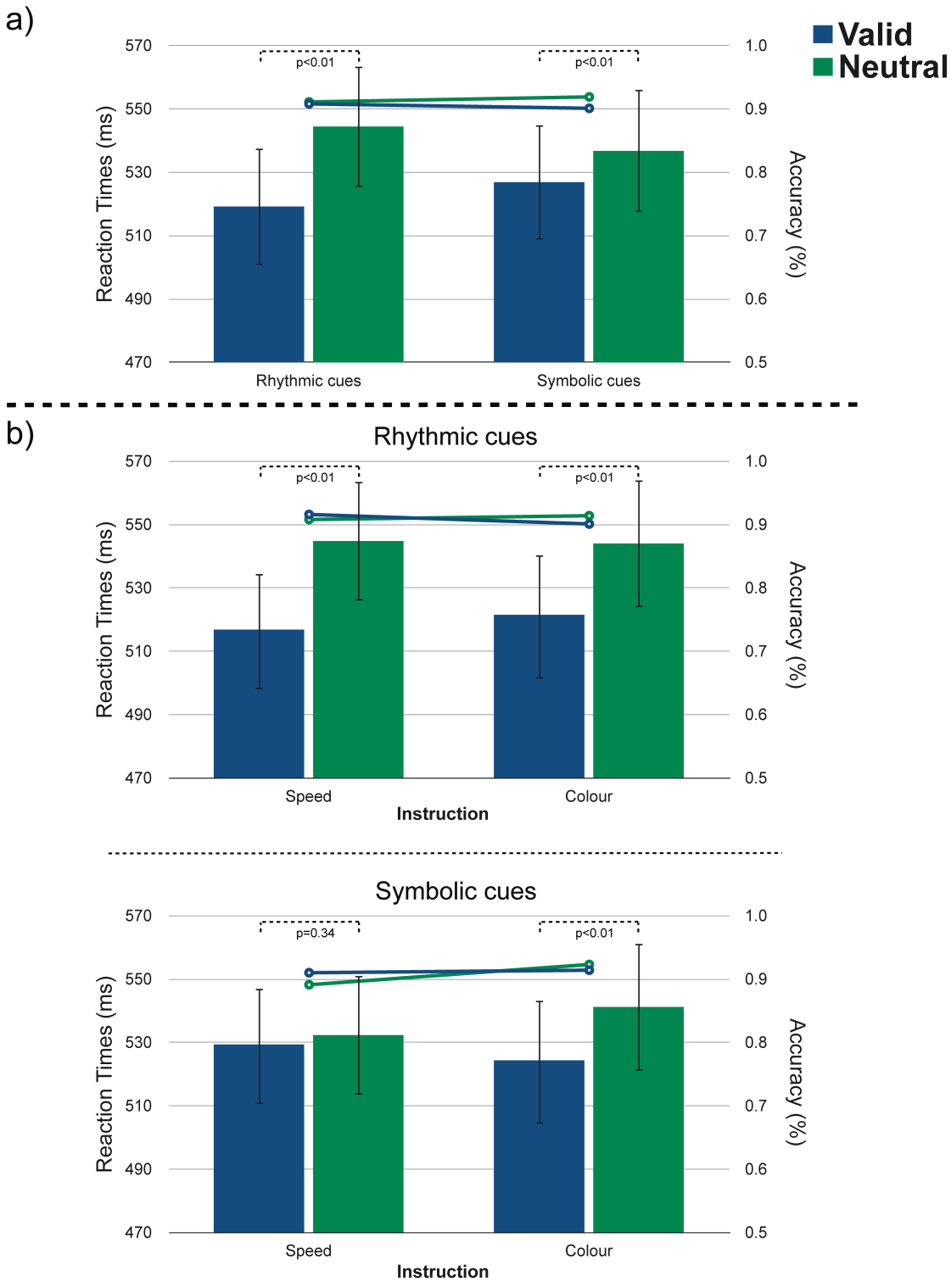


Figure 11. Reaction times results. *(A)* Main effect of temporal *rhythms* and *symbolic* cues *(B)* Effects of temporal rhythms and predictive cues broken down by task instructions. The bars represent reaction time values (left y-axis), and accuracy data is represented by the lines (right y-axis). Error bars represent standard errors of the means (SE).

3.3. Discussion

By using a paradigm combining temporal rhythms and symbolic cues, we provide direct evidence for the existence of separable exogenous and endogenous means of orienting of attention in time (Coull & Nobre, 2008b).

Similar to its spatial counterpart (Berger, Henik, & Rafal, 2005; Giordano, et al., 2009; Hopfinger & West, 2006; Mayer, Dorflinger, Rao, & Seidenberg, 2004; Rosen, et al., 1999), exogenous temporal orienting is triggered by stimulus properties and proceeds automatically. Our results confirm that the isochronous temporal rhythm of events automatically facilitates performance, regardless of whether participants focus on the temporal structure of the events. This *exogenous* orienting generated temporal expectation incidentally and automatically, allowing participants to anticipate the moment of target appearance and facilitating the perceptual discrimination process. On the other hand, *symbolic* cues were only effective if participants focused on the information provided by the cues and voluntarily oriented their attention to the time predicted by the cue. This *endogenous* type of orienting was therefore was goal-directed and strictly under top-down control.

Our results further suggested that exogenous and endogenous orienting reflect two sources of top-down biases acting upon the information-processing stream. The lack of interaction between temporal predictions carried by rhythms versus symbolic cues support the interpretation of two independent and additive mechanisms of temporal attention, at least at the processing stages

that determine reaction-time performance. Further experimentation testing the effects of exogenous and endogenous effects on different behavioural measures and in different task contexts will be required to verify the generalisability of the current findings.

These findings support Coull and Nobre's (2008b) dissociation between automatic (exogenous) and goal-directed (endogenous) temporal orienting. We have also introduced a novel paradigm that allows the study of exogenous and endogenous temporal attention independently, on a trial-by-trial basis, and without requiring extensive training. Future studies are necessary to investigate the neural substrates underlying these two different orienting mechanisms of temporal attention.

Chapter 4

4. Entrainment of slow brain oscillations as a mechanism for perceptual modulation of expected events

Timing is an essential dimension of our behaviour, but relatively little is known about how the brain uses temporal information to organise perception and action (Buonomano, 2007; Coull & Nobre, 2008a; Coull & Nobre, 1998a; Coull, et al., 2004; Eagleman, 2005; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009; Nobre & Coull, 2010; Trivino, Correa, Arnedo, & Lupianez, 2010). A survey across several areas of neuroscientific and cognitive research has made it clear that temporal expectations induced by temporal regularity or predictability of stimuli can influence several stages of neural processing and optimise several aspects of behaviour (Nobre, et al., 2007). In addition to marked effects in enhancing motor functions, recent studies have revealed strong effects of temporal expectations during early stages of information processing, enhancing responses in visual cortex in humans (Doherty, et al., 2005) and animals (Anderson & Sheinberg, 2008; Ghose & Bearl, 2010; Ghose & Maunsell, 2002). The study by Doherty and colleagues (2005), in particular, manipulated temporal versus spatial expectations about upcoming stimuli orthogonally, and found that temporal expectations exert the strongest effects when coupled with spatial pre-

dictions. The effects of temporal expectations upon perceptual functions may, therefore, work primarily by timing responses to other stimulus features which can be clearly mapped onto neural receptive-field properties (Nobre, 2010).

Whereas the ability of temporal expectations to impact upon performance is becoming increasingly acknowledged, how this is achieved remains a mystery. Jones has proposed that regular stimulus rhythms can entrain attentional processes to optimise the perceptual processing of forthcoming events occurring at the predicted intervals (Barnes & Jones, 2000; Jones, 2010; Large & Jones, 1999). Lakatos, Schroeder and colleagues have recently unveiled a putative neurophysiological mechanism for perceptual modulation by temporal entrainment. Using field-potential recordings in visual and auditory cortices of macaques, they have shown that oscillatory activity in neuronal ensembles becomes entrained to the timing of rhythmically presented stimuli (Lakatos, et al., 2008; Lakatos, et al., 2009). Based on these findings, Schroeder and Lakatos (2008) propose that attention can operate in two distinct modes - rhythmic and continuous. Much of the stimulation in natural settings, such as biological motion and vocal communication, occurs in a predictable rhythmic pattern (Schroeder & Lakatos, 2008). In these cases, sensory stimulation entrains low-frequency neural oscillations. Higher frequency oscillations, such as gamma, become nested within these slower rhythms, enhancing perceptual processing of subsequent rhythmic stimuli (Schroeder & Lakatos, 2008). Consistent with Jones' hypothesis (2010), Schroeder and Lakatos (2008) refer to this phenomenon as the 'rhythmic mode' of attention. In the absence of temporal predictions, a continu-

ous mode of attention is adopted, involving a general and sustained increase in high-frequency oscillations.

Here, we aimed to (1) test whether temporal regularity of moving stimuli can entrain oscillatory slow rhythms in anticipation of a target stimulus; (2) replicate the synergistic effect of temporal expectation when combined with spatial expectation in boosting perceptual analysis; and (3) test whether temporal expectation also enhances motor preparation after target discrimination. Similarly to Doherty et al (2005), rhythmic visual stimuli were used to orient attention to forthcoming events (Figure 12A) while EEG was recorded. The task consisted of a white ball (200 ms onset time) that moved diagonally across a computer screen in seven steps until reaching an occluding band. While the trajectory of the ball always predicted the spatial location of the target, the rhythm of the stimuli was manipulated to cue participants for the length of the occlusion interval (temporal expectation). Upon reaching the occluding band, the ball disappeared 'behind' the occluder for one step (600 or 1400 ms). When it reappeared, the target contained an upright or tilted cross, which participants were required to discriminate, using a forced-choice response with either their right or left hand. The rhythm was manipulated by changing the inter-stimulus interval (ISI) between each stimulus. Two different rhythms were used: fast (200 ms ISI) and slow (600 ms ISI). The target occurred at the valid, predicted interval after rhythmic stimuli on 44% of the trials, but occurred at the invalid, unpredicted interval on 12% of trials (i.e. fast speed followed by a long interval or slow speed and short interval). On the remaining 44% of trials, the stimuli appeared in an

arrhythmic manner (100-700 randomised ISIs), preventing participants from predicting the occlusion interval.

4.1. Materials and Methods

4.1.1. Participants

Data are presented from 20 healthy, right-handed participants [mean age, 23.9 years (SD, 4.9 years); range, 19–32 years; 9 males). Visual acuity was normal or corrected-to-normal. All experimental methods had ethical approval from the Central University Research Ethics Committee of the University of Oxford.

4.1.2. Stimuli and Task

The task is an adaptation from Doherty et al. (2005). The display consisted of a grey background, with a small white rectangle as the fixation point (0.16°) placed at the centre of the screen, and a white vertical occluding band (width: 3.5°) placed on the right (11.4-14.7° eccentricity) (Figure 12A). A stimulus (ball of 1.0° diameter) appeared on the upper (50%) or lower (50%) left side of the screen and moved across the screen in a diagonal and linear spatial trajectory in seven steps (200 ms for each step). Temporal expectation was induced by manipulating the inter-stimulus interval (ISI) between the successive

steps in three different conditions: *fast* (200 ms), *slow* (600 ms) and *neutral* (randomised between 100-700 ms). Upon reaching the "occluder", the ball disappeared for one of two intervals (600 or 1400 ms), and reappeared in the other side containing an upright (50%) or a tilted (50%) cross. Participants were then required to make a perceptual discrimination and a forced-choice speeded response indicating the tilt of the cross with either their right or left hand. It is important to note that the fast and slow conditions cued for *short* and *long* occlusion periods respectively, whereas there was no specific temporal expectation in the neutral condition. Invalid trials were also introduced to measure behavioural costs of temporal orienting (i.e. fast speed followed by a long occlusion or slow speed occlusion by short occlusion). On rhythmic trials, the target ball appeared at the predicted time on 75% of trials and at the alternative interval on the remaining 25% of trials. In the arrhythmic, neutral condition, the target occurred with equal probability at each of the two intervals. A total of 504 (224 valid, 56 invalid and 224 neutral) trials were presented, equally distributed in short/long occlusion and left/right-hand response.

4.1.3. Procedure

Participants were seated in a dimly illuminated, electrically shielded room, and positioned at a 100-cm distance from the screen. The stimuli were presented using Presentation® software (Version 12.2, www.neurobs.com), on a 21" CRT monitor (CTX ultra screen). The experimental session lasted approximately one hour. Participants were instructed to maintain central fixation

throughout the whole experiment. Eye movements were monitored online with a remote video-based infrared eye-tracker and by recording the electrooculogram (EOG). Trials with eye movements were very rare (< 1% of trials), and were discarded from the analysis.

4.1.4. EEG recording

The EEG was acquired continuously from 34 Ag/AgCl electrodes at 1000 Hz referenced to the right mastoid site (AFZ ground; 300 Hz low-pass filter). The electrodes were positioned according to the 10–20 International system (AEEGS, 1991) and recorded using NuAmp amplifiers (Neuroscan, El Paso, TX). Electrode impedances were kept below 5 kΩ. The montage included six midline sites (FZ, FCZ, CZ, CPZ, PZ, and OZ) and 14 sites over each hemisphere (FP1/FP2, F7/F8, F3/F4, FT7/FT8, FC3/FC4, T7/T8, C3/C4, TP7/TP8, CP3/CP4, P7/P8, P3/P4, PO7/PO8, PO3/PO4, and O1/O2). Six additional electrodes were used as ground and reference sites and for recording the EOG. EOG electrodes were placed to the side of each eye [horizontal EOG (HEOG)] and above and below the left eye [vertical EOG (VEOG)], and bipolar signals were subsequently derived by computing the difference between these electrodes. Eye movements and blinks were also monitored using a remote, video-based infrared eye tracker (ISCAN, ETL-400 system, 60 Hz).

4.1.5. EEG processing and analysis

To perform the ERP and LRP analysis, continuous EEG was re-referenced to the algebraic average of the right and left mastoids and filtered off-line with a 40-Hz low-pass filter (24 db/oct). ERPs elicited from valid and neutral trials were epoched from -200 to 600 ms relative to target onset. Trials with eye movements, blinks or errors were excluded. The interval from 0 to 50 ms was used to calculate the baseline for the ERP, while a baseline of -200 to 0 ms was use for the LRP. Epochs containing excessive noise or drift (±100 µV at any electrode) or eye artefacts (blinks or saccades) were rejected. Blinks and saccades were identified as large deflections (±50 µV) in the horizontal or vertical EOG electrodes. All traces were subsequently visually inspected to remove any residual blinks or saccades. An average of 87 (minimum of 74) trials was obtained per subject for valid and neutral conditions. The invalid condition was not included in the neurophysiological analysis due to the insufficient number of trials (<30). Except for the LRP segmentation analysis (performed using Cartool software, D. Brunet, Functional Brain Mapping Laboratory, Geneva, Switzerland), all ERP and LRP processing were performed using Neuroscan version 4.3 (Neuroscan, El Paso, TX).

The time-frequency analysis was performed on unfiltered data, epoched from -700 to 1800 ms relative to the beginning of the occlusion period. Due to the size of the epochs, data from three participants had to be excluded from the frequency analysis due to excessive artefacts during the occlusion period (<30 trials per condition). A multitaper time–frequency transformation (5 cycles

per time window) was applied to all electrodes in each trial. This transformation produced an estimate of oscillatory raw power for each time sample (20 ms) and frequencies between 4 and 20 Hz (in steps of 1Hz). In order to control for any non-specific change in neural state across the trial, the data were normalised by subtracting the signal of the neutral (i.e. arrhythmic) condition from the rhythmic (i.e. fast and slow) conditions. The subtraction isolates the effect of specific expectations set up by the temporal regularity of the preceding stimuli. In this way, we ensured that the oscillations present in the occlusion period reflect solely participants' temporal expectations about the target appearance.

4.2. Results

4.2.1. Behavioural Results

Performance in this task was very accurate (91.8-94.4% correct) and did not differentiate between conditions. The behavioural benefits conferred by temporal orienting in this task were observed mainly in reaction times (RTs). Figure 12B shows the average RTs after the two occlusion intervals. Reaction times from correct responses were submitted to a repeated-measures analysis of variance (ANOVA), testing the effects of temporal expectation (valid, neutral, or invalid) and occlusion interval (short or long). A significant interaction between temporal expectation and occlusion interval [$F(2,18) = 32.46$, $p < .001$] replicated the well established finding that temporal orienting effects are more pronounced at short occlusions (Anderson & Sheinberg, 2008; Correa & Nobre,

2008; Coull & Nobre, 1998a; Griffin, Miniussi, & Nobre, 2001). Post hoc analyses using paired-samples t tests adjusted for multiple comparisons (*Bonferroni*) demonstrated clear validity benefits (RTs valid $<$ neutral $<$ invalid) after the short occlusion interval [ts(19) $>$ 4.93, ps $<$.01], but no significant validity effects after the long occlusion [ts(19) $<$ 2.77, ps = ns] (Figure 12B).

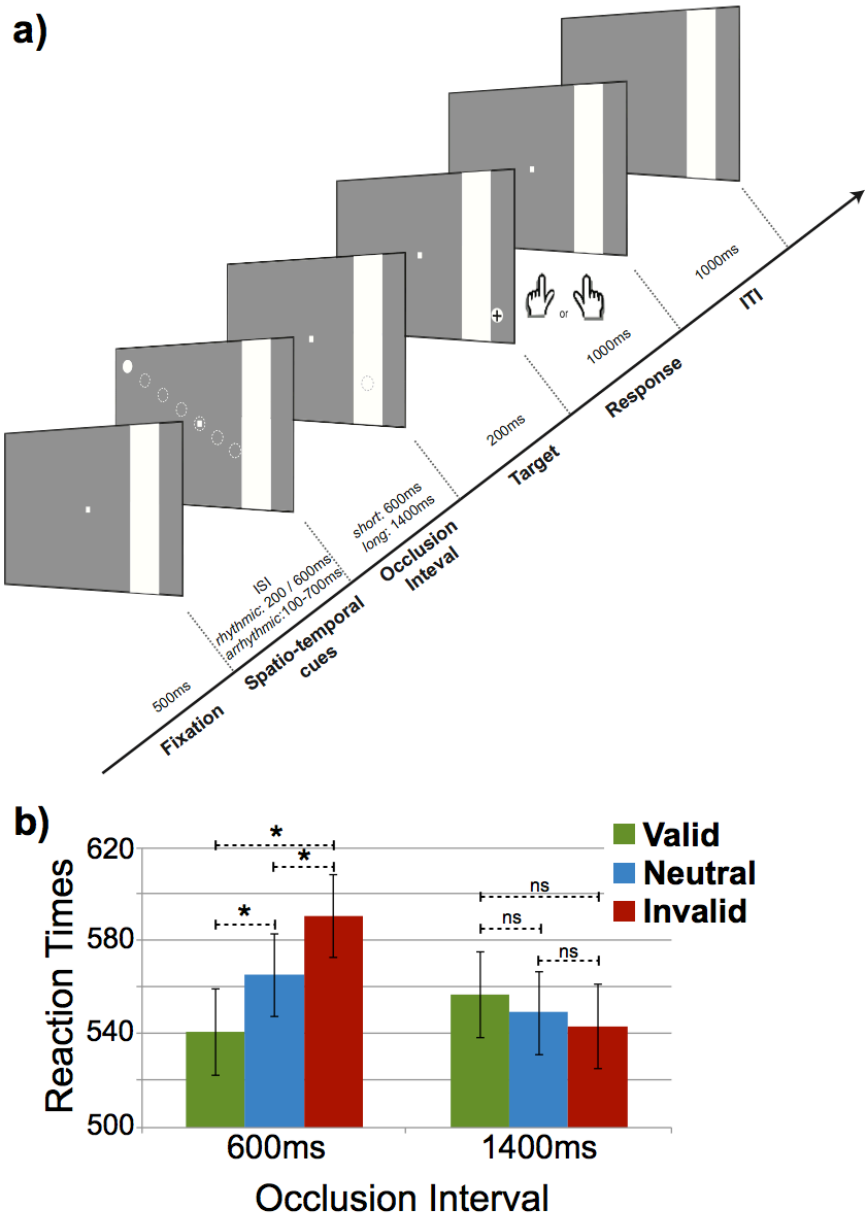


Figure 12. Task and behavioural results. (A) The three pictures represent the task at three different stages. First, a white ball appeared at the left side of the screen and moved diagonally across the screen in seven steps (its previous trajectory is indicated by the dashed line). After reaching the grey occluding band, the ball disappeared underneath for one steps. When the ball reappears it contains either an upright (50%) or a tilted (50%) cross. Temporal expectations were induced by the rhythm of the balls during the pre-occlusion period. (B) A bar graph indicating the mean reaction time averaged over subjects (n = 20). Error bars indicate SE.

4.2.2. Brain oscillations underlying visual perceptual enhancement

Time-frequency analysis was performed to track whether oscillatory brain activity became entrained to regular rhythmic events in a way that could drive preparatory increases in cortical excitability to temporally expected events. The analysis of oscillatory activity was performed during the occlusion interval, during which time no stimulus occurred for 600 ms (short occlusion) or 1400 ms (long occlusion). Therefore, the occlusion period is ideal to quantify fluctuations in oscillatory activity (4-20 Hz) related to temporal expectations in the absence of any stimulus-driven effects. During this interval, valid trials, with a preceding regular rhythm, should induce a temporal expectation for the target to appear. If temporal expectations entrain spatial attention mechanisms, one would expect desynchronisation of alpha band oscillations to occur at the moments preceding expected targets. Alpha-band desynchronisation has been repeatedly shown to correlate with anticipatory attention for target stimuli (Rihs, et al., 2009; Thut, et al., 2006). The arrhythmic, neutral condition was used as a baseline to control for general, and temporally nonspecific changes in oscillatory activity occurring through the occlusion period; and was subtracted from each of the rhythmic conditions. Planned t-tests were performed in the period preceding (200 ms) the predicted onsets of the occluded stimuli and then re-emerging targets.

Figure 13A shows the anticipatory frequency oscillations induced by slow rhythms during long occlusion interval over occipital electrodes (Oz,O1/2,PO3/4,PO7/8). The results show significant desynchronisation of alpha-band activity (8-12 Hz) in anticipation of the appearance of the target (black dotted

line) [t(16) = 2.11, p = .026]. Figure 13B also shows an earlier peak in alpha desynchronisation during the long occlusion. Interestingly, the first peak seems to occur in anticipation to the onset of the stimulus hidden behind the occluder (grey dotted line) [t(16) = 2.59, p = .010]. The topographic map and the time course of the 'entrained' oscillations are remarkably similar to the ones observed in anticipation of the reappearance of the target.

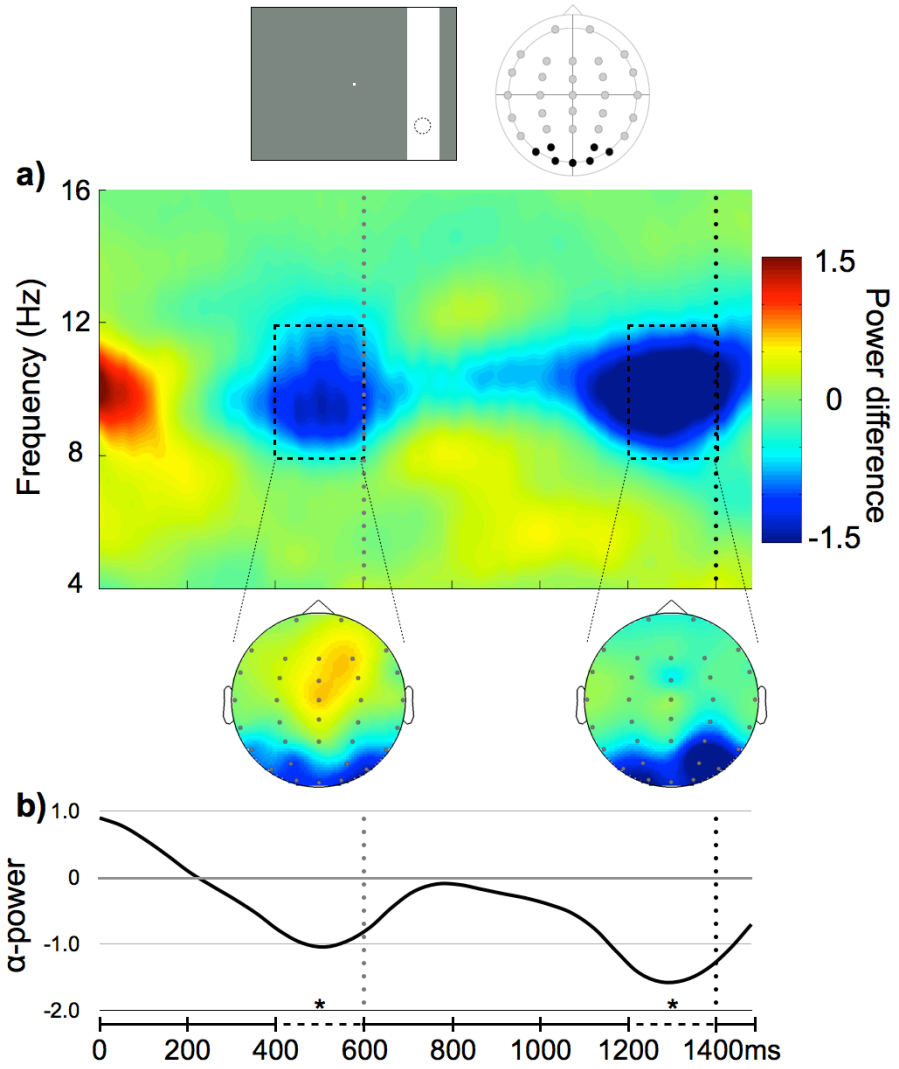


Figure 13. Alpha activity during the long occlusion period. The figure shows the subtraction of the signal of the neutral (i.e. arrhythmic) condition from the rhythmic conditions. The grey doted line shows the time that the occluded stimulus would be presented. The black doted line indicates the onset of the target. (A) Colormap of the frequency amplitude between 4 and 16 Hz. Black dashed boxes shows the time and frequency of interest analysed for the occluded stimulus and the target. Topographies showing the scalp distribution of anticipatory alpha activity (8-12Hz) preceding the occluded stimulus and target. (B) Lines showing the average of alpha power during the occlusion period. The significant differences are indicated by the dashed lines and stars ($p<.05$).

Similar effects were found during the short occlusion. Figure 14A shows the anticipatory desynchronisation of alpha-band activity preceding target onset (black dotted line) [$t(16) = 2.12$, $p = .024$]. As confirmed by the topographic analysis, this effect was restricted to posterior electrodes. Figure 14B presents the time course of alpha power for the fast-rhythm condition. The topographies of oscillatory activity in anticipation to the target induced by the fast (Figure 14A) and slow (Figure 13A) rhythms are very similar. Unlike the slow rhythm condition, for the fast trials the desynchronisation of the alpha-band oscillations before the time of the occluded ball did not reach significance [$t(16) = 1.03$, $p = .16$]

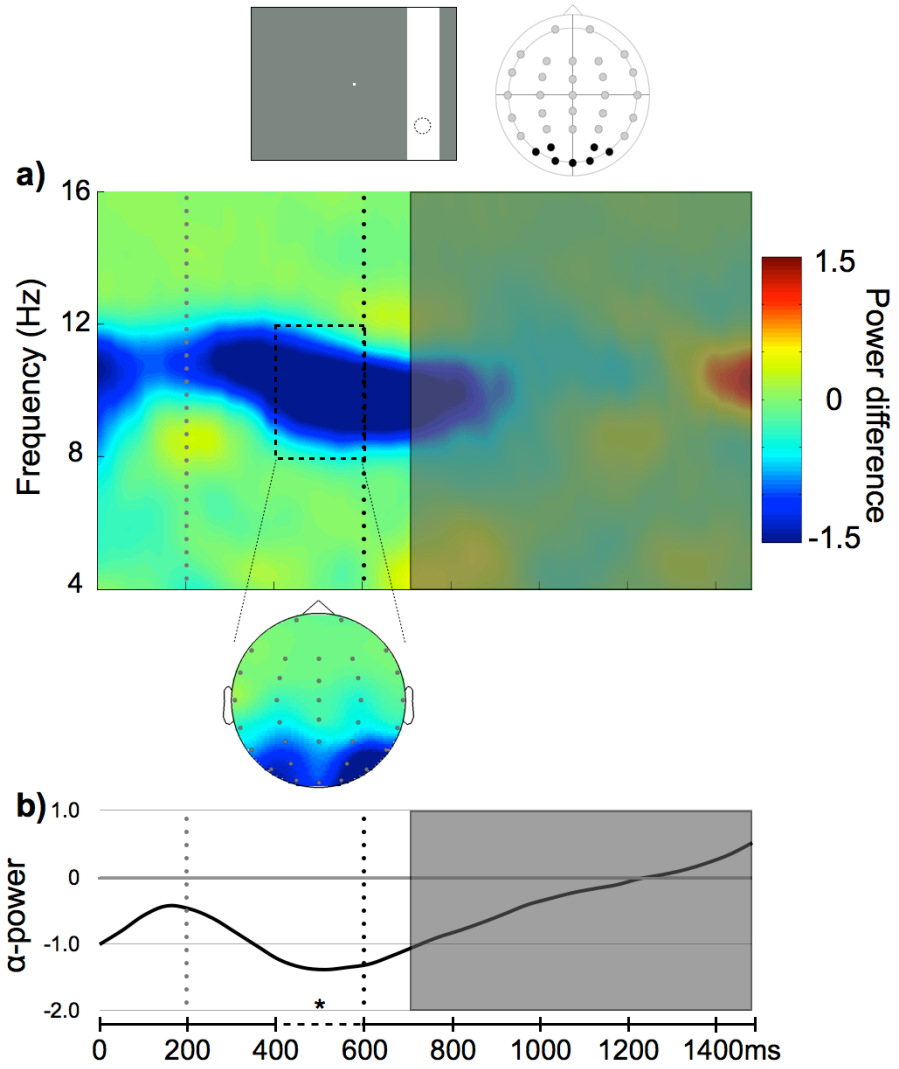


Figure 14. Alpha activity during the short occlusion period. The figure shows the subtraction of the signal of the neutral (i.e. arrhythmic) condition from the rhythmic conditions. The grey doted line shows the time that the occluded stimulus would be presented. The black doted line indicates the onset of the target. (A) Colormap of the frequency amplitude between 4 and 16 Hz. Black dashed boxes shows the time and frequency of interest analysed for the occluded stimulus and the target. Topographies showing the scalp distribution of anticipatory alpha activity (8-12Hz) preceding the occluded stimulus and target. (B) Lines showing the average of alpha power during the occlusion period. The significant differences are indicated by the dashed lines and stars ($p<.05$).

4.2.3. Early perceptual modulation by temporal expectation

In line with the behavioural findings, analysis of the neural consequences of temporal expectation on target-related processing focused on the short occlusion interval. In particular, we tested for enhancement of early visual activity in the first identifiable visual potential (P1) evoked by the target stimulus in the valid rhythmic, condition relative to the neutral, arrhythmic condition. The invalid condition could not be analysed due to insufficient number of trials (<30) after artefact rejection in the majority of participants.

The visual P1 potential was maximally distributed at lateral posterior electrodes PO7/8, PO3/4, and O1/2, and peaked earlier in electrodes over the left hemisphere, which was contralateral to the target location (~125 ms), than over the ipsilateral (~130 ms) hemisphere. Modulation of the mean amplitude of P1 was tested with a repeated-measures ANOVA including the factor of temporal expectation (valid, neutral), as well as hemisphere (contralateral, ipsilateral) and electrode pairs (PO7/8, PO3/4, O1/2). Temporal expectation exerted a significant main effect on the mean amplitude of P1 [$F(1,19) = 13.14$, $p = .002$], measured using a period of 20 ms around the peak latency in each hemisphere, P1 amplitude was significantly greater in valid compared to neutral trials (Figure 15A). An interaction between temporal expectation and hemisphere [$F(1,19) = 5.89$, $p = .025$] indicated that these effects were larger in the ipsilateral hemisphere [$F(1,19) = 8.78$, $p = .008$]. Subsidiary, follow-up ANOVAs testing the effect of temporal expectation at each hemisphere showed the effect to be signifi-

cant over both contralateral [F(1,19) = 5.85, p = .026] and ipsilateral [F(1,19) = 14.11, p = .001] sites.

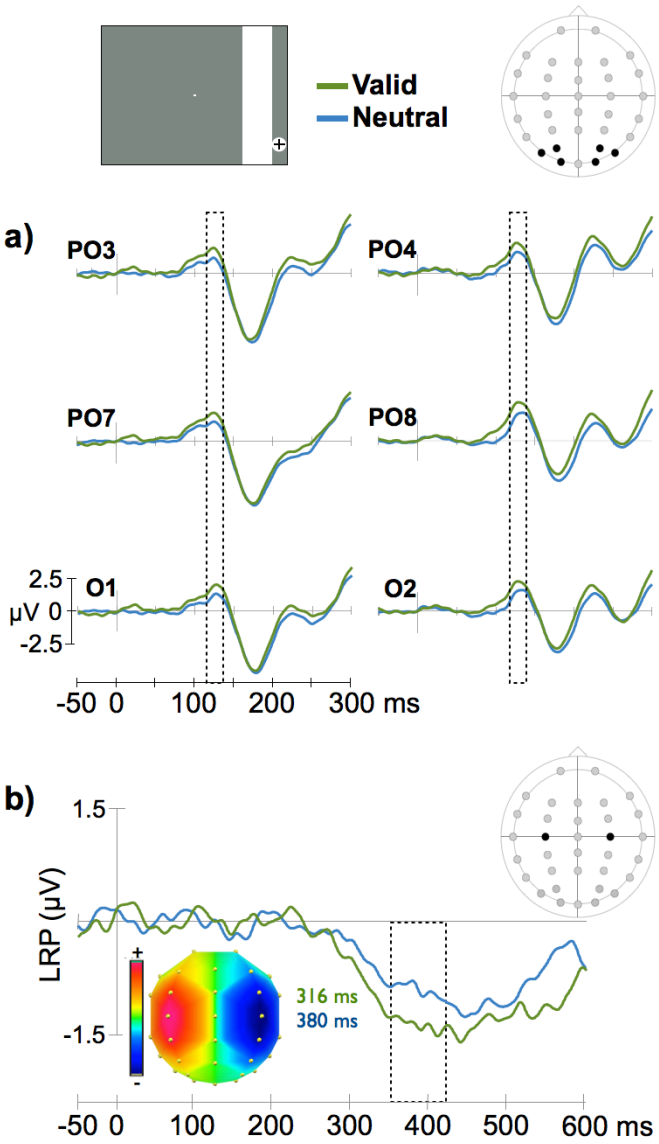


Figure 15. Enhanced temporal expectation modulation of visual (P1) and motor (LRP) components. (A) Visual components P1 from grand-averaged waveforms (n = 20 subjects) are shown for the lateral posterior electrodes analysed for the valid (rhythmic - *green line*) and neutral (arrhythmic - *blue line*) conditions. Dashed line indicates the time of interest. (B) Average of the lateralised readiness potential from the valid and neutral conditions. Dashed lines shows the time that the difference in LRP amplitude between valid and neutral conditions was statistically significant (p<.05).

4.2.4. Motor preparatory activity to forthcoming events

To analyse the effect of temporal expectation specifically on motor preparation, we analysed the *lateralised readiness potentials (*LRP), which compares activity over contralateral versus ipsilateral primary motor cortex (Coles, 1989; Osman, Moore, & Ulrich, 1995; Ulrich & Miller, 2001). To calculate the LRP the following formula was used: [mean $(C4\text{-}C3)_{\text{left-hand movement}}$ + mean $(C3\text{-}C4)_{\text{right-hand movement}}$]/2. Stimulus-locked LRP data were baselined from -200 to 0 ms. Linear trends present during this baseline period were also removed from the data to correct for residual drifts. The results revealed a significant increase in the mean amplitude of the LRP (350 - 420 ms) by valid temporal expectations [$F(1,19) = 4.91$, $p = .039$] (Figure 15B). Interestingly, these changes in LRP amplitude showed an inverse correlations with reaction times [valid - $r(19) = .513$, $p = .02$; neutral - $r(19) = .470$, $p = .037$]. To characterise the distribution and timing of the LRPs, a spatiotemporal clustering algorithm implemented in the Cartool (http://brainmapping.unige.ch/Cartool.htm) was applied on the grand-averaged LRP data (Atomise & Agglomerate Hierarchical Clustering; minimum segment duration 40 ms). This analysis revealed a stable and common topographical map in the two conditions, and showed that the LRP started earlier in the rhythmic (316 ms) than in the arrhythmic condition (380 ms).

4.3. Discussion

In this experiment, visual rhythmic stimuli were used to induce combined temporal and spatial expectations. Behavioural data confirmed the effect of rhythmic temporal cues in speeding up reactions times. Our time-frequency analysis showed that rhythmic cues can entrain slow brains oscillations, providing a putative mechanism for enhancing the perceptual processing of expected events. Early visual responses (P1) to the target stimuli were enhanced accordingly, showing that perceptual enhancement by combined spatial and temporal expectations (Doherty, et al., 2005) can also occur during a forced-choice discrimination task, where the target identity is uncertain. This study also provides new evidence for modulation of the timing and amount of preparatory motor activity by temporal expectations.

Our results support the ability of rhythmic events to entrain changes in task-relevant oscillatory activity (Lakatos, et al., 2008; Lakatos, et al., 2009). In our task, temporal regularity of visual events entrained the desynchronisation of alpha-band activity in anticipation of a target at a particular location. Alpha band activity has been well documented for its role in visual spatial attention (Capotosto, et al., 2009; Romei, Gross, & Thut, 2010; Thut, et al., 2006) and perceptual processing (Busch, Dubois, & VanRullen, 2009; Palva & Palva, 2007; Praamstra, 2006). These findings support the theoretical proposal by Schroeder and Lakatos (2008). According to their view, the entrainment of low-frequency neural oscillations coupled to the increase in higher frequencies amplitude (gamma-band) acts as a central mechanism for attentional selection (Schroeder

& Lakatos, 2008). These changes in oscillatory activity should lead to enhancement of perceptual analysis of stimuli occurring at the predicted time (see also Jones, 2010).

We might also expect to see concomitant increases in gamma-band amplitudes, which has also been reported during spatial attention (Fries, et al., 2001; Womelsdorf & Fries, 2007; Wyart & Tallon-Baudry, 2008). Due to its involvement in a vast number of cognitive functions (Fries, et al., 2008; Schroeder & Lakatos, 2009; Wyart & Tallon-Baudry, 2008), it has been proposed that gamma-band oscillations are a core mechanism for selection and segmentation of neural inputs in cortical computation (Fries, 2009a). However, recent studies have proved difficult to observe the modulation of gamma-band activity is e using EEG (Fries, et al., 2008; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). We expect that we would observe increases in gamma-band activity concomitantly with our described alpha-band decreases if we used a recoding method with higher sensitivity and spatial resolution, such as MEG.

In our study, temporal expectations greatly enhanced visual processing of target stimuli, as reflected by the increase of the visual P1 potential. The P1 potential reflects visual processing in a combination of ventral (Di Russo, et al., 2002) and dorsal (Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005) extrastriate visual areas. Its amplitude enhancement by spatial attention is a canonical finding, and is thought to reflect more intensive visual analysis for spatially attended relative to unattended stimuli through a gain-control mechanism (Hillyard, Vogel, & Luck, 1998). The finding replicates and extends previous studies showing the influence of temporal information for visual processing

in humans (Doherty, et al., 2005; Nobre, 2010; Praamstra, 2006) and animals (Anderson & Sheinberg, 2008; Ghose & Bearl, 2010; Ghose & Maunsell, 2002). Contrary to previous studies, in our task, participants were asked to discriminate between two possible targets, and the nature of the target was not certain until its presentation. Since we used EEG, it is not possible to determine exactly which visual area(s) was(were) modulated. In macaque monkeys, temporal expectations enhanced activity in distinct visual areas, such as V4 (Ghose & Maunsell, 2002), MT (Ghose & Bearl, 2010), and IT (Anderson & Sheinberg, 2008). This enhancement is attributed to a boost in the effects of spatial attention when targets were also presented at an expected time.

We used the LRP to isolate neural activity related to the final stages of motor preparation and execution (Coles, 1989; Masaki, et al., 2004). We found that the LRP was both enhanced in amplitude and brought forward in latency. Previous studies have suggested that temporal expectations can exert strong effects on motor processing (Nobre, et al., 2007). Single-unit studies have shown systematic changes in neural firing patterns to go-signals in primary motor cortex (Riehle, Grun, Diesmann, & Aertsen, 1997) and premotor areas (Lucchetti & Bon, 2001) as a function of temporal expectation. In humans, the effect of temporal expectations on motor processing is usually based in latency and amplitude modulations of late potentials, such as the P3 (Correa & Nobre, 2008; Doherty, et al., 2005; Griffin, et al., 2002; Miniussi, et al., 1999), as well as interactions of ERP effects with go versus no-go response requirements (Correa & Nobre, 2008; Doherty, et al., 2005). Previous tasks have not isolated motor-related activity directly. It is important to notice that in our task response is not

specified until target presentation. The modulation of LRP amplitude and latency presented in this experiment can be understood as reminiscent of changes in the timing and strength of pre-movement local field potentials during expected compared to unexpected intervals (Roux, Mackay, & Riehle, 2006). It is important to notice that this motor effect could be a consequence of a modulatory cascade starting with perceptual processing and/or an independent, separate effect acting directly at the level of motor cortex.

In summary, we have shown that combined spatiotemporal expectations modulate different stages of stimulus processing, from the anticipatory changes in alpha-band power to perceptual enhancement in P1 and motor preparation. To our knowledge, this is the first evidence showing that the entrainment of alpha band activity to the rhythm preceding cues primes the neural processing in visual areas to enhance the perception of forthcoming events. An important goal for future research will be to investigate the causal relationships between each of these different stages of processing and spatiotemporal expectations using transient (TMS) or permanent lesions.

Chapter 5

5. Dissociating spatial and temporal orienting in the human brain

It has long been reported in the literature that responses to a stimulus occurring at an expected time improves accuracy and speeds up reactions times, when compared to those appearing at unexpected intervals (Niemi & Naatanen, 1981). Nevertheless, it was not until recently that research started to demonstrate that attention can also be voluntarily directed to instants in time (Coull & Nobre, 1998b). Initial studies into the voluntary orienting of attention (Coull, et al., 2000; Coull & Nobre, 1998b; Miniussi, et al., 1999) relied on tasks that were similar to Posner's (Posner, 1980). In this type of task, cues predicted the time interval (short or long) at which a target would appear. A number of studies using different cue-target intervals, physical stimuli and response requirements have shown benefits to response times and/or accuracy when targets appear at the valid interval compared to when they are unexpected (Coull, et al., 2000; Coull & Nobre, 1998b; Miniussi, et al., 1999; Nobre, 2001a). The effects are more pronounced for targets appearing at the short interval, where the manipulation of the conditional probability for the appearance of the target is strongest (for reviews see Griffin, et al., 2001; Nobre, 2001a; Nobre, et al., 2007; Nobre & Coull, 2010).

One of the aspects of temporal orienting that has attracted particular interest in the literature is whether and how temporal expectations can influence early perceptual processing (Nobre, 2010). The first evidence of temporal expectations modulating early perceptual processing was found in the auditory modality (Lange, Rosler, & Roder, 2003). In an auditory adaptation of Coull and Nobre (1998b) task, Lange et al (2003) demonstrated that temporal orienting enhances early perceptual stages of auditory processing, expressed by the modulation of the N1 potential. This finding has proven to be reliable and has been consistently replicated (Lange, Kramer, & Roder, 2006; Lange & Roder, 2006; Roder, Kramer, & Lange, 2007).

In contrast, studies in the visual modality have tended to report no early perceptual modulation (Griffin, et al., 2001; Miniussi, et al., 1999; Nobre, 2001a, 2010). Findings in the visual modality have instead repeatedly emphasised the ability of temporal orienting to modulate later potentials, believed to be involved in decision making and motor planning, such as N2 and P300 (Correa & Nobre, 2008; Griffin, et al., 2002; Griffin & Nobre, 2005; Miniussi, et al., 1999; Nobre, 2010). One experiment by Correa and colleagues (2006a) stands as an exception in the visual temporal orienting literature. One exception in the literature was published by Correa and colleagues (2006a). However, Correa and colleagues (2006a) used verbal cues in a blocked design experiment, which can lead to a late cue-related activity confound in P1. Also, in their experiment they found an unusual late peak for the P1 potential (>150 ms).

However, Doherty et al (2005) showed the first evidence that temporal orienting can also modulate early visual processing. Using an ingenious paradigm, Doherty et al (2005) used rhythmic stimuli, instead of endogenous cues (for a review see Coull & Nobre, 2008b), to induce temporal expectations. In their task, participants were required to focus attention covertly on a ball that moved from left to right across a computer screen, until reaching an occluding band. Temporal expectations - created by conditions where the ball moved in a rhythmic fashion (i.e. fixed SOA) - cued participants to when the ball (target) would reappear after occlusion. Spatial expectations were also manipulated by whether the ball moved along a predictable linear trajectory or an unpredictable erratic trajectory. Temporal and spatial expectations were crossed in a factorial design. ERP recordings showed that the combined spatial-temporal expectations modulated early visual P1 potential to a greater extent than spatial expectation alone. Interestingly, temporal cues alone did not elicit any modulation of early visual potentials. Supported by single-unit findings (Anderson & Sheinberg, 2008; Ghose & Bearl, 2010; Ghose & Maunsell, 2002; Janssen & Shadlen, 2005), this result led to the hypothesis that temporal expectations can modulate perceptual processes by interacting synergistically with spatial expectations to boost the top-down biasing the activity of neurones with receptive fields at the relevant location at the predicted time (Doherty, et al., 2005; Nobre, 2010). These findings were also replicated in the experiment presented in chapter 4.

As mentioned in chapter 4, anticipatory modulation of occipito-parietal alpha-band oscillations preceding target onset has been associated with the allocation of selective visuospatial attention (Capotosto, et al., 2009; Foxe,

Simpson, & Ahlfors, 1998; Thut, et al., 2006; Worden, et al., 2000). The study presented in chapter 4 also indicated that alpha desynchronisation is putative mechanisms for the perceptual enhancement induced by temporal expectations.

Therefore, the aim of this study was to develop a novel flexible task in which temporal and spatial attention are orthogonally manipulated. We explored the neural modulatory effects of spatial and temporal expectations on early visual perceptual processing acting in isolation or in coordination (P1), as well as low-frequency brain oscillations in anticipation to an expected target. Like Posner's original cost-benefit paradigm (Posner, 1980), participants were required to respond to a target (Gabor) presented at one of two locations, following a symbolic cue. To induce temporal expectation, the cues were presented in either a rhythmic (temporally ordered intervals between each cue) or arrhythmic fashion (random time intervals between each cue).

5.1. Materials and Methods

5.1.1. Participants

Data were collected from a group of 21 healthy volunteers (aged 19-27 years, 8 females and 13 males). All were students at Oxford University. All participants were right-handed and had normal or corrected-to-normal vision. Data were only analysed from 18 participants, due to unsatisfactory ERP recordings from three of the participants.

5.1.2. Stimuli and task

The display consisted of black background with a small white rectangle as the fixation point (0.16°) placed at the centre of the screen. At the beginning of each trial, a series of five cues (Figure 16A) was centrally presented (200 ms) (0.57°) in either a rhythmic fashion (with fixed inter-stimuli intervals of 200, 250, 300, 350 or 400 ms) or arrhythmic fashion (with inter-stimuli intervals which varied randomly between 100 ms and 700 ms). The shape of these cues was used to indicate the side at which that the target would occur (Figure 16A). After the series of central cues, an array of two Gabor patches was laterally presented (200 ms) (4.5° eccentricity). One of the patches was oriented horizontally or vertically, serving as the target for discrimination. The other, distractor patch was diagonally oriented (left or right tilt). Targets were defined by a combination of colour and orientation of the Gabor patches, so that neither feature alone specified the correct response: e.g., left-hand button-press for red/vertical and green/horizontal, and right-hand button-press for green/vertical and red/horizontal (figure 16B). The balanced display containing Gabors at the two locations avoided contamination of the results by reflexive shifts of spatial attention to the target location. Importantly, the ISI between the last cue and the target was the same for both rhythmic and arrhythmic conditions (200, 250, 300, 350 or 400 ms). The shape of cues used to signal target location and the response assignments for the different combinations of orientation and colour features were counterbalanced across participants.

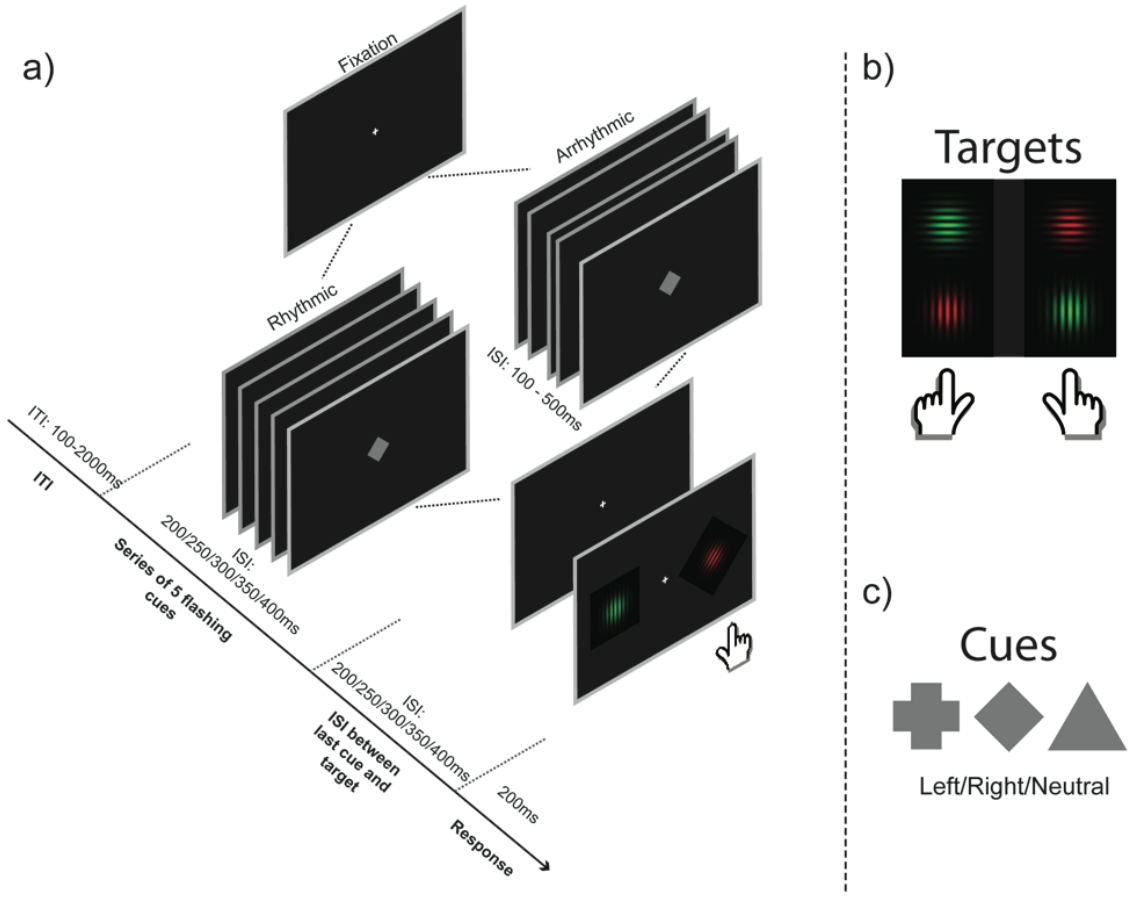


Figure 16. Task schematic. (A) A series of five cues were presented either rhythmically or arrhythmically to create temporal expectation. Spatial orienting was endogenously manipulated using symbolic cues. (B) One either horizontal or vertical red and green Gabor grating signalled a left hand response, whilst the other red and green Gabor grating signalled a right hand response. The orientation-colour combination signalling a left / right hand response associations were learned and reinforced during a training phase, and counterbalanced across trials. (C) Endogenous spatial cues.

Spatial and temporal orienting effects were tested in a 2 x 2 full factorial design: *spatial-temporal* (ST) - rhythmic cues that predict target location; *temporal* (T) - rhythmic cues that did not predict target location; *spatial* (S) - arrhythmic cues that predicted target location; and *neutral* (N) - arrhythmic cues that did not predict target location. It is important to notice that in this design the effect of the temporal and spatial orienting is orthogonally manipulated.

5.1.3. Procedures

Participants were comfortably seated in a dimly illuminated and electrically shielded room which contained a chair, a desk with a modified keyboard, and a 21-inch CRT (CTX ultra screen) computer monitor. A chin-rest positioned at 100 cm from the computer screen was used throughout the experiment.

Participants were required to respond to a peripherally presented target stimulus (5° eccentricity) as quickly and accurately as they could. Temporal and spatial expectation was orthogonally manipulated by a series of five centrally presented cues. Participants were told to use the rhythm of these cues to predict *when* (temporal orienting) a forthcoming target would appear, and its shape (spatial orienting) for the information on the target location (Figure 16A). Both temporal and spatial cues, when valid, were 100% informative. Participants were required to make either a left-hand or right-hand response, depending on the colour (red of green) and orientation (vertical or horizontal) of the target stimulus presented (Figure 16B). In 50% of the trials the spatial cues would correctly inform the location (spatial trials) and in the other 50% the cues did not predict spatial location (neutral trials). In a third of the trials, no target was presented (catch trials), hence no response was required.

Since the spatial cues and the target-response assignment were based on a learned association, each experimental session started with an extensive training phase. The training phase started with a simple association between target (based on the colour and orientation of the Gabor patches) and hand re-

sponse (left/right) using feedback after each response (Figure 16B). After a satisfactory learning of the target-response association, participants were trained on the association of the endogenous spatial cues. Only after a satisfactory performance level was reached (error rate $< 15\%$), participants were able to start the main experiment. The main experiment consisted of 720 trials presented in 15 blocks. To ensure central fixation throughout the whole session, eye movement was monitored using a monocular (right eye) remote, video-based infrared eye tracker (ISCAN, ETL-400 system, 60 Hz).

5.1.4. EEG recording

The EEG was recorded continuously from 35 scalp sites using Ag/AgCl electrodes mounted on an elastic cap and positioned according to the 10-20 International system (American Electroencephalographic Society, 1991) using NuAmp amplifiers (Neuroscan, El Paso, TX). The montage included seven midline sites (FZ, FCZ, CZ, CPZ, PZ, POZ, and OZ) and 14 sites over each hemisphere (FP1/FP2, F3/F4, F7/F8, FC3/FC4, FT7/FT8, C3/C4, T7/T8, CP3/CP4, TP7/TP8, P3/P4, P7/P8, PO3/PO4, PO7/PO8, and O1/O2). Additional electrodes were used as ground and reference sites. Horizontal and vertical electrooculogram (EOG) were recorded bipolarly with electrodes placed around the eyes to measure saccades and detect blinks. Electrodes were referenced to the right mastoid site (A2) and impedances were kept below 5 kΩ. The ongoing brain activity at each electrode site was sampled at 1000 Hz (analog-to-digital sampling rate). Digital codes were sent from the stimuli presentation computer

to the EEG-acquisition computer via the parallel port, flagging the occurrence and type of each event.

5.1.5. EEG processing and analysis

For the ERP analysis, the continuous EEG was re-referenced to the average of the two mastoids and filtered offline with a 40-Hz low-pass filter (24 db/oct). The epoching of ERPs was performed around the presentation of the target arrays (starting 200 ms before and ending 800 ms after). The pre-stimulus interval (-200 to 0 ms) was used to calculate the baseline. Epochs containing excessive noise or drift (±100µV) at any electrode were rejected. Blinks and saccades identified as large deflections (±50 µV) in the horizontal or vertical EOG electrodes by a computer algorithm, and the EOG recordings were then checked manually to remove any residual ocular artefacts. Separate averaged ERP waveforms were constructed for the spatial-temporal (ST), temporal (T), spatial (S), and neutral (N) conditions. Trials containing targets located on the left and right hemifield were combined by an averaging procedure preserving the electrode location relative to the target side (ipsilateral or contralateral).

The effect of temporal orienting on motor readiness was investigated by comparing the lateralised readiness potentials (LRP). The LRP is a marker of motor preparation in primary motor cortex. The LRP is derived from the C3 and C4 electrodes (which are positioned over the left and right motor cortices respectively). To calculate the LRP, the following formula was used [mean (C4-

$C3)_{\text{left-hand movement}}$ + mean $(C3\text{-}C4)_{\text{right-hand movement}}]/2$. The LRP was analysed between 500 and 600 ms.

The time-frequency analysis was performed on unfiltered data, downsampled to 256 Hz, and epoched from -600 to 400 ms relative to the onset of the target. A multitaper time–frequency transformation with a length of four cycles was applied to all electrodes in each trial. This transformation produced an estimation of the oscillatory power spectrum for each time bin of 20 ms, and frequencies between 6 and 30 Hz (in steps of 1Hz). To analyse the effects of temporal expectations on anticipatory slow brain oscillations, non baselined data in the arrhythmic conditions were subtracted from the data in the rhythmic trials. By subtracting trials carrying only *spatial* information from trials carrying combined *spatial-temporal* information (ST - S) we derive an estimative of the effect of temporal expectations when this is accompanied by spatial expectations. To investigate the effect of temporal expectations independent of spatial orienting, we subtracted data in the *neutral* trials from data in the *temporal* trials (T - N).

5.2. Results

5.2.1. Behavioural results

Behavioural accuracy and response times were analysed separately using a 2 x 2 repeated-measures analysis of variance (ANOVA) testing the effects of temporal (valid vs. neutral) and spatial expectation (valid vs. neutral).

Reaction-time analyses revealed a main effect of spatial [$F(1,17) = 43.34$, $p<0.01$] and temporal expectation [$F(1,17) = 5.79$, $p<0.05$], but no significant interaction [$F(1,17) = 0.11$, $p = 0.75$]. The main effect of spatial expectation indicated that valid spatial cues speeded up reaction times compared to neutral cues (Figure 17). Similarly, for temporal expectation, mean reaction time in the rhythmic condition was significantly faster than in the arrhythmic condition. Accuracy was high overall and was not significantly affected by spatial [$F(1,17) = 1.17$, $p = 0.21$] or temporal expectation [$F(1,17) = 0.16$, $p = 0.69$]. This pattern of results indicates that the reaction-time effects do not result from a speed-accuracy trade-off.

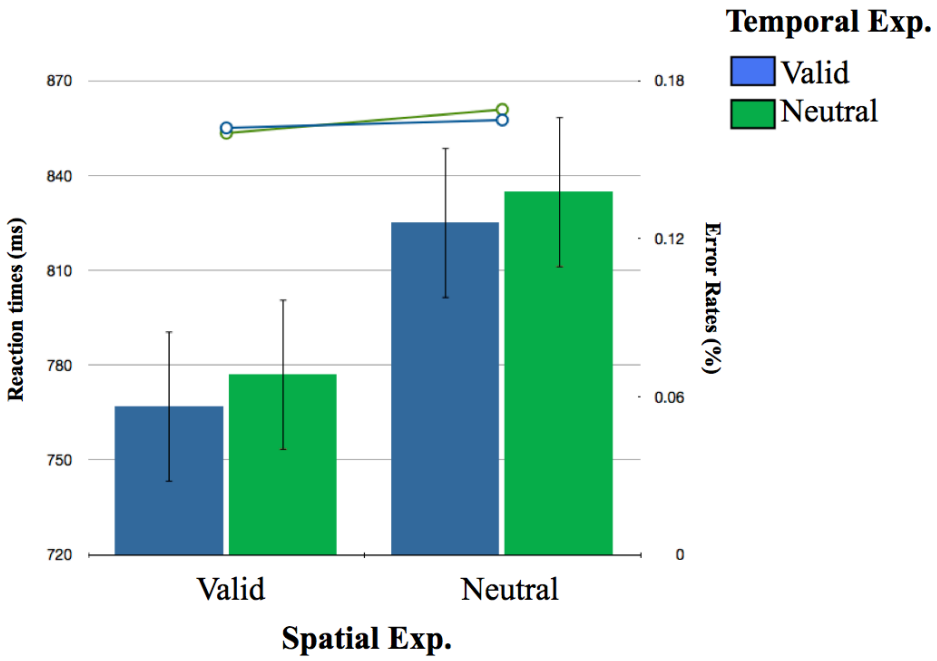


Figure 17. Mean reaction time and error rates. The bars represent reaction time values (left y-axis), and accuracy data is represented by the lines (right y-axis). Error bars indicate SE.

5.2.2. ERP Results

To investigate the effect of temporal and spatial expectations on early visual processing, a four-way repeated-measures ANOVA was computed on the mean amplitudes of P1, including the factors: *temporal expectation* (rhythmic vs. arrhythmic), *spatial expectation* (valid vs. neutral), *hemisphere* (ipsilateral vs. contralateral to target), and *electrode pair* (P3/4, P7/8, PO7/8) -. Since the P1 peaked around 135 ms, mean amplitudes were tested at a time window between 125 and 145 ms (i.e. ±10 ms from the peak).

The analysis revealed a main effect of temporal expectation [$F(1,17) = 6.20$, $p<0.05$] as well as an interaction between temporal expectation and hemisphere [$F(1,17) = 9.81$, $p<0.01$] on P1 amplitude (Figure 18). P1 modulation by temporal expectation was driven by an enhancement of the amplitude in the ipsilateral hemisphere [$F(1,17) = 19.57$, $p<0.01$]. Spatial expectation alone did not significantly enhance the P1 amplitude [$F(1,17) = 0.31$, $p = 0.59$]. However, spatial expectations interacted significantly with hemisphere [$F(1,17) = 9.82$, $p<0.05$]. Subsidiary comparisons revealed that spatial expectations enhanced P1 on the electrodes positioned over the hemisphere contralateral to the target [$F(1,17) = 4.52$, $p<0.05$]. There was no interaction involving spatial and temporal expectations [$Fs(1,17) <2.98$, $ps>.05$].

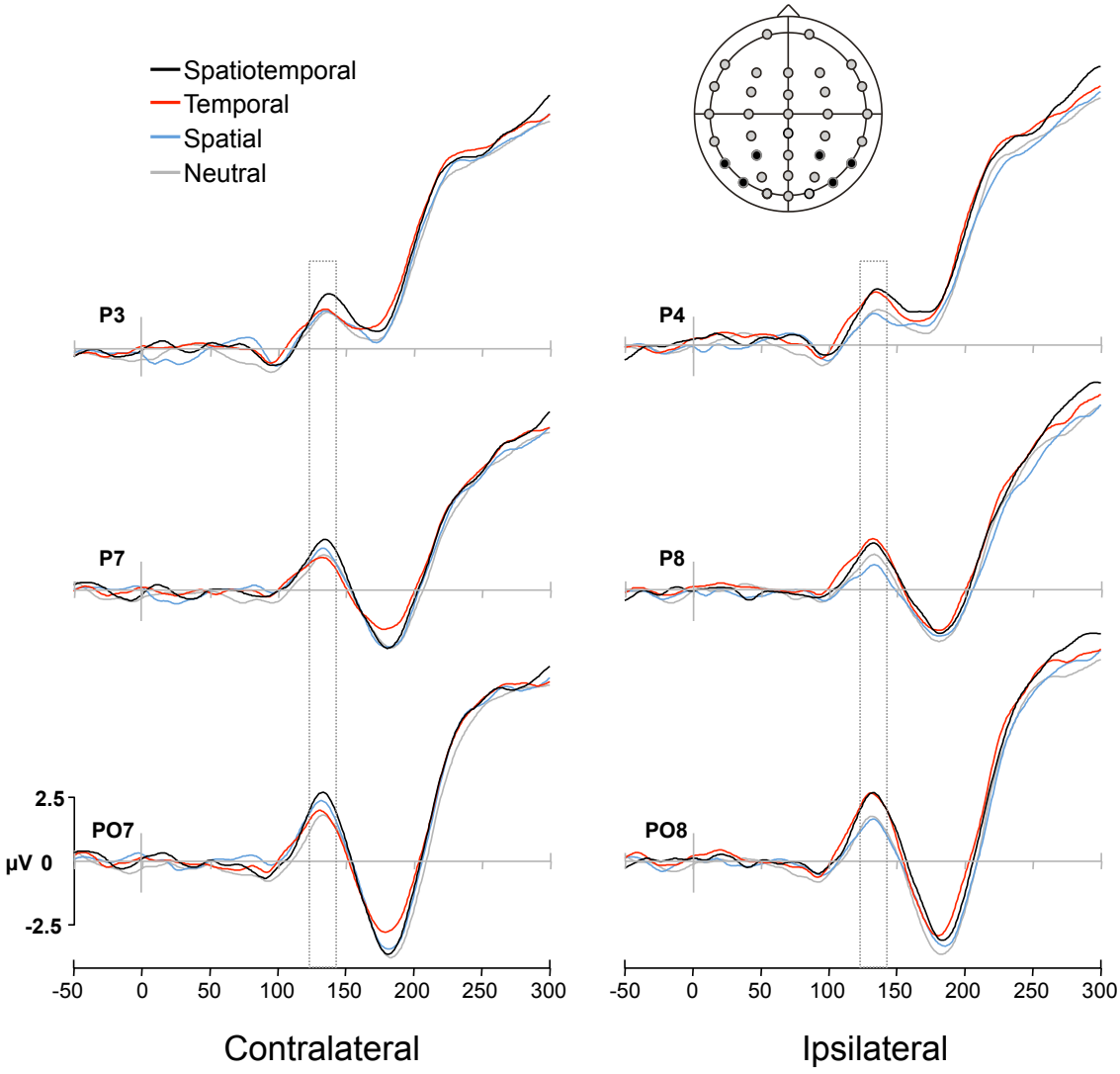


Figure 18. P1 enhancement in temporal expectation conditions. The dotted box shows the epoch that the P1 difference was analysed.

To confirm that our data replicate classic findings on temporal expectations, an analysis of the later P300 potential was performed. P300 was analysed at a time window between 300 and 500 ms at the midline electrodes Cz, CPZ, PZ. As expected, temporal expectation modulated the P300 amplitude [$F(1,17) = 6.99$, $p<0.05$].The mean amplitude was greater for the rhythmic conditions compared to the arrhythmic conditions (Figure 19). The P300 also rose

earlier in the rhythmic (ST - 266 ms; T - 264 ms) than in the arrhythmic (S - 273 ms; N - 271 ms) conditions . There were no significant effects on the LRP [Fs(1,17) $<$ 0.61, ps $>$ 0.45].

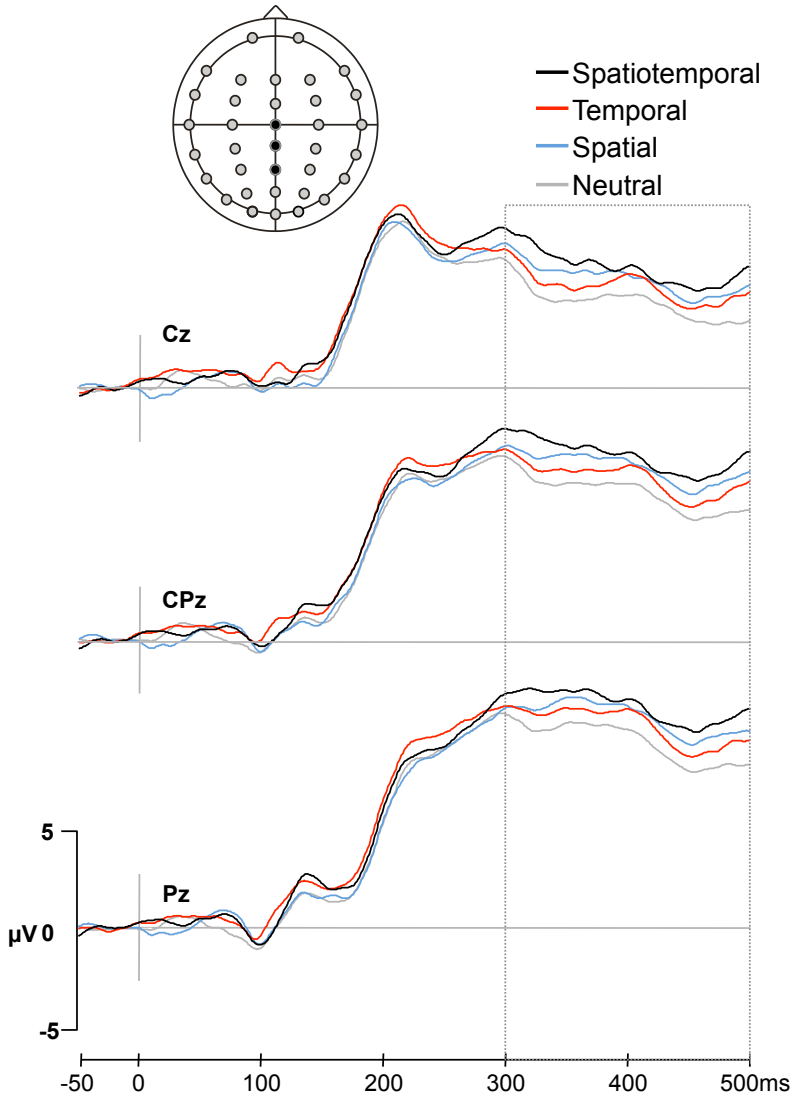


Figure 19. Enhancement of the P300 component. Dotted box shows the time of interest for the P300 analysis.

5.2.3. Time-frequency analysis

Time-frequency analysis was used to investigate the effect of temporal expectation on anticipatory brain oscillations in the alpha range (8 - 14Hz). Two main contrasts (see Methods) were performed to examine possible differences between temporal expectation when combined with spatial expectation (ST - S), or temporal expectation in isolation, in the absence of spatial information about the location of a forthcoming target (T - N). Since the main hypothesis concerns oscillatory activity in anticipation to the target, this analysis focused on the period 100 ms preceding target presentation. This anticipation period have been widely used in studies investigating anticipatory alpha activity (Foxe, et al., 1998; Rihs, et al., 2009; Sauseng, et al., 2005; Worden, et al., 2000). To test for differences in hemisphere lateralisation relative to the target location, t-tests were performed on clusters of three posterior electrodes each: contralateral (PO7/PO3/P3), central-parietal (CPz/Pz/POz), and ipsilateral (PO8/PO4/P4).

Figure 20 shows a desynchronisation of alpha oscillations preceding target presentation induced by temporal expectation, both in the presence and in the absence of spatial expectation. Interestingly, there is a clear difference between the topographical distribution of these oscillations yielded by the two conditions. The desynchronisation induced by temporal expectation alone (i.e. in absent of spatial information) was restricted to central-parietal electrodes [$t(17) = 2.63$, $p = .009$] (Figure 20A). No difference in alpha power occurred over the posterior electrodes (contra or ipsilateral) [$ts(17) < 0.88$, $ps > 0.1$]. When temporal expectation was combined with spatial expectation, the distribution of al-

pha desynchronisation changed considerably (Figure 20B). Whereas, the difference in oscillations over central-parietal electrodes matched the results found in the previous condition [$t(17) = 1.99$, $p = .031$], there was also an increase of alpha desynchronisation over the posterior electrodes preceding the target presentation when temporal expectation was accompanied by spatial expectation. Interestingly, this desynchronisation was only significant in the contralateral [$t(17) = 1.95$, $p = .034$], and not in the ipsilateral [$t(17) = 1.23$, $p > .1$], hemisphere.

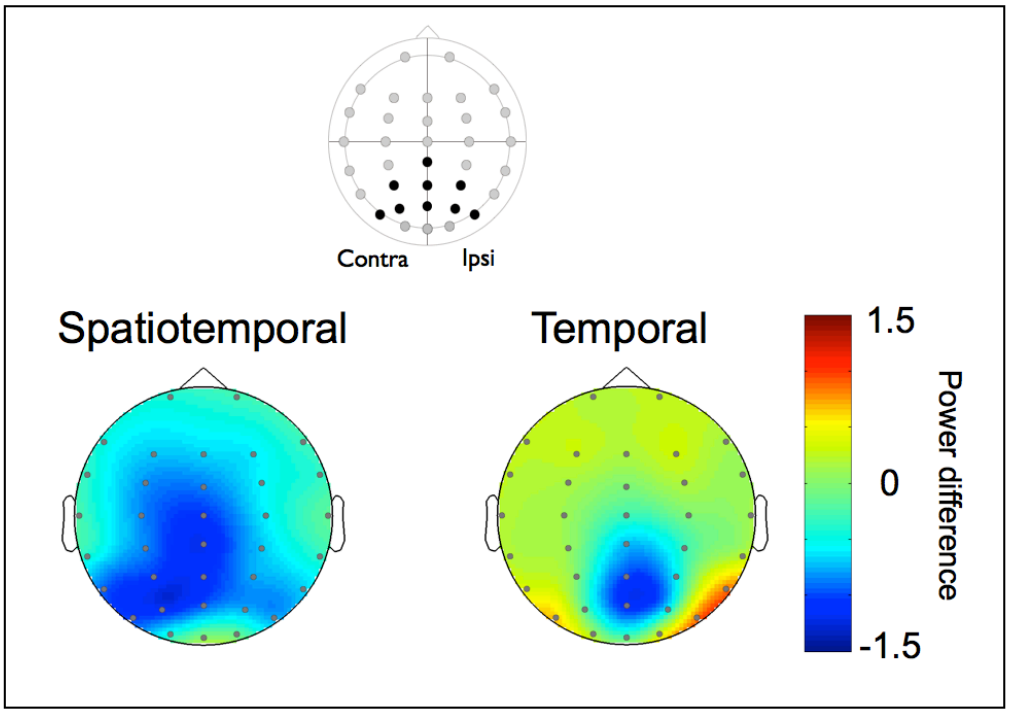


Figure 20. Topographies of the alpha activity (8-14Hz) preceding target presentation. Non baselined data in the arrhythmic conditions were subtracted from the data in the rhythmic trials. The *spatiotemporal* topography was derived by subtracting trials carrying only *spatial* information from trials carrying combined *spatial-temporal* information (ST - S). The *temporal* topography was derived by subtracting the data in the *neutral* trials from data in the *temporal* trials (T - N).

5.3. Discussion

In this chapter, an original paradigm was developed to explore the neural mechanisms of the interaction between spatial and temporal expectations. Behavioural findings showed additive effects of spatial and temporal expectations in speeding up reaction times. The ERP findings replicated the earlier rising and increased amplitude of the P300 potential associated with temporal expectation. Surprisingly, the analysis of the P1 potential demonstrated that temporal expectations alone, independently of spatial orienting, can enhance early visual perceptual processes. In addition, time-frequency data showed that temporal expectation enhanced alpha desynchronisation in anticipation of the target. In isolation, temporal expectation enhanced alpha desynchronisation over central-parietal electrodes. When temporal expectation was combined with spatial expectation, the desynchronisation of alpha oscillations was extended to occipital areas in the hemisphere contralateral to the target location.

Reaction-time measures showed that both temporal and spatial expectations enhanced behavioural performance. These behavioural findings replicate previous studies of endogenous and exogenous temporal orienting (Coull, et al., 2000; Doherty, et al., 2005; Miniussi, et al., 1999). The effects validate the effectiveness of the rhythmic temporal cues and of the predictive spatial cues to drive orienting of attention in time and space in this new paradigm.

Modulation of late ERP potentials also replicated the consistent pattern of previous studies using either endogenous (Griffin, et al., 2001; Miniussi,

et al., 1999) or exogenous cues to guide temporal expectation (Correa & Nobre, 2008; Doherty, et al., 2005; and experiment in chapter 4). As expected, we found that the late-positive P300 potential rose earlier and was more positive in conditions where the target occurred at the temporally anticipated moment, compared to when targets appeared at an unanticipated moment. Modulation of P300 amplitude is typically associated with decision-making and response selection processes (Correa, et al., 2006a; Griffin & Nobre, 2005; Ikeda, et al., 1996; Makeig, et al., 2004). Therefore, given that the discrimination of the target Gabors (and therefore selection of the correct motor response) was difficult, it comes as no surprise that P300 was modulated by cues that were presented in a predictable rhythmic manner.

Similarly to Experiment presented in chapter 4, the task was designed to enable measurement of the LRP in order to assess the consequences of temporal and spatial expectation upon preparation of a specific response. Unlike the previous experiment, however, there was no significant modulation of the LRP by temporal expectation. The LRP measure of motor excitability was also not influenced by spatial expectation in this task. The reason for the null result is unclear. One can speculate that the difficulty of the target-response associations greatly slowed the motor selection and preparation phase, as shown by the generally slow response times, and reduced the possibility that preparation of a motor response could be initiated prior to full evaluation of the target stimulus. However, slow reaction times resulted in atypically long time windows to the analysis of the LRPs, therefore it is also possible that the LRP effect just was not detected due to some noise issue.

Contrary to the initial hypothesis based on the findings by Doherty and colleagues (2005), there was no significant interaction between the influences of spatial and temporal expectations on the amplitude of the P1 potential. Rather, temporal expectation alone increased the amplitude of the early visually evoked P1 potential. Doherty and colleagues (2005) was the first to show that processes related to visual perception can be modulated by making accurate predictions of when and where an event will occur in time. Results from this previous study showed that the combination of spatial and temporal expectations led to greater enhancement P1, compared to spatial expectation alone. This led to the hypothesis that temporal expectations are only able to modulate perceptual processes when coupled with predictions about other features that can be clearly mapped onto neural receptive-field properties (for a review see Nobre, 2010). However, contrary to this hypothesis, the current findings showed that the brain can use rhythmic information to enhance perceptual analysis in conditions where spatial information is not present. One can speculate that the synergist effect between temporal and spatial expectations described by Doherty and colleagues (2005) could be due to a stronger sense of rhythmicity when temporal cues were combined with a stable spatial trajectory. In the condition of isolated temporal expectation in the study by Doherty and colleagues (2005), the stimulus moved in an erratic trajectory while the interval of each step remained constant. In their spatiotemporal condition, the movement of the ball followed a natural linear trajectory. It is conceivable that the temporal expectations induced by the spatiotemporal cues were stronger than the ones induced by temporal cues alone. In the real world, spatial and temporal factors are tightly bound in the movement or dynamics of stimuli, and this type of learned

association may have amplified the effects of each factor when combined with the other in their task. Thus, one possible explanation is that this amplification of the effects of temporal expectation induced within predictable spatiotemporal sequences, simulating natural movement sequences, relative to temporal expectation unnaturally unbound from spatial regularity, accounted for the differences in the P1 potential. However, it is important to highlight that since this is the first finding of this effect, more studies are necessary to replicate this result.

Another interesting finding in our study was the modulation of anticipatory alpha-band activity by temporal expectation. We compared the modulatory effects of rhythmic cues alone, and when the rhythm was accompanied by spatial expectation, in alpha activity during the period preceding target presentation. The data showed a desynchronisation of alpha oscillations focused over central-parietal electrodes induced by rhythmic cues, independent of spatial expectations. When rhythmic cues carried spatiotemporal information, the alpha desynchronisation at the central-parietal areas was accompanied by alpha desynchronisation at contralateral occipital electrodes. Alpha-band desynchronisation has been consistently associated with spatial attention (Capotosto, et al., 2009; Foxe, et al., 1998; Palva & Palva, 2007; Rihs, et al., 2009; Thut, et al., 2006; Worden, et al., 2000; Wyart & Tallon-Baudry, 2009) and with improvements in visual perception (Busch, et al., 2009; Romei, et al., 2010). Based in these findings, we suggest that the central-parietal alpha desynchronisation induced by temporal cues alone may reflect a mechanism of top-down control of visual areas when there is no information about the location of target appearance. However, when temporal and spatial expectations are combined, this desynchronisation

also spreads to occipital areas, possibly indicating a more direct modulation. Hence, one can speculate that when spatial information is coupled with temporal expectations, there is an enhancement of the baseline activity directly onto the visual areas, similarly to what has been proposed by the biased competition model (Desimone & Duncan, 1995). Whereas, when temporal expectations were present in absence of spatial expectations, this desynchronisation was focused in central parietal regions. Overall, our time-frequency analysis suggests different modulatory mechanism underlying spatiotemporal and temporal expectations.

This study introduces an effective novel paradigm with which to explore the flexible neural mechanisms of temporal expectations and their interactions with other sources of top-down biasing signals. Future studies are necessary to replicate our findings, specially the finding that rhythmic temporal cues can enhance the visual P1 potential. The results also propose a role of alpha desynchronisation at central-parietal and lateralised occipital sites in mediating the modulatory effects of isolated temporal and combined spatiotemporal expectations respectively. To test the causal involvement of these neural oscillations in temporal expectations, it would be interesting to disrupt parietal and lateralised occipital alpha using TMS (see Romei, et al., 2010). Importantly, this new paradigm allows the study of temporal expectations set up by rhythmic stimulation not only in the context of spatial expectations, but also in the context of expectations about other task requirements of feature attributes, such as motor responses or feature values of upcoming stimuli.

Chapter 6

6. Dissociating temporal orienting and motor preparation[2]

While spatial orienting of attention has long been linked to right parietal cortex (Corbetta, Miezin, Shulman, & Petersen, 1993; Mesulam, 1981), both temporal (Coull & Nobre, 1998b) and motor (Hesse, Thiel, Stephan, & Fink, 2006; Rushworth, et al., 2003) orienting of attention recruit similar regions of left parietal cortex. Neuroanatomical overlap in frontoparietal circuits for spatial orienting and saccade preparation (e.g. Corbetta, et al., 1998; Nobre, et al., 2000a) has been used to support the premotor theory of attention (Rizzolatti, Riggio, & Sheliga, 1994), which posits that oculomotor preparation for a spatially defined action guides the deployment of attentional resources in space. By analogy, preparation for a delayed action may also guide appropriate deployment of attentional resources in time. If so, the aforementioned neuroanatomical overlap in left parietal cortex for temporal and motor orienting could reflect their functional overlap. For example, preparation for action may induce a concomitant expectation of when that action is likely to be executed (Requin, Brener, & Ring, 1991). Conversely (though not mutually exclusively), temporal expectation

[2] I am not the first contributor on the eventual publication of this study, although (as second author) I have contributed substantively to the design, data collection, analysis and writing.

of an event's onset may automatically invoke (or "afford") preparation of a motor effector suitable for responding to that event (Gibson, 1979). The aim of this experiment was to determine whether it is possible to dissociate motor and temporal orienting, from both a behavioural and neuroanatomical point of view.

Prior fMRI studies have used hand movements to measure performance benefits of temporal and motor orienting (Coull & Nobre, 1998b; Rushworth, et al., 2003) or predictability (Sakai, et al., 2000). To test whether activation of left parietal cortex in these studies was specific to preparation of manual responses, we also examined temporal and motor orienting for saccadic eye movements. Prior behavioural studies have confirmed that temporal predictability can speed both smooth pursuit (De Hemptinne, Nozaradan, Duvivier, Lefevre, & Missal, 2007; Jarrett & Barnes, 2005) and saccadic eye movements (Bronstein & Kennard, 1987). In a mixed fMRI design we compared and contrasted behavioural and neural correlates of temporal and motor orienting on hand versus eye movements within the same experimental paradigm. Moreover, we deliberately disentangled motor preparation from potential spatial confounds by using endogenous cues that did not allow preparation of a spatially selective response (e.g., left/right hand) but, rather, selective preparation of an entire effector system (ocular/manual) (Beurze, de Lange, Toni, & Medendorp, 2009; Dickinson, Calton, & Snyder, 2003). Both motor and temporal orienting could therefore be investigated independently of spatial orienting influences.

6.1. Materials and Methods

6.1.1. Participants

Fourteen right-handed healthy volunteers (mean age: 24 years; 5 males) with no record of neurological or psychiatric disorders and normal or corrected-to-normal vision were tested. All subjects gave informed written consent to the study protocol, which had been approved by the Oxfordshire Local Research Ethics Committee.

6.1.2. Stimuli and task

Subjects performed a choice-RT task. A background scene, comprising one central and two peripheral compound crosses (located ±10 deg horizontally from screen centre), was present throughout the task (Figure 21B & C). The central cross acted as a place-marker for the presentation of cues and targets, while the peripheral crosses acted as response zones for lateral eye movements. Every trial had the same sequence of events. Trials started with central fixation for a variable period (600~800 ms). A visual cue was presented centrally for 100 ms. After one of two possible delays (ISI: 750 ms/1500 ms) a visual target was then presented centrally for 100 ms. Subjects were required to react to it as quickly as possible using one of two possible movements (hand/eye), which was indicated by the orientation of the target. A vertical target specified a hand movement (manual button-press) whereas a horizontal target specified an eye movement (oculomotor saccade). The laterality (left/right) of the response was

determined by the horizontal black-to-white grating of the target, with subjects being required to respond on the side corresponding to the lighter side of the target. Therefore, subjects pressed a button placed under the index finger of the hand corresponding to the lighter side of vertical targets (for example see Figure 21B) or produced a rapid eye movement (saccade) toward the response zone located on the lighter side of horizontal targets (for example see Figure 21C). In all four cueing conditions (see below), the motor effector used to produce the response (eye/hand) *and* the time between cue and target presentation (750 ms/ 1500 ms) varied on a trial-by-trial basis. All four conditions were therefore matched for sensorimotor requirements and trial timing, with the only difference between conditions being the attentional set of the subject.

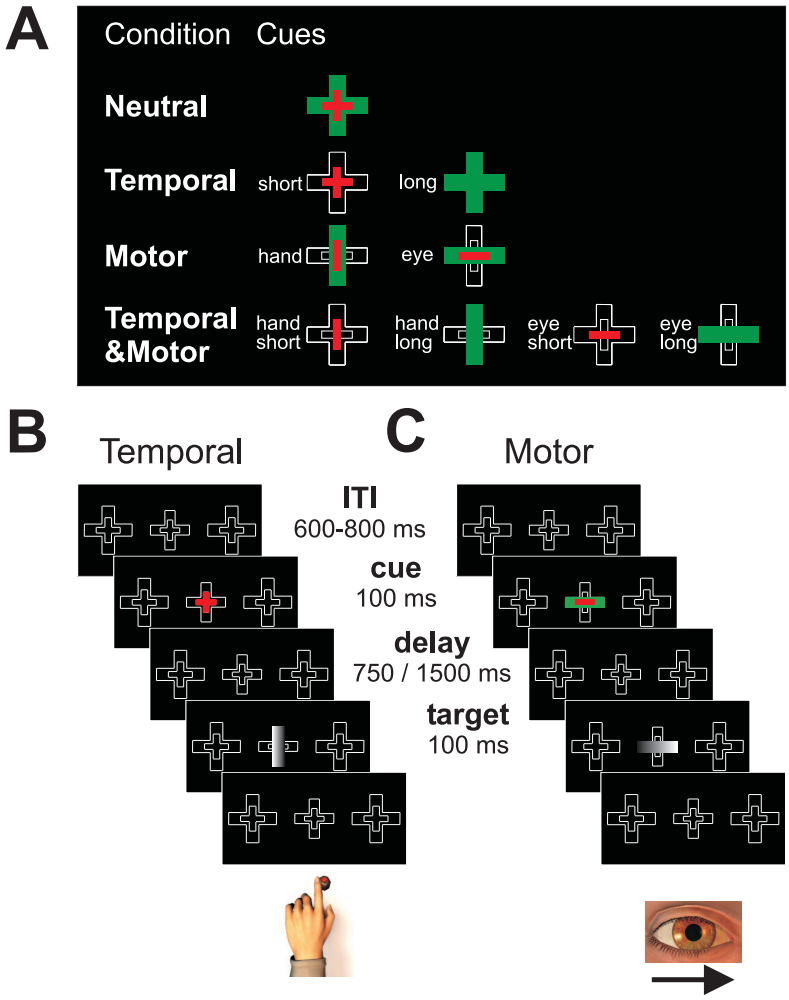


Figure 21. Sequence of events in a trial. After a random inter-trial interval (ITI), a cue was presented centrally for 100 ms. After one of two possible delays (750 / 1500 ms), a target was presented centrally for 100 ms. The motor response to be given was indicated by the orientation of the target, with vertical targets specifying button-presses and horizontal targets specifying saccades. The laterality of the response was determined by target shading, such that subjects made left-/right-hand button-presses or left/rightward saccades to the lighter side of the target. (A) The presence (+) or absence (-) of temporal (T) or motor (M) orienting cues were crossed in a 2 x 2 factorial design, yielding four cueing conditions: Temporal (T+M-), Motor (T-M+), Temporal&Motor (T+M+), Neutral (T-M-). Each of these conditions was associated with a specific set of centrally presented cues, which are illustrated here. (B) Illustrative example of a trial in the „Temporal" condition. The cue informed the subject that the target would appear after a short delay. After a short delay, the appearance of a vertical target with the lighter side on the left instructed the subject to produce a leftward manual response. (C) Illustrative example of a trial in the „Motor" condition. The cue informed the subject that the response to be produced would be a saccade. After a variable delay, the appearance of a horizontal target with the lighter side on the right instructed the subject to produce a rightward saccadic response. These are simply illustrative examples: all combinations of cue-type/delay/effector/side were presented.

The task was designed to manipulate subjects' expectations of when or with which motor effector a response would be made. A 2 x 2 factorial design, comprising the factors of motor effector and temporal cueing, yielded four cueing conditions (Figure 21A):

1. In the "Motor" orienting condition, the cue indicated which motor effector should be used to respond (eye/hand), with saccadic and manual trial-types varying on a trial-by-trial basis. No information was provided concerning the time between cue and target, which varied (short/long) in a counterbalanced manner across saccadic and manual trial-types.

2. In the "Temporal" orienting condition, the cue provided predictive information concerning the time between cue and target (750 ms/1500 ms), with short and long trial-types varying on a trial-by-trial basis. No information was provided concerning the motor effector that should be used to produce the response, which varied (eye/hand) in a counterbalanced manner across short and long trial-types.

3. In the "Temporal&Motor" orienting condition, the cue indicated both the time between cue and target (750 ms/1500 ms) and which motor effector should be used to make the response (eye/hand), with all four possible combinations (manual short; manual long; saccadic short; saccadic long) varying on a trial-by-trial basis.

4. In the "Neutral" condition, the cue provided neither temporal nor motor information: both the time between cue and target, and the motor effec-

tor to be used to respond, were determined only upon target presentation, with all four possible combinations varying on a trial-by-trial basis.

6.1.3. Procedures

Each of the four experimental conditions was presented in 16 mini-blocks of 10 trials each. The mini-blocks began with a brief (2 s) static instruction screen, comprising the name of the cueing condition and a visual reminder of its associated cue. A trial began with brief (100 ms) presentation of a central cue, followed by a delay (ISI: 750 ms/1500 ms), then brief (100 ms) presentation of a central target (vertical/horizontal bar). Average trial length was 1395 ms (range = 1020 ms-1770 ms). Trials were separated by a variable (1500 ms-3300 ms) inter-trial interval to ensure random sub-sampling of the brain volume relative to each of the trial-types. The motor effector used to produce the response (eye/hand) and the time between cue and target presentation (750 ms/1500 ms) varied randomly on a trial-by-trial basis to ensure optimisation of event-related signal strength (Josephs & Henson, 1999).

Two mini-blocks of the same cueing condition were presented successively, separated by one shorter block (~16s, range = 13.7-18.3s) of a central fixation baseline condition, during which no visual event occurred. This "sandwich" structure was chosen to optimise both the block-design aspect of the fMRI analysis and the attentional set of the subject. By inserting a baseline block between the two cueing mini-blocks, the attentional set of the subject is simply put "on-hold" rather than switching to a new cueing condition, and each cueing

mini-block lasts only 35 s thus avoiding being filtered out as a source of low-frequency drift. Each of the four cueing blocks (each block comprising 2 mini-blocks and the intervening baseline block) was presented in pseudo-randomised permuted order, with the proviso that the same cueing block could not be presented twice in a row. Presentation order of each cueing block was counterbalanced across subjects. In total, subjects performed 360 trials in a session. An initial familiarisation session, performed outside the scanner, ensured subjects had learnt the task.

6.1.3.1.Functional magnetic resonance imaging

Subjects lay supine in a Siemens Trio whole-body scanner (Erlangen, Germany) operating at 3T and equipped for echo-planar imaging. Each volume of 35 slices (4 mm thickness) was acquired using blood-oxygen-level-dependent (BOLD) contrast (in plane resolution = 3 x 3 mm, TR = 2.11 s, interleaved acquisition, oblique slices 30° to the axial). Visual stimuli projected on a screen placed at the back of the scanner were presented to the subject (LCD projector, 60 Hz) via a mirror system that also allowed eye position monitoring using a remote infra-red eye-tracker (Applied Science Laboratories, Bedford, MA; 60 Hz). Magnet-compatible electronic switches attached to a response box were used to record button-presses performed with left or right index fingers (1000 Hz). A structural MRI was also acquired (using a standard T1-weighted scanning sequence, $1mm^3$ resolution) to allow anatomically specific localisation of significant areas of brain activation.

6.1.4. Behavioural data analysis

Percentage correct and mean RTs for saccadic and manual responses performed during the scanning session were analysed separately using ANOVAs. Significant effects were submitted to post-hoc breakdown analyses (Newman-Keuls post-hoc tests). Statistical threshold was fixed at $P < 0.05$ for all analyses.

6.1.5. fMRI data analysis

Image processing and analysis of fMRI data were conducted with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). 1777 fMRI volumes were acquired for each subject. The first 5 images allowed for magnetic field saturation and were discarded. All remaining functional images were slice-time corrected using the middle slice in time as reference (slice #33; 35 slices total; interleaved acquisition). After discarding the last two volumes, these images were then realigned to correct for head movement between scans. Each structural MRI was co-registered to the corresponding mean realigned functional image, in order to put structural images into the functional brain space. All functional images were then spatially normalised by matching each image to the standard SPM8 EPI template, resampled to 3-mm isotropic voxel size, and were spatially smoothed using isotropic Gaussian kernels of 8 mm full-width half-maximum (FWHM). Stimulus-evoked neural responses were modelled as single events that were time-locked to the onset of the cue and then convolved with a

canonical haemodynamic response function (HRF). Data were analysed for regionally specific changes in HRF amplitude.

We modelled 16 regressors, comprising the factorial combination of the 4 cueing conditions (Motor, Temporal, Temporal&Motor, Neutral), the 2 response effectors (hand, eye), and the 2 delays (750 ms/15000 ms) (i.e., MotorHand750 ms, MotorHand1500 ms, MotorEye750 ms, MotorEye1500 ms, TemporalHand 750 ms… etc.). Experimental effects were estimated according to the general linear model at each voxel in brain space in each of the 14 subjects. Images were adjusted for low-frequency physiological drifts, using a high-pass filter of 128 s. At the first level of analysis, 14 separate single-subject analyses were performed for each contrast of interest. These individual statistical parametric maps (SPM) of the t statistic (transformed into corresponding Z values) were entered into a second level analysis to derive statistical inferences using one-sample t tests.

Primary contrasts of interest identified regions associated with temporal orienting in the absence of motor predictability, or with motor orienting in the absence of temporal predictability. To index temporal orienting, we compared trials in which the time of target onset, but not the motor effector for response, could be predicted to trials in which neither could be predicted (i.e., Temporal -Neutral). Similarly, to measure motor orienting we compared trials in which information concerning the motor effector, but not the time of target onset, was provided to trials in which neither source of information was provided (i.e., Motor -Neutral). Finally, to assess the interaction between temporal and

motor orienting, we compared trials in which both temporal and motor information was provided to trials in which only one of these sources of information was provided (i.e., [Time&Motor – Time] – [Motor-Neutral]).

These contrasts averaged cue-specific responses across short and long delays, and across manual and saccadic response effectors. However, one of the aims of this study was to explore temporal orienting during saccadic response trials and to compare its neural correlates to those of temporal orienting during manual trials. Any overlap in temporal orienting areas during manual versus saccadic trials would provide evidence for a centralised, effector-independent mechanism for temporal orienting. Therefore, to evaluate the simple main effects of cue-type separately for manual and for saccadic responses we further subdivided the Motor and Temporal orienting contrasts by effector-type (i.e., [TemporalHand-NeutralHand]; [TemporalEye-NeutralEye]; [MotorHand-NeutralHand]; [MotorEye-NeutralEye]).

As well as exploring each of these four contrasts individually, we also searched for areas that were common to pairs of contrasts. We first looked for temporal (or motor) orienting regions that were common to both manual and saccadic response trials. Effector-independent temporal orienting regions were identified by inclusively masking [TemporalHand-NeutralHand] with [TemporalEye-NeutralEye], and vice versa (both maps thresholded at $p<0.001$, uncorrected). Similarly, effector-independent motor orienting regions were identified by masking [MotorHand-NeutralHand] with [MotorEye-NeutralEye], and vice versa. We then looked for manual-(or saccade-) specific regions that were

common to temporal and motor orienting by inclusively masking [TemporalHand-NeutralHand] with [MotorHand-NeutralHand] (or [TemporalEye-NeutralEye] with [MotorEye-NeutralEye]).

Finally, in order to identify effector-specific temporal and motor orienting regions, we directly contrasted manual and saccadic trials against one another. For example, temporal orienting regions specific to saccadic or manual responses were identified by the interaction terms ([TemporalEye-NeutralEye]-[TemporalHand-NeutralHand]) and ([TemporalHandNeutralHand]-[TemporalEye-NeutralEye]) respectively. Equivalent interactions were interrogated for the Motor orienting condition.

The resulting activations were characterised in terms of both peak amplitude and spatial extent. The significance of each activation was estimated using distributional approximations from the theory of Gaussian fields. In regions for which we had strong *a priori* hypotheses based on previous studies, we adopted a significance threshold that was uncorrected for multiple comparisons ($p < 0.001$). These regions comprised left parietal and left premotor cortices (Coull and Nobre 1998; Rushworth et al. 2003). These regions were further subject to a small volume correction procedure, thresholded at $p<0.05$ corrected for Family Wise Error (FWE). We used pre-defined anatomical regions of interest (ROI) from the Marsbar ROI toolbox (Brett, Anton, Valbregue, & Poline, 2002) (viz., left parietal (inferior, superior and supramarginal gyrus) cortex and left BA44) to define restricted search volumes. For all other regions, we adopted a significance threshold of $p<0.05$ corrected for multiple comparisons (FWE). So

as to ensure that reported clusters were due to activations induced by the experimental condition (Temporal or Motor cues), rather than deactivations induced by the control condition (Neutral cue), all statistical maps resulting from the contrasts described previously were inclusively masked by the map of direct interest, thresholded at $p < .05$, uncorrected for multiple comparisons (e.g., the effect of Temporal orienting [Temporal-Neutral] was masked by the map [Temporal], thresholded at $p < .05$). Finally, parameter estimates (beta values) in clusters of theoretical interest were extracted using the Marsbar ROI toolbox and were then plotted to aid data interpretation.

6.2. Results

6.2.1. Behavioural

The analysis of behavioural data showed benefits of both motor [$F(1,12)=67.78$, $p<0.0001$] and temporal cueing, although the temporal cueing effect interacted with delay [$F(1,12)=15.85$, $p<0.005$]. Post-hoc tests revealed that the temporal cueing benefit was significant only at the short, not long, delays (Figure 22). This asymmetric cueing benefit is consistent with previous studies (Coull, et al., 2000; Coull & Nobre, 1998b) and is due to changing conditional probabilities of target appearance as a function of elapsing time (the "hazard function", Luce, 1986; Nobre, et al., 2007): in neutral trials, when the target does not appear at the short delay it must, by process of elimination, appear at the longer one, thus effectively removing the cost of the neutral cue.

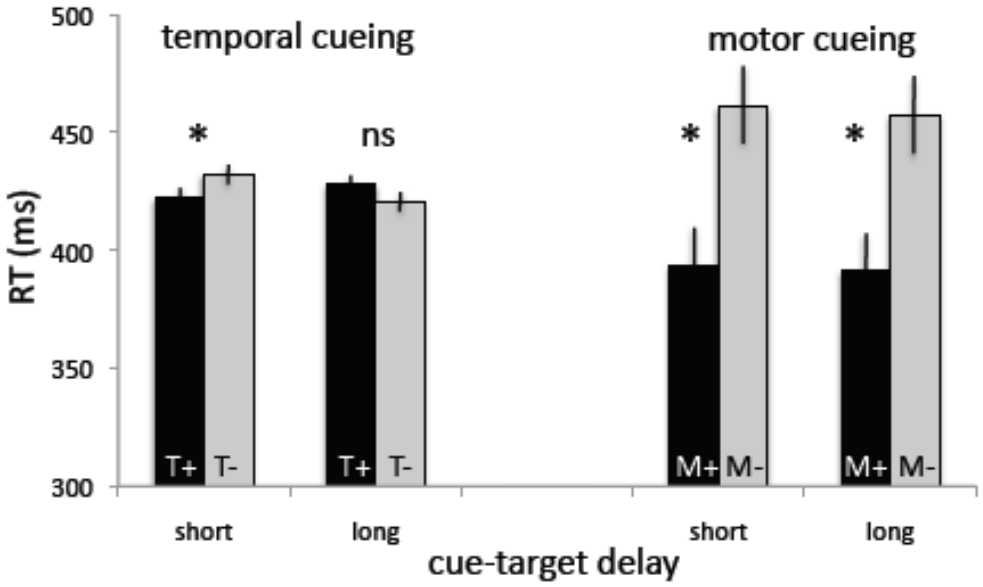


Figure 22. Mean reaction times (RTs) for as a function of the type of advance information delivered by the cues (M: motor effector information, T: temporal information; + = information present, - = information absent) and the delay between the cue and target (short=750 ms, long=1500 ms). Statistically significant effects are indicated by an asterisk; ns=non-significant.

A significant main effect of response effector [$F(1,12)=124.34$, $p<0.0001$] was qualified by an interaction with temporal delay [$F(1,12)=11.71$, $p=0.005$] demonstrating that although RTs were faster (by 11 ms) at long versus short delays for saccadic RTs, manual RTs did not differ across delays. As in the behavioural experiment, motor and temporal orienting did not interact [$F(1,12) = 2.17$, ns]. All other interactions were non-significant. Taken as a whole, these results confirm that during the fMRI session subjects used temporal and motor cues to orient attention towards the predicted onset time, or response effector, respectively.

Across conditions, a large majority (90%) of trials were performed correctly. However, a significant main effect of motor orienting [$F(1,12) = 8.35$,

$p < .05$] revealed that responses were more accurate when subjects could prepare the motor effector to be used (91%) than when they could not (88%) while a significant main effect of response effector [$F(1,12)=14.69$, $p<0.005$] showed that responses were more accurate for saccadic responses (91%) than manual ones (88%). No other main effects or interactions reached significance.

6.2.2. Neuroimaging

6.2.2.1. General response preparation networks

Compared to baseline, all four experimental conditions activated largely overlapping regions of frontal, parietal and occipital cortices, as would be expected for performance of a visual choice RT task (Figure 23). Planned contrasts (see below) identified differential areas of activation within these networks, depending on whether temporal or motor effector information was used to predict when or how the response would be executed.

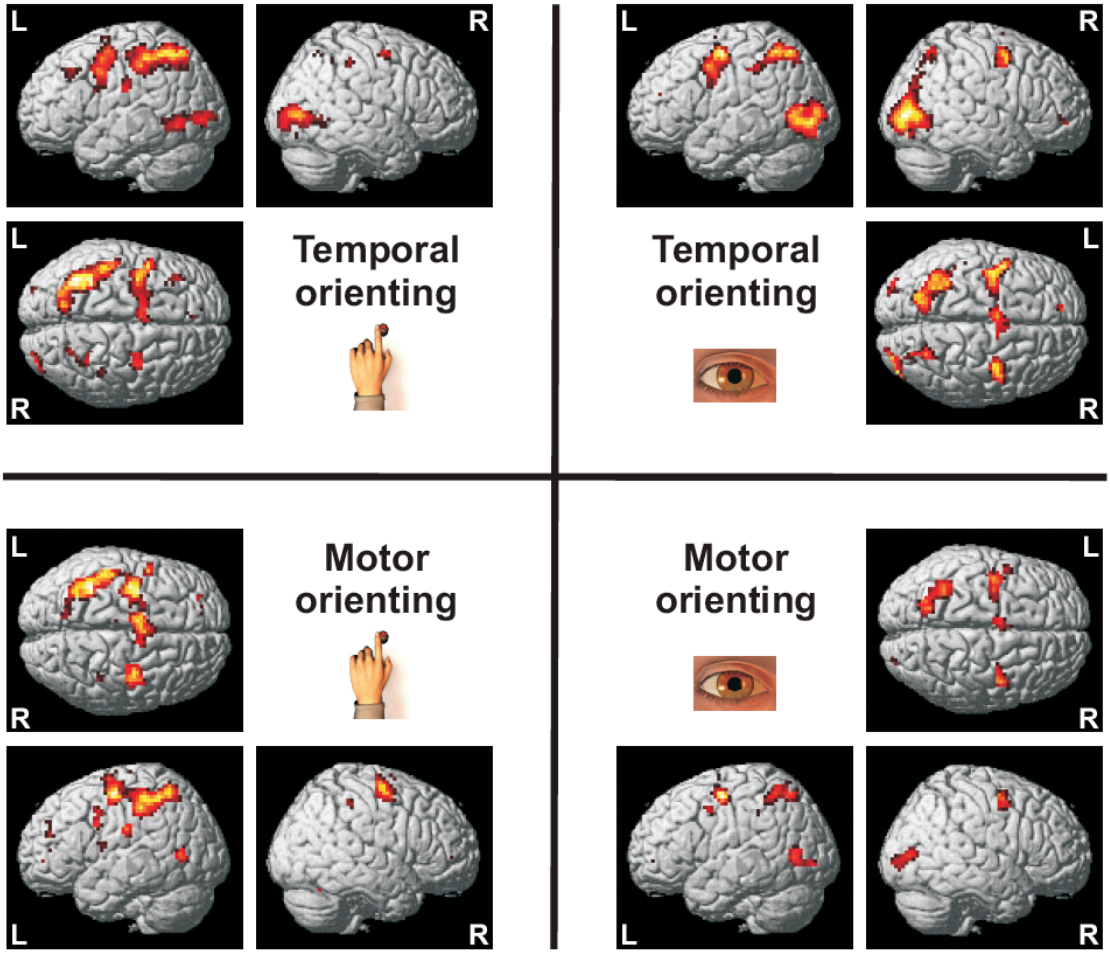


Figure 23. Activations invoked by temporal and motor orienting, for hand and eye responses as compared to baseline. The baseline condition consisted of a static visual fixation, and required no motor response. Comparisons between each of these conditions to a well-matched Neutral cue condition are reported in the Results section. The activations are rendered onto lateral and dorsal views of a standard brain template.

6.2.2.2. Temporal orienting

Based on previous fMRI studies assessing neural substrates of temporal orienting (Coull & Nobre, 1998b; Coull, Nobre, & Frith, 2001), we predicted selective activation of left inferior parietal and left premotor regions when par-

ticipants could predict the moment at which the target would be presented. Indeed, the effect of temporal orienting, averaged across response effectors [Temporal - Neutral], revealed significant activity ($p<0.05$, corrected for multiple comparisons using Family Wise Error) in a large left-lateralised parietal network (Table 2A). These activations centred around left intraparietal sulcus (IPS), extending into left inferior and superior parietal cortices. We found no evidence for activation of left ventral premotor cortex. Since previous studies (Coull, et al., 2000; Coull & Nobre, 1998b) reporting premotor activations employed manual responses only, it is possible that premotor activations are absent when subjects do not have a fixed manual response-set but must switch from manual to ocular responses on a trial-by-trial basis.

Table 2. Brain regions recruited by temporal orienting. Activations were assessed either by (A) averaging across response effectors (B) assessing hand and eye movements trials separately (C) assessing areas that were common to eye and hand movements. L=left.

Brain areas	x y z (mm)	Z score
(a) TEMPORAL ORIENTING		
Temporal-Neutral		
L intraparietal sulcus	-24 -69 45	5.14**
(b) EFFECTOR-SPECIFIC TEMPORAL ORIENTING		
HAND		
TemporalHand-NeutralHand		
L intraparietal sulcus	-24 -69 45	4.86*
Interaction: manual-specific		
-	-	-
EYE		
TemporalEye-NeutralEye		
L supramarginal gyrus	-51 -51 33	4.32
L intraparietal sulcus	-21 -72 54	4.00
Interaction: saccade-specific		
L supramarginal gyrus	-51 -66 30	3.50
(c) EFFECTOR-INDEPENDENT TEMPORAL ORIENTING		
[TemporalHand-NeutralHand] & [TemporalEye-NeutralEye]		
L intraparietal sulcus	-21 -72 54	4.00

Z scores of activations significant at $p<.001$ (uncorrected for multiple comparisons) in the hypothesised region of left parietal cortex. All activations were significant at a level of $p<0.05$ (FWE) when small volume corrections were applied using anatomically pre-defined ROIs corresponding to the hypothesised brain region. Asterisks correspond to activations that also survive a more stringent whole brain correction (FWE) for multiple comparisons at a level of ** $p<.01$, * $p<.05$.

To examine the possibility that distinct, effector-specific, networks may underlie temporal orienting, the [Temporal - Neutral] contrast was examined for trials in which responses had been registered with manual responses

separately from those in which responses were saccadic. Temporal orienting activated left-lateralised parietal cortex both for manual and for saccadic responses (Table 2B; Figure 24 A&B). Inclusively masking temporal orienting during saccadic trials with temporal orienting during manual trials revealed a large cluster of common activity in left intraparietal sulcus (Table 2C; Figure 25). To identify effector-specific temporal orienting areas we directly compared temporal orienting during saccadic trials to temporal orienting during manual trials. Temporal orienting in saccadic trials invoked selective activation of left supramarginal gyrus (Table 2B; the transverse section of Figure 24B illustrates its spatial discontinuity with the intraparietal sulcus cluster). By contrast, temporal orienting in manual trials did not selectively activate any brain areas over and above those activated during saccadic trials, even at an uncorrected threshold. In summary, the neural network involved in temporal orienting principally comprises left parietal cortex, centred around the intraparietal sulcus, with this area being engaged whether temporal orienting is eventually followed by a saccadic or a manual response.

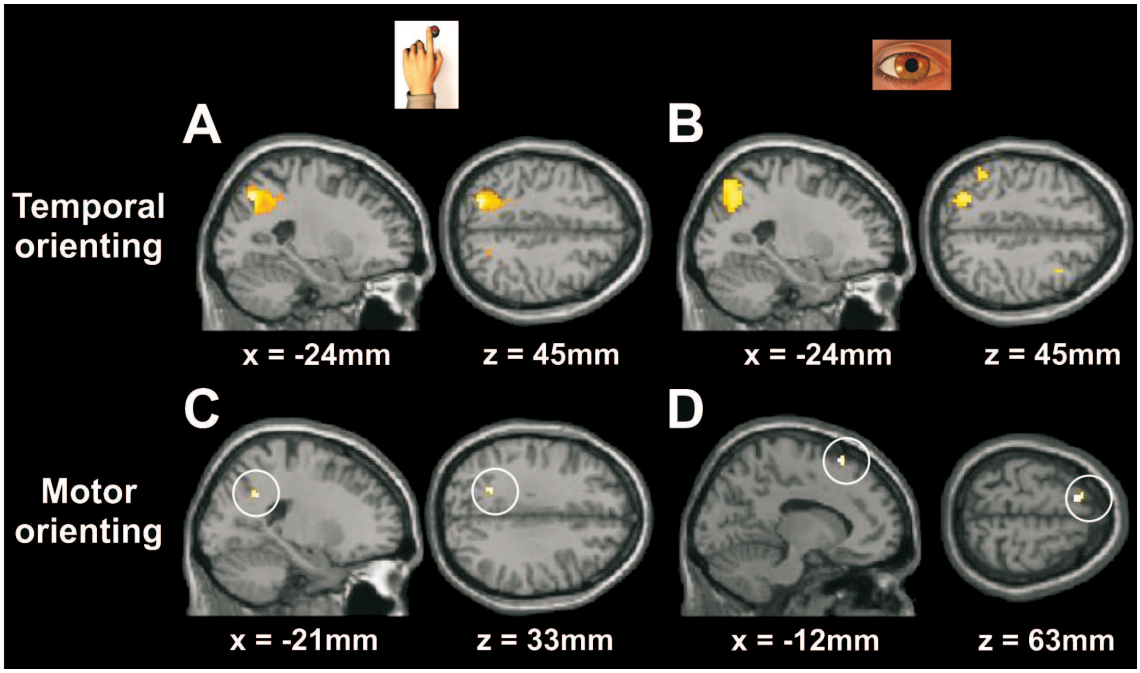


Figure 24. Temporal orienting invoked activations in left intraparietal sulcus for both (A) manual and (B) saccadic response trials. Motor orienting invoked activation (C) deep in left intraparietal sulcus for manual responses and (D) in left preSMA for saccadic eye responses. Activations are displayed on a standard SPM template brain. Spatial co-ordinates (mm) define the anatomical location of each slice.

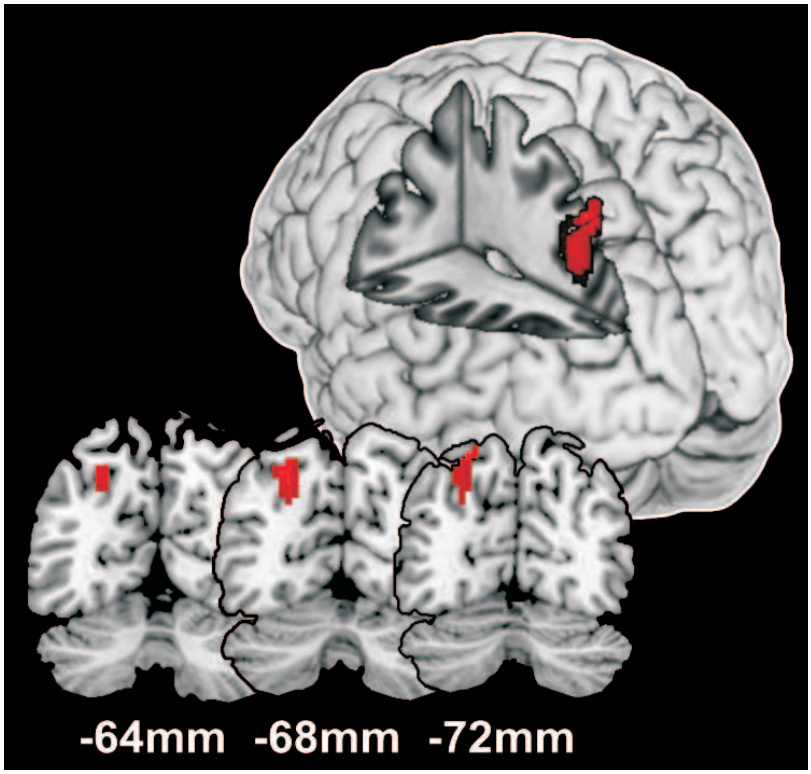


Figure 25. The only cluster of activation common to both manual and saccadic temporal orienting trials lies in left intraparietal sulcus. This activation is displayed on a standard template brain using MRIcron software (www.mricro.com/mricron). Spatial co-ordinates (mm) define the anatomical location of each slice in the y-dimension. The left hemisphere is on the left side of the figure.

6.2.2.3. Motor orienting

Based on previous data (Rushworth, et al., 2003), we predicted activation of left parietal regions (supramarginal gyrus and intraparietal sulcus) when subjects could selectively prepare the motor effector that would be required to produce the response. Motor orienting [Motor - Neutral] showed no significant areas of activation, even at a liberal threshold ($p < .01$ uncorrected for multiple comparisons). However, this contrast was averaged across response

effectors. Given the largely segregated nature of the manual and oculomotor systems, this null result is not particularly surprising. We therefore examined the [Motor - Neutral] contrast for manual and saccadic responses separately. The simple main effect of motor orienting for manual responses [MotorHand – NeutralHand] revealed activation deep in left intraparietal sulcus (Figure 24C; peak at -21 -54 33mm, z = 3.80; p<0.001 uncorrected for multiple comparisons). By contrast, the simple main effect of motor orienting for saccadic responses [MotorEye – NeutralEye] revealed a single cluster of activation in left preSMA, anterior to the Supplementary Eye Fields (Figure 24D; peak at -12 18 63mm, z = 3.70; p<0.001 uncorrected for multiple comparisons). Although we had no *a priori* hypothesis that preSMA would be activated by saccadic motor orienting, we have nevertheless decided to report it given 1) preSMA"s involvement in motor preparation processes in general (Cunnington, Windischberger, Deecke, & Moser, 2003; Curtis & D'Esposito, 2003; Lee, Chang, & Roh, 1999) and 2) the role of rostral preSMA in resolving saccadic response competition (Nachev, Rees, Parton, Kennard, & Husain, 2005). Interaction analyses directly comparing saccadic versus manual motor orienting revealed no significant areas of activation. However, it is of note that, in contrast to manual motor orienting, saccadic motor orienting did not activate left parietal cortex, even at a more liberal threshold (p<0.01, uncorrected for multiple comparisons). Inclusively masking manual motor orienting with saccadic motor orienting confirmed that there were no areas of common activity across response effectors. In summary, results show that motor orienting engaged anatomically distinct regions during saccadic versus manual response preparation. These effector-dependent activations stand in

stark contrast to the effector-independent temporal orienting activation in left intraparietal sulcus reported above.

6.2.2.4. Motor and Temporal Orienting Commonalities

Activations common to both motor and temporal orienting were identified by inclusive masking procedures. Masking the simple main effect of temporal orienting during manual trials by the simple main effect of motor orienting during manual trials (or vice versa) revealed an activation common to temporal and motor orienting deep in left IPS (Figure 24C; peak at -21 -54 33mm, $z = 3.80$; $p<0.001$ uncorrected for multiple comparisons). By contrast, performing an analogous inclusive masking procedure for saccadic trials revealed no areas of common activity (even at a liberal threshold, $p < .01$ uncorrected for multiple comparisons).

6.2.2.5. Motor x Temporal orienting Interaction

The interaction between Motor and Temporal orienting [(Temporal&Motor -Motor) – (Temporal -Neutral)] failed to reveal any areas of significant activation, whether conditions were averaged across response effectors or assessed separately for saccadic and manual responses. This lack of neural interaction parallels the lack of behavioural interaction between temporal and motor orienting, noted above.

6.3. Discussion

6.3.1. Temporal and motor orienting are functionally discrete attentional processes

We used a fully factorial experimental design to disambiguate the functional consequences and neural systems mediating temporal and motor orienting. Specifically, a choice-RT task employed symbolic pre-cues to inform subjects as to when (short/long delay) and/or with which motor effector (oculomotor saccade/index finger button-press) a speeded response to a subsequent target would be required. Behaviourally, temporal cues speeded responding as compared to neutral cues, even when the motor effector used to register the response was unpredictable. This confirms that temporal orienting can benefit performance independently from motor orienting and, therefore, that time is a useful stimulus parameter for optimising behaviour. Moreover, behavioural benefits were observed whether responses were registered with saccades or button-presses. This result extends and clarifies prior reports of temporal orienting paradigms that used only manual responses to measure performance (Coull & Nobre, 1998b; Griffin, et al., 2001). Previous behavioural studies have shown speeding of smooth pursuit eye movements with symbolic temporal cues (Barnes, 2008; Barnes & Jones, 2000; Jarrett & Barnes, 2005), or of saccadic eye movements with a more exogenous manipulation of temporal predictability of inter-stimulus intervals (Bronstein & Kennard, 1987), but this is the first study to show improved performance on saccadic onset times with symbolic cues.

We not only provide evidence that temporal and motor effector cues speed performance independently, we also show that they do not interact with one another. Knowing both *how* and *when* to execute the response did not improve performance to any greater extent than simply knowing *how* to execute it which itself improved performance to a significantly greater extent than knowing *when* to execute it. These behavioural results highlight the primacy of motor effector, rather than temporal, information in response preparation. Second, they confirm that the observed effects are not due simply to variations in the number of response possibilities but, rather, reflect differences in selectively preparing discrete components of the response. If informative cues were speeding RTs due to a reduction in response uncertainty then (1) RT benefits should be greatest when response uncertainty is at its lowest, i.e., during the combined Temporal&Motor condition. This is not the case. (2) RT benefits should be equivalent for Temporal and Motor conditions in which response uncertainty was matched. Again, this is not the case. Although it may be argued that the Motor condition contained implicit temporal information (omission of the target at the short delay guaranteed its appearance at the longer delay), RTs in the Motor condition were equally fast at both short and long delays, suggesting this implicit form of temporal preparation had minimal impact on resulting behaviour.

6.3.2. Effector-independent substrate for temporal orienting in left intra-parietal sulcus

Temporal, compared to neutral, cueing selectively activated left intra-parietal sulcus (IPS), thus confirming previous reports using this paradigm

(Coull, et al., 2000; Coull & Nobre, 1998b; Coull, et al., 2001). Notably, left-sided lateralisation persisted despite the fact that subjects responded equally with left or right-sided movements. Left-lateralised parietal activation is also consistent with the results of previous collision judgement studies (Assmus, et al., 2005; Assmus, et al., 2003; Coull, et al., 2008) in which the dynamics of stimulus motion allowed subjects to predict the time at which a moving stimulus would reach a certain location. Despite the spatial component of these studies, as well as the fact that subjects were making perceptual judgements, and not speeded motor responses as in our temporal orienting paradigm, the inherent temporal predictability of stimulus motion selectively activated *left* parietal cortex. By contrast, other studies have linked temporal predictability to right-sided prefrontal and parietal cortices (Bueti, Bahrami, Walsh, & Rees, 2010; Vallesi, McIntosh, Shallice, & Stuss, 2009; Vallesi, et al., 2007b). However, these studies measured how temporal predictability evolves as a function of the passage of time itself (the "hazard function") rather than whether temporally predictable information is available (e.g., via temporal cues) or not (e.g., neutral cues). Considered as a whole, these data suggest that right-sided cortical areas are critical for updating temporal predictions as a function of time-in-passing, whereas left parietal cortex is engaged when a temporal prediction is deployed in the first place.

Moreover, our factorial design revealed, for the first time, that this activation was independent from potentially coincident motor preparation processes. Previous studies (Coull & Nobre, 1998b) measured temporal orienting for a single (manual) response effector, giving subjects the opportunity to prepare

not only the time, but also the hand, of response. Moreover, the fully factorial design of the present experiment, in which temporal and motor components of response preparation were cued independently, confirmed unambiguously that temporal cues activate left IPS even when the response effector that will be used to register the response is, as yet, unknown. Temporal cues activated the same region of left IPS whether the eventual motor response constituted a manual button-press or an oculomotor saccade. In other words, left IPS represents an effector-independent substrate for temporal orienting. Temporal orienting therefore appears to function as an attentional mechanism that operates with similar principles on the ocular or manual control systems. Spatial orienting has previously been shown to modulate the neural substrates of oculomotor or manual behaviour in similar ways (Astafiev, et al., 2003; Eimer, Forster, Van Velzen, & Prabhu, 2005). Our data provide a temporal analogue to these spatial studies.

The region of parietal cortex particularly implicated in temporal orienting is the left IPS and adjacent supramarginal gyrus. The left hemisphere plays a dominant role in action selection, particularly in feedforward aspects of motor control (Serrien et al. 2006), while IPS is heavily implicated in reaching, pointing and grasping movements of the hand (Culham & Valyear, 2006). Fittingly therefore, left IPS is precisely the area we have also found to be activated by motor orienting to *hand* movements in particular (see also (Rushworth, Krams, & Passingham, 2001b) and has previously been implicated in both motor preparation (Krams, et al., 1998) and motor intention (Lau, Rogers, Haggard, & Passingham, 2004) for hand movements. Neuroanatomical overlap between temporal orienting and manual motor orienting is reminiscent of the neu-

ral overlap between spatial orienting and oculomotor preparation predicted by the premotor theory of attention (Rizzolatti, et al., 1994); although see Liu et al. (2010) for recent evidence of functional dissociation within discrete regions of intraparietal cortex). In its simplest form, the premotor theory of attention suggests that spatial orienting is a functional corollary of oculomotor preparation. By analogy therefore, one could hypothesise that temporal orienting could be conceptualised as a corollary of manual motor preparation. However, our observations that temporal orienting is functionally dissociable from motor orienting, that it speeds saccadic, as well as manual, responses, and that the neural substrates of temporal orienting are effector-independent refute this hypothesis, and instead suggest that temporal orienting is not merely a causal effect of hand movement preparation.

So if temporal and manual motor orienting are behaviourally dissociable, what is the functional significance of their (partial) neuroanatomical overlap? One possibility is that manual motor areas are being recruited, or "neurally recycled", for temporal prediction in much the same way that, for example, spatial areas are recruited for number processing (Dehaene & Cohen, 2007). In everyday situations, anticipating *when* an action will take place may be associated more often with preparation of limb movements (see also (O'Reilly, et al., 2008)), for example catching a ball or hitting the brake before the traffic light turns red, than of saccadic eye movements. The same brain area may therefore become functionally specialised for these distinct, yet often coincident, processes.

6.3.3. Effector-dependent neural substrates for motor orienting

Rushworth et al. (2001b) concluded that, in contrast to the oculomotor spatial attention system of the right parietal cortex, left parietal cortex embodied a *manual* motor attention system. Our event-related fMRI data confirm this conclusion by demonstrating that, as compared to neutral cue trials, left IPS was activated by motor orienting to hand movements but not by motor orienting to eye movements. Our data further reveal a distinct neural basis for oculomotor orienting in an area of preSupplementary Motor Area (preSMA) that lies anterior to the Supplementary Eye Fields. preSMA has previously been linked to voluntary saccade control (Curtis & D'Esposito, 2003; Nachev, et al., 2005) and, more specifically, to postponement of saccade onset (Boxer, et al., 2006; Yang, Heinen, & Missal, 2008). These data, along with our own, indicate a specific role for preSMA in non-spatially selective preparation of the oculomotor system in general. More generally, the dissociable pattern of results for eye and hand motor orienting reflect effector-dependent neural substrates for motor orienting that stand in direct contrast to the effector-*in*dependent substrates for temporal orienting discussed above.

6.3.4. Dissociating motor orienting for hand and eye movements from spatial orienting

We have shown attentional benefits of motor effector cues on eye, as well as hand, movements. Eye movements have previously been shown to share

neural substrates with spatial attention (Corbetta, et al., 1998; Moore & Fallah, 2001; Nobre, et al., 2000a), a result that is taken as evidence for shared functional substrates and, more specifically, for the premotor theory of attention (Rizzolatti, et al., 1994). According to these views, saccadic eye movements are functionally coincident with the spatial orienting of attention. Could the benefits of motor effector cues on saccade speed in our own data therefore be due to spatial, rather than motor, orienting effects? Moreover, given that shifts in spatial attention have been associated not only with saccade preparation (Awh, et al., 2006; Deubel & Schneider, 1996) for a review) but also with preparation of spatially discrete manual responses (Eimer, et al., 2005; Eimer, Van Velzen, Gherri, & Press, 2006), the observed motor orienting benefits on manual responses may also be due to spatial orienting effects. Critically, however, we asked subjects to select and prepare an entire effector system (manual/ocular) rather than spatially specified components within that effector system (e.g., left/right manual response), therefore confirming that saccadic oculomotor preparation can occur in the absence of spatial orienting. Although prior fMRI studies have also investigated the neural correlates of non-spatial saccade preparation (Brown, Vilis, & Everling, 2007; Curtis & Connolly, 2008), these paradigms manipulated only whether the spatial location of the planned saccade was known in advance or not. Here, by contrast, we show that attention can be selectively directed between-effectors, allowing subjects to prepare the oculomotor system in favour of another distinct effector system (here, the manual response system).

The fact that our paradigm entails a non-spatial form of oculomotor preparation may also be crucial in interpreting the lack of parietal activation for

motor orienting to eye movements. This result may seem surprising given that many electrophysiological and imaging studies have already implicated the lateral intraparietal area (LIP) in oculomotor preparation (for a review see Grefkes & Fink, 2005), even when the spatial location of the planned movement is unknown (Dickinson, et al., 2003). However, a direct comparison of spatial to non-spatial oculomotor preparation shows that LIP is engaged particularly when the spatial location of the planned saccade is known in advance (Curtis & Connolly, 2008). In this case, our finding that non-spatial oculomotor orienting does not preferentially activate parietal cortex any more than a neutral cue condition becomes less surprising.

Chapter 7

7. General Discussion

"Time is a very mysterious entity. It's the most mysterious entity, in some ways, in Science". This quote by David Gross - Nobel in Physics in 2004 (Gross, 2008) - emphasises the difficulty that anyone who chooses to study the *time* dimension faces. Even though Gross was referring to the problem of space-time in particle physics, I believe that a similar statement could be made about the problem of studying time in neuroscience and psychology. In this thesis I explored different aspects of how orienting attention to instants in time can bias our perception and behaviour.

7.1. On exogenous and endogenous temporal orienting

In Chapter 3, I aimed to test the existence of two separate types of temporal orienting of attention, analogous to the distinction between *exogenous* and *endogenous* orienting made in spatial attention - automatic orienting based either on intrinsic properties of dynamic stimuli (exogenous) versus controlled orienting based on predictive symbolic cues. In this task, the *rhythm* (exogenous

cue) or *colour* (endogenous, symbolic cue) of a moving stimulus was used to direct participants' attention to the time of target appearance after a brief occlusion. The target contained an upright or tilted cross, which participants were required to discriminate. In the beginning of each block, participants were instructed to "*attend-to-speed*" (rhythm) or "*attend-to-colour*".

The results indicated that both *rhythmic* and *symbolic (colour)* cues speeded up reaction times. However, whilst the *rhythmic* cueing effects were independent of instruction, the effects of *symbolic* cues were dependent on the instruction given. *Symbolic* cues speeded up reaction times only when participants were explicitly instructed to "*attend-to-colour"*. Taken together, these results provide evidence for the existence of separable exogenous and endogenous types of temporal orienting of attention.

7.1.1. A neural dissociation hypothesis

In spatial attention studies, the neural mechanisms underlying exogenous and endogenous orienting are better established. Similarly to temporal orienting studies, the P1 potential is more strongly modulated by exogenous cues (Hopfinger & West, 2006). Evidence for two distinct systems in temporal attention can also be found in studies investigating the effect of temporal expectation on the early visual P1 ERP potential. Up to this date, ERP studies have failed to find any modulation early visual potential (P1) by endogenous temporal expectation (Griffin, Miniussi, & Nobre, 2002; Miniussi, Wilding, Coull, & Nobre, 1999). On the other hand, when rhythmic stimuli are used to induce spatiotem-

poral expectations, there can be a reliable enhancement of the P1 potential (Doherty, Rao, Mesulam, & Nobre, 2005 and experiments presented in Chapter 4 and 5 in this thesis). One study using single-unit recordings in non-human primates has shown a modulation of the inferior temporal cortex in monkeys by endogenous symbolic cues (Anderson & Sheinberg, 2008). However, in this study, the symbolic cues also informed the animals about which hand they should use to respond (i.e. combined temporal and motor expectations). Since this kind of manipulation has not been tested using EEG, future experiments are necessary to confirm that similar effects could be found in humans. Effects in visual cortex have also been shown in animal studies that manipulated exogenous temporal orienting, by changing the probability of a delay interval between a warning signal and the target across different blocks of trials (hazard-function manipulations of foreperiod) (Ghose & Bearl, 2010; Ghose & Maunsell, 2002).

It is important to note that even if both endogenous and exogenous temporal expectations can modulate visual activity, this does not necessarily mean that such modulation occurs through the same mechanisms. Previous findings using fMRI indicate that endogenous temporal expectations activate areas such as IPS, that could modulate perceptual or motor processing in a top-down fashion (Coull, 2010; Coull, Frith, Büchel, & Nobre, 2000; Coull & Nobre, 1998). To date the neural systems controlling exogenous temporal expectations have not been tested using fMRI, so it is hard to speculate about the neuroanatomical mechanisms underlying this type of expectations. However, findings from animals indicate that activity in early visual areas (such as V1) can become entrained to the rhythm of attended visually presented events (Lakatos, Karmos,

Mehta, Ulbert, & Schroeder, 2008; Lakatos, et al., 2009; Schroeder & Lakatos, 2008). This entrainment of early visual areas could be a central mechanism for enhancing the perceptual processing of events based on the intrinsic temporal regularity of events. As mentioned in the Introduction, these findings gave further support to the entrainment model of attention (for a review see Jones, 2010). According to this model, attention can narrow its focus when entrained to the pattern of external stimuli. This entrainment of attention result in an enhancement of processing of stimulus that occurs 'in tune' with the rhythm of attention. Therefore, it is possible to speculate that whilst endogenous temporal orienting modulation of perceptual processing is originated from top-down control of parietal areas, exogenous orienting enhances stimuli processing by directly entraining the activity in perceptual areas to the rhythm of events. This dissociation could explain the reason why enhancement of the P1 component, so far, is only found in manipulations using exogenous temporal orienting.

7.1. On the interactions between temporal and spatial orienting of attention

Chapters 4 and 5 focused on exogenous temporal orienting mechanisms, and presented two experiments whose aim was to study the association between temporal and spatial attention at the behavioural and neural levels. Whilst in Chapter 4 temporal orienting was always accompanied by its spatial counterpart, in Chapter 5 temporal and spatial orienting were orthogonally manipulated.

7.1.1. Temporal orienting using moving objects

In chapter 4, I tested the effect of exogenous temporal expectations on attentional orienting to moving targets. The task involved making a speeded perceptual discrimination about the target stimulus that reappeared after the occlusion. In this task, a moving stimulus was used to cue for spatial and temporal expectation. The trajectory of the stimulus was used to cue for the spatial location while its speed served as the temporal orienting cue. Temporal attention was always accompanied by spatial orienting. The ERP results showed that temporal expectations facilitated both early visual and late motor potentials. More importantly, I found temporal orienting entrained alpha desynchronisation during the occluding period, preceding the target presentation.

The experiment presented in chapter 4 is an extension to the study by Doherty and colleagues (2005), with the exception that in the Chapter 4 experiment a forced-choice response was used, as opposed to the go/no-go task used by Doherty and colleagues (2005). The P1 enhancement induced by spatio-temporal orienting, first reported in Doherty's study, was replicated in this experiment. This finding gives further support to the 'synergistic effect' between temporal and spatial expectations, showing that when temporal expectations are coupled with spatial information, there is a boosting of the spatial attention enhancement of visual perceptual processing. Since the experiment presented in chapter 4 used a forced choice response, it also enabled the investigation of lateralised motor preparation potentials. This finding indicated that temporal orienting also modulated motor readiness. This is the first direct demonstration of

the facilitatory effects of temporal expectations on the neural mechanisms of motor planning and execution in the human brain. This finding is supported by observations in single unit studies using fixed foreperiods (Riehle, Grun, Diesmann, & Aertsen, 1997). Arguably, the most interesting finding is this experiment was the modulation of anticipatory alpha band activity by temporal orienting. Schroeder, Lakatos and colleagues (Lakatos, et al., 2008; Schroeder & Lakatos, 2008; Schroeder, Wilson, Radman, Scharfman, & Lakatos, 2010) have suggested that attention can operate in a *rhythmic mode* by entraining brain oscillations to the temporal regularities in the environment. The anticipatory alpha desynchronisation found in this experiment corroborates their hypothesis. It is important to point out that according Schroeder, Lakatos and colleagues, this entrainment occurs to the phase of low-frequencies (theta-band), which, in turn, enhances the power in higher-frequencies (gamma-band). This phase-power nesting reflects the entrainment of excitability in a local ensemble and it can be used to determine the time of an input, priming the perceptual areas of the brain to its arrival. In this experiment I was not able to explicitly test for these effects because the stimulation used was too slow to enable accurate measurement of phase-power coupling during the occlusion period without contamination by spill-over activity from previous balls. Alpha-band desynchronisation has been reliably associated with attentional processes, and it is believed to be one of the brain mechanisms used to enhance perceptual processing of visual events (Busch, Dubois, & VanRullen, 2009; Capotosto, Babiloni, Romani, & Corbetta, 2009; Rihs, Michel, & Thut, 2009; Romei, Gross, & Thut, 2010; Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Wyart & Tallon-Baudry, 2009).

7.1.1. Interactions and dissociations between spatial and temporal orienting

In chapter 5, an original paradigm was used to explore the exogenous temporal orienting of attention. In this study, a series of five central cues were used to direct attention to a temporal interval or spatial location. Similar to Posner's original cost-benefit paradigm (Posner, 1980), participants were required to respond to a target presented at one of two locations, following a symbolic cue indicating the spatial location that the target was more likely to happen. To induce temporal expectations these central cues were presented in either a rhythmic (temporally constant intervals between each cue) or arrhythmic fashion (random time intervals between each cue).

As expected, both temporal and spatial expectations improved behavioural response measures. As in the previous experiments, these effects were additive (Doherty, et al., 2005). However, contrary to what was predicted, there was no significant interaction between spatial and temporal expectations at the P1 component. Whilst the characteristic amplitude enhancement of the contralateral visual P1 by spatial attention was observed, this effect was not significantly greater when spatial and temporal expectations were simultaneously present. Rather, temporal expectation alone also increased the amplitude of the early visual P1 potential. The findings from this experiment shed new light on how focusing attention in time can modulate perceptual analysis.

Studies using the moving-ball task (Correa & Nobre, 2008; Doherty, et al., 2005; experiment in chapter 4), showed that processes related to visual

perception can be modulated by making accurate predictions of when an event will occur in time. Results from these studies showed that the combination of spatial and temporal expectations led to greater enhancement P1, compared to spatial expectation alone. The different pattern of results in the Experiment of chapter 5 compared to previous results is intriguing. One possible reason for the discrepancy is that attentional effects may be amplified by expectations related to the strong intrinsic relationship between spatial and temporal factors in the movement dynamics of moving stimuli in the real world. In the task used by Doherty et al (2005) or its variants, temporal regularity occurs in the context of a predictable, linear spatial trajectory. The natural, learned association between temporal intervals and spatial trajectories could strengthen the effects of combined spatial and temporal expectations in this task. In the experiment of Chapter 5, this learned association is unbound, leaving only temporal regularity in the context of a spatial expectation generated by a symbolic, endogenous cue.

Similarly to the experiment presented in chapter 4, in this experiment the time-frequency analysis also revealed an increase in alpha desynchronisation preceding target presentation. Interestingly, since in this study spatial and temporal attention were orthogonally manipulated, I tested the effect of temporal orienting in anticipatory alpha activity when temporal orienting was combined versus when it was independent of spatial orienting. The results revealed different distributions for the desynchronisation of alpha when it was induced by rhythmic cues in each case. Rhythmic cues that were independent of spatial expectations led to alpha desynchronisation focused over central-parietal electrodes. When spatial expectations were combined with rhythmic cues, the alpha

desynchronisation at the central-parietal areas was accompanied by alpha desynchronisation at contralateral occipital electrodes. This finding suggests that spatiotemporal and temporal expectations have discrete modulatory mechanisms to enhance the perception of an expected event. One possibility is that central-parietal alpha desynchronisation induced by temporal cues alone may reflect a mechanism of top-down control of visual areas. When temporal and spatial expectations are coupled there may be an additional enhancement of the baseline activity in the visual areas, similarly to what has been proposed by the biased competition model (Desimone & Duncan, 1995). This enhancement of the baseline may have been indicated by an increase in the desynchronisation of alpha activity preceding target presentation over visual areas of the cortex.

7.1. On the neuroanatomical differences between motor and temporal attention

In chapter 6, I used a factorial design to cue motor and temporal components of response preparation independently within the same experimental paradigm. By differentially cueing either ocular or manual response systems, rather than spatially lateralised responses within just one of these systems, potential spatial confounds were removed. Behavioural results indicated that temporal and motor orienting were behaviourally dissociable, each capable of improving performance alone. Crucially, fMRI data revealed that temporal orienting activated left IPS even if the motor effector that would be used to execute the response was unpredictable. Moreover, temporal orienting activated left IPS

whether the target required a saccadic or manual response, and whether this response was left- or right-sided, thus confirming the ubiquity of left IPS activation for temporal orienting (Coull & Nobre, 2008). Finally, a small region of left IPS was also activated by motor orienting for manual, though not saccadic, responses.

Despite their functional independence therefore, temporal orienting and manual motor orienting nevertheless engage partially overlapping regions of left IPS, possibly reflecting their shared ontogenetic roots (O'reilly, Mesulam, & Nobre, 2008). This result suggests that temporal orienting is an effector-independent attentional mechanism that relies critically upon the functioning of left IPS, thus providing a temporal analogue to the more right-lateralised processes of spatial orienting.

7.1. Future directions

The experiments presented in this thesis provide a basis for several lines of future investigation. There are currently many unanswered questions regarding the neural mechanisms underlying temporal attention. Possibly, the main open question regarding the mechanism of temporal orienting today was 'inherited' from *timing* literature: is interval timing coded by a dedicated system or by emergent properties within distributed systems? From the temporal orienting perspective, this question would be formulated as whether there exists a core control network responsible for coding temporal regularities and signalling these

in a top-down fashion to perceptual and/or motor areas engaged in ongoing tasks; or whether temporal expectation is coded locally within brain areas engaged by a given task. Despite the growing evidence gathered from the temporal attention studies, this question remains unanswered. Results from this thesis further suggest that the answer may partly depend on whether temporal expectations are driven in an endogenous or exogenous manner.

As discussed in the Introduction, one of the main open questions in the temporal attention literature relates to the mechanisms of control versus modulation. Up to this day, there is no study using transcranial magnetic stimulation (TMS) in a temporal orienting task. Testing the causal involvement of areas such as left IPS and pre-SMA would greatly help in clarifying the control mechanisms of temporal attention, and their association with or dissociation from motor-related processes. The nearest evidence found in the literature today comes from studies using *timing* tasks (e.g. time-to-contact, time reproduction, time estimation). According to these studies, TMS applied to the cerebellum impairs timing of sub-, but not supra-second durations (Fierro, et al., 2007; Koch, et al., 2007; Lee, et al., 2007), whereas TMS to the right prefrontal cortex impairs timing of supra-, but not sub-second durations (Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Koch, et al., 2007). Based on these findings, the cerebellum appears as one of the main candidate brain areas that could provide a critical source of timing estimates for guiding temporal expectations in attentional orienting tasks. Future studies are necessary to confirm the function of cerebellum in temporal orienting tasks.

As mentioned previously, in chapter 3 I reported the first direct evidence for a dissociation between endogenous and exogenous temporal orienting. However, further work is necessary to study the neural mechanisms underlying these two subsystems of temporal attention using EEG and fMRI. Another interesting question that has not been answered yet concerns the functional neuroanatomy of exogenous orienting. Some indication of brain areas has been provided by O'Reilly and colleagues (2008), such as the cerebellum, IPS, preSMA, FEF and dorsolateral prefrontal cortex. However, their study was not focused on the attentional aspect of time, and their task used temporal judgement as their depended variable, which hinders the dissociation between *timing* and *temporal expectations*.

Finally, it would be fruitful to investigate further the suggestion by Schroeder, Lakatos and colleagues (Lakatos, et al., 2008; Lakatos, et al., 2009; Schroeder & Lakatos, 2008, 2009) that oscillatory activity in neuronal ensembles becomes entrained to the timing of rhythmically presented stimuli that are relevant to the task demands.

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