Dynamics of temporal anticipation in perception and action

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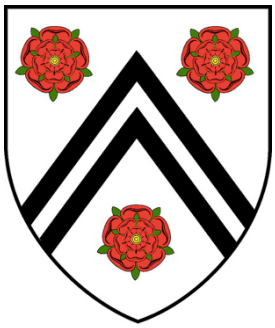

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Abstract

The selective deployment of attention over time optimises our perception and action at the moments when relevant events are expected to happen. Such "temporal orienting" to moments *when* something is going to happen is especially useful when this information can be combined with predictions about *where* and *what* events are likely to occur. A large body of research has already established how temporal predictions dynamically influence our perception and action, but questions remain regarding the neural bases of these attentional mechanisms. In this thesis I present three magnetoencephalography (MEG) studies that I conducted to investigate anticipatory neural dynamics associated with spatial-temporal orienting of attention for perception and action. I also investigate and discuss how such anticipatory dynamics change with ageing and neurodegeneration in Parkinson's disease (PD), and how these anticipatory neural dynamics behave in situations where a complex, hidden spatial-temporal structure is present. In Chapter 1, I introduce the topic of this thesis by reviewing the literature on temporal orienting of attention and by introducing my specific research questions. In Chapter 2, I present an MEG study on anticipatory neural dynamics of joint spatial-temporal orienting of attention in the visual domain, in younger and older adults. This study shows that neural dynamics with spatial, temporal and spatial-temporal orienting are all differentially affected by ageing. In Chapter 3, I describe an MEG experiment that investigates anticipatory neural dynamics during spatial-temporal motor preparation and compares PD participants to healthy control participants. This study reveals that both behavioural and neural dynamics with temporal orienting are affected in PD. In Chapter 4, I describe an experiment that explores how an implicit spatial-temporal structure is utilised to predict and prepare for upcoming actions. This study shows that motor cortical excitability is dynamically modulated in anticipation of the location and timing of events, even when such expectations are hidden in complex visual-motor sequences that remain largely implicit. In Chapter 5, the General discussion, I place these results in their wider context and discuss limitations and future directions.

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List of publications

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Heideman SG, van Ede F, Nobre AC (2017b) Temporal alignment of anticipatory motor cortical beta lateralisation in hidden visual-motor sequences. Eur J Neurosci 2017, 1-12.

Part of Chapter 1 is based on a book chapter on temporal orienting that I wrote with one of my supervisors:

Nobre AC, Heideman SG (2015) Temporal Orienting of Attention. In: The Handbook of Attention (Kingstone A, Fawcett JM, Risko EF, eds), pp 57–78. Cambridge: The MIT Press.

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Chapter 1: General introduction

This thesis investigates temporal orienting of attention, and its interaction with the anticipation of spatial targets and upcoming motor responses. The first set of empirical studies in the thesis use well established spatiotemporal cueing tasks to explore anticipatory neural modulations in young, healthy adults, and how these processes change with ageing and neurodegeneration in Parkinson's disease. The final empirical study develops a new task methodology to investigate how spatiotemporal anticipation is utilised in the context of learned complex spatial-temporal relationships among sequences of events. To introduce the topic of this thesis, I start by reviewing the early investigations that started this field. Second, I outline the literature on different types of temporal orienting and on how these processes may be supported in the brain. I explain why it is particularly interesting to look at the oscillatory dynamics that are involved in these processes and why MEG is well suited to study the fast time scales on which these processes evolve in the human brain. I discuss why it is important to investigate interactions between temporal orienting and other types of modulatory attention-related signals, like information about where perceptual events are going to happen, or what actions should be prepared and executed. Finally, I introduce the three experiments that constitute this thesis.

Part of this chapter is based on a book chapter on temporal orienting (Nobre & Heideman, 2015).

1.1 Overview

Attention is a highly selective and dynamic process that focuses our behavioural and neural processing on the relevant aspects of our environment to guide our behaviour in concordance with our current goals. It is well established that expectations about different attributes of forthcoming events allow us to orient our attention to relevant stimuli and to facilitate perception and action (Nobre and Kastner, 2014). The field of attention has focused primarily on expectations about the location (spatial attention) and identity (object-based and feature-based attention) of anticipated stimuli. More recently, the ability to orient attention selectively in time has also been recognised. The experiments in this thesis explore how such selective temporal expectations combine with expectations about other attributes to guide adaptive perception and action. Arguably, being able to predict *when* something is going to happen is not very useful in itself, but this information becomes highly relevant when it is combined with predictions about *where* and *what* events will occur and how you should respond to these events. By understanding how such expectations about the timing of events interact with preparation for selective perceptual analysis and preparation of relevant actions, we gain information about how the brain optimises our perception and actions within a dynamic framework. Before I outline the contents of this chapter, I first give a short historical overview of the research that started the field of temporal orienting.

1.1.1 Historical overview

The importance of the predictable temporal structure of events was already recognised by some of the pioneers in psychology. Early investigations by Wundt (1874) and Woodrow (1914, 1916) show that the *foreperiod*, that is, the interval between a warning stimulus and a target requiring a response, is an important determinant of response time. Wundt (1874) conducted an experiment in which participants had to release a key when they heard the sound of a steel ball hitting a metal plate. The mechanism releasing the ball could be adjusted to increase or decrease the foreperiod. Wundt showed that participants responded more quickly when they were able to view the release mechanism dropping the ball. In other words, participants performed better when they could predict the timing of the upcoming target. Woodrow (1914, 1916) showed that reaction times are faster with regular, compared to variable, unpredictable foreperiods. Later studies showed that the benefits of predictable foreperiods also appeared in choice reaction-time tasks, in which the nature of the stimulus and response is unknown in advance, although the effects are smaller in size (Bertelson and Boons, 1960).

Egan and colleagues showed in 1961 that temporal certainty not only speeds up responses, but can also enhance perception of tones that were presented in an interval of varying duration. Tone detectability decreased progressively with interval lengthening, and thus, with temporal uncertainty. Later studies found similar results in the visual domain (Lowe, 1967; Earle and Lowe, 1971; Lasley and Cohn, 1981; Westheimer and Ley, 1996), showing that

temporal information not only improves reaction times, but also perceptual processing.

Besides associations involving a predictable interval between a warning stimulus and an imperative target, there are many other types of temporal expectations that bias our perception and action to relevant moments in time. Another frequently studied type of temporal structure are rhythms. Newhall (1923) was the first to test the effect of temporal expectations induced by rhythms. In his experiment, participants had to report changes in stimulus brightness under three different experimental conditions. Targets occurred 1 second after a series of nine regular auditory stimuli separated by 1-second intervals (i.e., on the next beat), 4 seconds after a series of five regular auditory stimuli separated by 1-second intervals, or after a 9-second empty interval. Perceiving the change in brightness was clearly facilitated in the first case, thus when the stimulus occurred immediately after the next temporal interval of the regular rhythm.

1.1.2 Overview of this chapter

Although these early investigations did not always describe their effects in terms of temporal preparation, these studies provided fundamental insights about how temporal orienting can be used to guide and optimise our perception and action. In the next section I review the behavioural literature on three important types of temporal bias: hazard rates, rhythms and temporal cues. In section 1.3 I discuss models that have been proposed to explain how the brain keeps track of time, and review work that specifically investigated the locus of temporal information in

the brain. In section 1.4 I discuss why magnetoencephalography (MEG) is particularly suitable to study temporal orienting and describe the different oscillatory markers that have been associated with changes in sensory and motor excitability linked to attention. In section 1.5 I present EEG and MEG work on hazard rates, rhythms and temporal cues, while in section 1.6 I discuss the commonalities and dissociations that exist between these different types of temporal bias. In section 1.7 I argue why it is especially interesting to look at interactions between temporal- and other types of attentional orienting. In this section I also discuss some of the studies that inspired the work presented in this thesis. Finally, in the last section, I dive into the focus of this thesis and explain why it is interesting and important to study changes in temporal orienting that occur with ageing and neurodegenerative diseases like Parkinson's disease (PD), and why it is relevant to investigate more complex, sequential temporal expectations.

1.2 Types of temporal orienting, and their influence on behavioural performance

As these early studies already showed, temporal expectations can appear in different forms. They for example, emerge from learned associations between relevant events, can be induced by the beat of a rhythm, and differ with the passage of time. I will now discuss behavioural research on 3 of such "modes" of temporal orienting, namely hazard rates, rhythms and temporal cues, that all influence temporal expectations in their own unique ways. In a later section (1.5)

I will review the research on neural modulations related to these three types of temporal bias.

1.2.1 Hazard rates.

The "hazard function" is the conditional probability of an event occurring at a given time, given that it has not yet occurred (Luce, 1986). Many cognitive experiments have a fixed temporal structure. In such tasks, the influence of hazard rates is visible in anticipatory saccades (Kingstone and Klein, 1993) and manual responses (Nickerson, 1965). Furthermore, hazard rates influence perceptual thresholds (e.g., Lasley and Cohn, 1981; Westheimer and Ley, 1996) and attenuate attentional-blink effects (Martens and Johnson, 2005; Shen and Alain, 2012). Other studies have shown strong effects on reaction times and motor preparation (Schoffelen et al., 2005; Cravo et al., 2011, see also section 1.5 in this chapter).

1.2.2 Rhythms

Rhythms are everywhere around us, and they are important in many of our interactions with the environment. Rhythms are inherent to bodily processes like breathing and heart rate, and they are evident in speech and music, as well as in walking and performing other movements. We even sample the world in a rhythmic fashion since eye movements are primarily rhythmic (McAuley et al., 1999). Thus, rhythm is a powerful source of predictive temporal information (see also Schroeder et al., 2010).

As Newhall demonstrated in 1923, stimuli coinciding with the beat of a rhythm have a clear perceptual advantage. Jones (1976, 2010) launched the modern-day research on rhythmic orienting of attention, investigating the effects of rhythm on auditory discrimination. Auditory discrimination is maximal for targets occurring on the beat, and the bigger the interval between the predicted beat and the target, the worse performance becomes. Perceptual facilitation by rhythms (e.g. Lawrance et al., 2014; ten Oever et al., 2014) appears to be largely automatic, since the effects occur even when the rhythm is not predictive (Sanabria et al., 2011), or when targets are more likely to occur off-beat. Rhythmic benefits to perception are also found in the visual domain (e.g., Mathewson et al., 2010; Rohenkohl et al., 2012; Cravo et al., 2013; de Graaf et al., 2013).

1.2.3 Temporal cues

Besides foreperiods, hazard rates and rhythms, temporal orienting of attention can also be based on learned associations between two stimuli. Temporal cues, containing information about the likely time of an upcoming target or response signal, are an effective way of manipulating such associations.

The first study to use temporal cues (Coull and Nobre, 1998; see also Kingstone, 1992, experiment 4) adapted Posner's spatial orienting task (Posner et al., 1980) to test whether it is possible to orient attention voluntarily to anticipated moments of relevant events. The task required simple target detection of a left or right visual stimulus occurring after 300 or 1500 ms. Symbolic cues preceding the target predicted (with 80% validity) its spatial

location, time interval, or both the location and the interval. In these types of tasks, performance is generally measured by comparing performance for validly predicted targets, to performance for targets preceded by an invalid or neutral cue (i.e. a cue that contained either incorrect or no relevant information). In the study by Coull and Nobre (1998), validity benefits and invalidity costs occurred for both spatial and temporal cues and were even larger for temporal cues. The effects of temporal cues were restricted to targets at the short interval, since after a short interval with no target, target appearance became predicted to occur at the long interval with absolute certainty. Note that the absence of a validity effect at the long interval is dependent on the precise task that is used. When catch trials are included, in which no target is presented, thus when cues still manipulate the conditional probability for targets occurring at the long interval, a temporal orienting effect is found for both short- and long-interval trials (Correa et al., 2004, 2006b).

The effects of temporal cueing have been extensively replicated and extended. The effects are flexible and robust; they occur using different tasks, sensory modalities, interval ranges, stimulus parameters, and response requirements (Miniussi et al., 1999; Griffin et al., 2001; Correa, 2010; Lange and Röder, 2010; Nobre, 2010; Nobre and Rohenkohl, 2014).

Studies investigating neural modulations have found that temporal cues can influence early stages of visual processing (e.g. Correa et al., 2006a; Lange and Röder, 2010, see also section 1.5 in this chapter). That perceptual processing can be influenced by predictive temporal cues is also suggested by attentional blink tasks, where cues predicting short intervals greatly improved detection

performance (Martens and Johnson, 2005; Shen and Alain, 2012). Interestingly, a recent study involving temporal cues and targets presented at one of three possible time points showed a clear perceptual trade-off following temporal cues, with improved perceptual performance for the cued time point, but worse performance when the target appeared earlier or later (Denison et al., 2017), illustrating the specificity and selectivity of cue-based temporal orienting.

1.3 Neural representations of temporal orienting

In this section I review the literature on models that have been proposed on how temporal information is presented in the brain, and what functional magnetic resonance imaging (fMRI) studies have taught us on what brain areas and networks are involved in temporal processing.

1.3.1 Models and mechanisms of timing

While it is clear that the brain can extract and utilise predictive temporal information from the environment, how timing is represented in the brain remains a mystery. Currently debated models tend to fall into two classes (see Ivry and Schlerf, 2008, for a review). One class of models proposes a general timing control network regardless of the goals and domains involved. Within such models, temporal expectations would be generated within this control network, or at least in interaction with this dedicated neural clock (e.g., Merchant et al., 2013a).

A classic "clock" model is the pacemaker-accumulator model (Treisman, 1963; Gibbon et al., 1984). In this model, an internal pacemaker emits regular pulses that can be recorded by an accumulator or counter on the basis of sensory signals, for example, a warning cue or a target duration that has to be remembered. The number of pulses counted represents the interval duration. Series of pulses can be compared with previously stored pulse series to compare intervals.

The other class of models questions the existence of a central-clock mechanism and proposes that timing is intrinsic to the neural processing in many or all brain areas. In this scenario, the source of temporal expectations would depend on brain areas involved with the task at hand. State-dependent network models (Mauk and Buonomano, 2004), for example, contain no clocks or brain areas dedicated to temporal processing. In such models, timing arises from computations that include temporal processing but are not mediated by central mechanisms. In such models timing is an intrinsic property of areas dedicated to the processing of other features, like space, and involves state-dependent changes in network dynamics. Thus, timing is distributed across the brain. An alternative distributed view of temporal processing proposes "climbing neural activity" as the process which tracks time (Wittmann, 2013). This model suggests that neural activity ramps up until it reaches a peak at the end of a tracked interval. Others argue that the representation of durations is dependent on memories, whereby the decaying strength of memory traces is used to keep track of time (Staddon, 2005).

At the moment it remains difficult to arbitrate between the competing accounts. What is becoming evident is that oscillatory activity likely plays an important role in the utilisation of temporal information to guide perception and action.

1.3.2 Temporal orienting and the brain

Echoing the debate concerning central versus distributed models of timing, the neural correlates of temporal expectations are not fully resolved. Neuroimaging, lesion, and patient studies have consistently implicated the cerebellum, basal ganglia, supplementary motor area, and inferior frontal cortex in explicit temporal processing while parietal and left premotor areas seem more involved in temporal orienting (Ivry, 1996; Coull et al., 2004; Ivry and Spencer, 2004; Buhusi and Meck, 2005; Coull and Nobre, 2008). However, the precise combination of areas that are activated together seems to be highly dependent on task demands (Coull and Nobre, 2008). Furthermore, different brain structures may participate at different timescales; for example, the cerebellum has been implicated in temporal processing in the millisecond range (Ivry and Spencer, 2004) while the basal ganglia have been implicated in timing ranging from hundreds of milliseconds to minutes (Buhusi and Meck, 2005).

A frontoparietal network containing the intraparietal sulcus, the anterior parietal lobule, and the inferior premotor cortex is often found to be activated in studies looking at temporal orienting (Coull and Nobre, 1998; Coull et al., 2000; Cotti et al., 2011; Davranche et al., 2011; Coull et al., 2013). A meta-analysis including eight studies on temporal cueing and related tasks (Nobre and

Rohenkohl, 2014), confirmed reliable activations in posterior portion of the intraparietal sulcus, anterior inferior parietal lobule, and premotor cortex. In addition, activations in the cerebellum were found although this area is not consistently reported in the temporal orienting literature. The left parietal cortex seems selectively involved in temporal orienting compared to other types of orienting. It is more active for temporal cueing compared to spatial (Coull and Nobre, 1998) or motor-effector cueing (Cotti et al., 2011). Furthermore, activity in parietal areas was more strongly correlated with task-relevant areas during a perceptual as well as a motor task (Davranche et al., 2011). The functional overlap between brain areas involved in temporal orienting and in manual sensorimotor control has often been noted (e.g., Coull and Nobre, 1998; Nobre, 2001; Nobre and Rohenkohl, 2014). One intuitive possibility is that temporal orienting relies on computations available in manual-control circuits in an analogous way to how spatial orienting relies on computations available through the oculomotor circuitry (O'Reilly et al., 2008b).

1.4 Using MEG to study spatial-temporal orienting of attention

Temporal orienting of attention is studied in different modalities, using a variety of tasks, and using a number of different techniques. Before I introduce the specific research questions that I addressed in this thesis, I first want to elaborate further on the question of why MEG is a highly suitable method for studying temporal orienting of attention, complementing other methods like fMRI or EEG,

and why it is interesting to study modulations of neuronal oscillations as a key candidate substrate.

1.4.1 The MEG signal

Since the discovery of alpha oscillations in human electroencephalography (EEG) by Hans Berger (1929) a lot of progress has been made in our recording and understanding of neuronal oscillations. Both EEG and magnetoencephalography (MEG) can be used to study neural processes with sub-millisecond temporal resolution (Hari et al., 2000). EEG picks up electrical potentials at the scalp, while MEG measures changes in magnetic fields, resulting mainly from postsynaptic currents in cortical[1] pyramidal neurons (see Lopes da Silva, 2010).

Magnetic fields can be recorded with superconducting quantum interference devices (SQUIDS; see also Hari and Puce, 2017). The data in this thesis were recorded using an Elektra Neuromag system, that contains 306 SQUIDs, distributed across two sensor types: 102 magnetometers and 204 planar gradiometers. The data presented in this thesis reflects data from 102 combined planar gradiometer pairs, which has the advantage that the signal is now independent of the orientation of the source and therefore can be projected at the sensor locations roughly overlaying the source location.

[1] Although, at the moment, MEG is used mainly to investigate cortical activity, considerable progress is made in the investigation of deeper structures. For example, it is now possible to reliably measure hippocampal activity with MEG (Meyer et al. 2017).

1.4.2 The benefits of using MEG

Compared to functional magnetic resonance imaging (fMRI), MEG has two major advantages (see also Hari et al., 2000; Hari and Puce, 2017). First, MEG has a much higher temporal resolution than fMRI, which is necessary to study processes that rapidly evolve over time, like modulations subserving the influence of temporal expectations. Second, MEG picks up signals generated by neuronal activity directly, instead of indirectly inferring activity from blood flow. Although both of these benefits are also carried by EEG, MEG has a number of additional benefits over EEG[2]. Unlike EEG, the activity picked up by MEG is not distorted by the skull and scalp. Furthermore, MEG can be combined with structural MRIs to determine the sources[3] of activity. Other benefits hold that MEG reflects absolute measurements, while EEG requires a reference electrode and that MEG is generally more comfortable for the participant and quicker in preparation, which is especially useful when recording from older adults and patient groups. Finally, MEG is more suitable than EEG to study modulations in higher frequency activity (gamma band oscillations around 60-90Hz; which I did in Chapter 2), since the signal is less contaminated by high-frequency electromyography (EMG) artefacts (Claus et al., 2012).

[2] Note that, of course, both EEG and fMRI also have some benefits over MEG, like the better spatial resolution of fMRI, and the much cheaper costs of performing an EEG study.

[3] In the current thesis I did not go to "source space" and therefore do not discuss the relevant methods here. Good descriptions of the basic principles of source localisation in MEG can be found in e.g. Hansen et al. (2010) and Hari and Pruce, (2017).

1.4.3 Neural oscillations involved in perceptual anticipation and motor preparation

MEG and EEG signals can be studied both in terms of event-related activity and in terms of oscillations, or the frequency content. Event-related potentials (ERPs) are electrical scalp potentials that can be recorded with EEG, and are generally a direct result of a specific cognitive, sensory or motor event (Luck, 2005). The MEG counterpart of ERPs are called event-related fields (ERFs). ERPs and ERFs are generally named after the polarity (N: negative/P: positive) and latency or ordinal occurrence of the component. For example, N1 reflects the first negative component, while P600 reflects a positive component starting after 600 ms. In addition to event-related fields, the MEG (and EEG) signal can also be studied in relation to its frequency content, which is what I predominantly focused on in this thesis.

Oscillations are thought to play an important role in information processing in the brain (Fries, 2005; Jensen and Mazaheri, 2010; Thut et al., 2012; Fries, 2015), because they reflect rhythmic fluctuations in the level of neuronal excitability across a population of neurons, which is thought to influence the likelihood that neurons in a population will fire as a function of time. Oscillations are generally classified in a number of frequency bands, although the precise ranges that are use tend to vary. I will now introduce the two frequency ranges that were most relevant for the research presented in this thesis, namely the alpha and beta band.

Oscillations in the alpha (~8-12 Hz) band

Fluctuations in oscillatory power are thought to reflect increases and decreases in the synchrony of underlying neuronal populations (Pfurtscheller and Lopes da Silva, 1999). Alpha oscillations are generally (mainly) found in visual, auditory, and sensorimotor areas and are generally strongest at rest, while they decrease in amplitude during attentional processing (Hari and Salmelin, 1997; Pfurtscheller and Lopes da Silva, 1999). A decreased amplitude of alpha in sensory-motor areas – either due to spontaneous fluctuations, or during task performance – has been shown to reflect higher excitability states (e.g. Sauseng et al., 2009; Haegens et al., 2011) and has been associated with improved behavioural performance (e.g. van Dijk et al., 2008; Gould et al., 2011). Accordingly, Jensen and Mazaheri (2010) proposed that enhanced alpha oscillations reflect a state of functional inhibition (see also Klimesch et al., 2007 and Foxe and Snyder, 2011).

Oscillations in the beta (~14 – 28 Hz) band

Beta oscillations are an important characteristic of the motor system, which includes cortical areas and deeper structures like the basal ganglia and cerebellum. Beta oscillations are generally found to decrease prior to and during movement (Pfurtscheller and Lopes da Silva, 1999). Although the precise functional significance of beta-band oscillations in the motor system is still unclear, it is generally agreed that beta suppression is an indicator of motor readiness (Jenkinson and Brown, 2011). Beta has been proposed to reflect a similar inhibitory function to alpha, in the motor network (Hari and Salmelin,

1997; Jensen et al., 2005), although others have suggested a more active role (e.g. Engel and Fries, 2010). Interestingly, excessive synchrony in basal ganglia-cortical circuits is a well-known characteristic of Parkinson's disease (Hammond et al., 2007; Brittain and Brown, 2014; see also Chapter 3 in this thesis), where it is related to motor impairment (Jenkinson and Brown, 2011).

Frequency bands involved in temporal orienting

It is important to note that the frequency bands that are involved in temporal processing are likely to be highly dependent on the task context (Wiener and Kanai, 2016). For example, in the visual domain, alpha oscillations are likely to play a key role (see e.g. Rohenkohl and Nobre, 2011; Zanto et al., 2011), while for temporally specific motor preparation, the beta frequency range is generally found to be most important (Schoffelen et al., 2005; Praamstra et al., 2006; Jenkinson and Brown, 2011; te Woerd et al., 2014). Interestingly, the beta range has also been shown to be involved in temporal tasks without a strong motor component, for example in the auditory (Fujioka et al., 2012; Todorovic et al., 2015), and somatosensory (van Ede et al., 2010, 2011) domains. Others have shown that slower frequency ranges like theta (~4 – 7 Hz) and delta (~1 – 4 Hz) can play a role in temporal orienting as well (Cravo et al., 2013; Lakatos et al., 2013; Wilsch et al., 2015), especially when coinciding with the rate of rhythmic stimulus presentation (entrainment). Furthermore, a number of studies have revealed important interactions between different frequency bands, that are often expressed as coupling between the phase of a lower frequency and the amplitude of power modulations in a higher frequency (Cravo et al., 2013; Arnal

et al., 2015), or between cortical areas and muscles (expressed as cortico-muscular coherence; Schoffelen et al., 2005). Some studies have focused on the phase of oscillations instead of, or in addition to, the power (Stefanics et al., 2010; Lakatos et al., 2013; Samaha et al., 2015). For the purpose of this thesis, I will particularly focus on modulations in power in the alpha (8 – 12 Hz) and beta (15 – 28 Hz) range.

1.5 EEG and MEG studies on temporal orienting of attention

As we saw earlier, hazard rates, rhythms and temporal cues all can have a strong influence on behaviour. In this section I will review research on the neural modulations that accompany such behavioural effects on perception and action.

1.5.1 Hazard rates

Temporal expectations induced by hazard rates influence neural activity across many brain areas, from early perceptual input to late motor output stages. Animal studies have reported effects on spiking and oscillatory activity over many sensory areas, and as early as V1 (Ghose and Maunsell, 2002; Ghose and Bearl, 2010; Lima et al., 2011).

At the endpoint stages of information processing, Schoffelen and colleagues (2005) showed that reaction times, beta power in motor cortex, and motor cortex output, measured as corticospinal coherence in the gamma band, were all strongly affected by hazard-rate manipulations. A Go/NoGo study performed

with EEG also showed hazard-rate effects on reaction times and indices of motor preparation (Cravo et al., 2011). A recent study using an implicit, probabilistic hazard rate manipulation showed effects in both behaviour and EEG data, that differed with the distribution of foreperiods that was used, i.e. with the specific time points that targets were more or less likely to occur (Herbst and Obleser, 2017).

1.5.2 Rhythms and entrainment effects

Jones (1976, 2010) proposed a "dynamic attending theory," in which entrainment to rhythmic regularities within our environment provided a mechanism for enhancing perception. Recently, neuroscientists have suggested that behavioural entrainment to rhythmic input streams may be accompanied by neural entrainment. In non-human primates, oscillatory activity in the lower frequency ranges (e.g., delta and theta bands) has been shown to entrain to regular events in the environment by means of a phase alignment (Lakatos et al., 2008, 2009; Schroeder and Lakatos, 2009). Entrainment of low-frequency oscillations in turn modulates excitability in local neuronal assembles, thereby synchronising brain activity at higher frequencies (e.g., in the gamma band) coding information in these local ensembles (Canolty et al., 2006; Canolty and Knight, 2010). A recent study in human volunteers (ten Oever et al., 2017) underscores the mechanistic role of entrainment, by showing that rhythmic entrainment can take place even before participants are able to detect a sound stream, and before any significant evoked responses can be seen.

Rohenkohl and Nobre (2011) showed an effect of temporal expectations on anticipatory alpha desynchronization, in a task where a rhythmic target disappeared behind an occluder. Bursts of alpha foreshadowed the invisible jump of the ball during occlusion and its reappearance after occlusion. Temporal predictions thus influenced the time course of oscillatory activity related to anticipation of the target. In a separate experiment, investigating temporal expectations in the absence of spatial expectations, responses to targets appearing after a predicted (50% valid) or unpredicted foreperiod were compared using a large set of possible isochronous (i.e., equally spaced) rhythms (Correa and Nobre, 2008). The results showed that temporal expectations were flexibly induced by multiple regular rhythms, and that the effects of temporal expectations strongly interacted with the foreperiod effects associated with the length of the occlusion period.

To probe the influences of rhythm on perception in greater depth, psychophysical experiments involving challenging perceptual discriminations were combined with modelling and EEG recordings. Behavioural accuracy and response times for target discrimination were compared when targets were embedded within a stimulus stream presented in a regular, rhythmic, or irregular, arrhythmic fashion (Rohenkohl et al., 2012; Cravo et al., 2013). Stimuli consisted of Gaussian noise patches, in which a Gabor grating of different contrast levels could be embedded. Participants had to indicate the orientation of the grating in a forced-choice fashion. Importantly, the intervals immediately surrounding each target were identical for both the rhythmic and arrhythmic condition. Having a regular rhythm enhanced response times and lowered the

threshold contrast levels for target discrimination (Rohenkohl et al., 2012). Diffusion modelling (see Palmer et al., 2005) showed that temporal expectations influenced perceptual processing by enhancing the signal-to-noise gain of the visual targets. In a subsequent replication using EEG (Cravo et al., 2013), the same pattern of behavioural effects was observed, and these benefits followed entrainment of oscillatory activity in the delta band (the same range as the stimulus trains). Delta phase across the target events was better aligned for the rhythmic compared to the arrhythmic condition, and the correlation between delta phase and target discriminability was higher. These studies all suggest that rhythms are important sources of temporal expectations, and that entrainment to environmental rhythms has significant perceptual benefits.

The timing of slow, anticipatory brain potentials, like the contingent negative variation (CNV; Walter et al., 1964) has also been shown to follow rhythms. Praamstra and colleagues (2006) showed rhythmic modulation of slow event-related potentials (ERPs), as well as preparatory desynchronization in the alpha and beta bands, when they presented series of targets with regular stimulus-onset asynchronies (SOAs). The time course of the CNV and oscillatory modulations varied with the length of the regular SOA in each series. Behavioural and neural responses to targets occurring after deviant intervals were compromised.

1.5.3 Temporal cues

ERP recordings during visual tasks have typically shown that, in the absence of spatial information, the visual P1 potential is unaffected by temporal cues, with

effects occurring at later N2 and P3 potentials (Miniussi et al., 1999; Griffin et al., 2002). These effects are similar to those in experiments using rhythmically induced temporal and combined spatiotemporal expectations (Doherty et al., 2005; Correa and Nobre, 2008, see also section 1.6 in this introduction).

Cueing tasks involving demanding perceptual discriminations for targets appearing at constant locations show that temporal cues may influence early stages of visual processing. Correa and colleagues (2006a) used temporal cues to predict the occurrence of a target within a rapid serial visual presentation stream. They found that valid cues enhanced perceptual sensitivity (d′) measures and modulated early P1 potentials. Auditory cueing tasks have also consistently reported modulation of early auditory N1 potentials (see Lange and Röder, 2010). However, some of the early perceptual modulations reported in both the visual and auditory domains remain inconclusive, because they might have been caused by blocked hazard rates. In these experiments, temporal cues were manipulated in a blocked fashion, so that hazard rates and cueing effects were indistinguishable.

1.6 Modes of temporal orienting: commonalities and dissociations

In the previous overview we saw that hazard rates, rhythms, and temporal cues share some similar features in terms of behavioural as well as neural effects. Behaviourally, all these modes of temporal orienting can speed up reaction times and enhance accuracy of performance. The neural pattern of target modulation is

similar, with a clear influence on later potentials (e.g., N2, P3 in vision) and flexible modulation of early potentials (P1) depending on whether spatial information is also present (Miniussi et al., 1999; Griffin et al., 2002; Doherty et al., 2005; Correa et al., 2006a; Praamstra et al., 2006).

Modulation of anticipatory activity also follows similar patterns. The time course of anticipatory CNV-like brain potentials follows temporal expectations (e.g., Miniussi et al., 1999; Trillenberg et al., 2000; Praamstra et al., 2006; Cravo et al., 2011; Capizzi et al., 2013). These preparatory CNV effects are similar to effects found in explicit timing tasks, where the CNV time course adjusts to the remembered standard interval (Pfeuty et al., 2003, 2005). Modulation of preparatory oscillatory activity is also observed. Alpha- and beta-band desynchronization over sensory and motor areas precedes temporally predictable targets depending on the specific task parameters and demands (Schoffelen et al., 2005; Praamstra et al., 2006; van Elswijk et al., 2007; Rohenkohl and Nobre, 2011; van Ede et al., 2011; Zanto et al., 2011). These anticipatory oscillatory effects often interact with other available information, like spatial expectation in visual tasks or effector expectation in motor tasks (such interactions will be discussed further in the next section).

Despite these commonalities, there are some clear differences between different types of temporal biases. Rhythms seem to have more automatic influences than other types of temporal information. Rohenkohl and colleagues (2011) showed that rhythmic, regular motion patterns enhanced responses to visual targets automatically, but that symbolic colour cues only enhanced behaviour when participants were instructed to use cue predictions. Others

showed that the automatic effects of rhythms occur even when they are unintentional and detrimental to the task that has to be performed (Breska and Deouell, 2014). Behavioural improvements have also been reported for auditory targets occurring on the beat of a rhythm, even when this rhythm is task-irrelevant and non-informative (Sanabria et al., 2011). Furthermore, benefits associated with rhythms resist simultaneous performance of a demanding working memory task (de la Rosa et al., 2012). In a similar dual-task experiment, a competing working-memory task interfered with temporal cueing effects, but not with other types of temporal orienting effects (Capizzi et al., 2012, 2013).

In many tasks, and often in daily life, different types of temporal expectation are intermixed. An example is waiting for a traffic light to become green, with the cue given by the light turning amber signalling the upcoming change, and the hazard rate building during the wait. Furthermore, it remains unclear how multiple sources of temporal expectation interact and give rise to more complex patterns of expectations, for example, in the case of non-isochronous sequences, which have ordinal as well as temporal information embedded in them (see O'Reilly et al., 2008a and Chapter 4 in this thesis), or other types of aperiodic temporal regularities (Morillon et al., 2016).

1.7 Interactions between temporal and spatial orienting for perception and action

Flexible preparation involves the system being ready not only for the specific type of input that is expected, or the specific action that has to be performed, but

also for the time that this information is expected to appear within the constant flow of external input. The studies discussed in the sections above all show that temporal expectations can have a strong and flexible influence on behaviour, and a prevalent idea holds that early perceptual effects may occur primarily by enhancing other types of top-down attention effects (like spatial, of feature-based expectations) that map onto receptive-field properties of relevant neuronal populations in sensory areas, i.e. affects the timing of the excitability of these neuronal populations (an idea that was discussed in Nobre and Rohenkohl, 2014; and we saw in for example Praamstra et al., 2006; Ghose and Bearl, 2010; Rohenkohl and Nobre, 2011; and van Ede et al., 2011, which is discussed below). Similarly, relevant responses to such items can be prepared by (pre-) engaging the relevant motor areas (see e.g. Schoffelen et al., 2005; Alegre et al., 2006, Praamstra et al., 2006).

To ensure such optimal preparation and prioritisation, it is essential to investigate how temporal expectations interact with, or influence, other anticipatory processes. In previous studies, temporal expectations have often been studied in isolation. However, to truly understand how these processes emerge, it is key to study temporal orienting jointly with other types of expectations. In this thesis I investigated temporal together with spatial anticipation in both the visual and the motor domain, and the extent to which such processes change or break down with ageing and neurodegeneration. Furthermore, I explored how these processes behave in the context of an implicitly acquired sequence, which has a spatial (both visual and motor) and temporal structure. Before I get to the specific experiments performed in this

thesis, I first want to discuss a number of studies that looked at joint spatial-temporal orienting of attention, and therefore formed a relevant background to many of the ideas and experiments presented in this thesis.

Doherty and colleagues (2005) investigated effects of rhythmic temporal expectations in the presence or absence of spatial expectations to visual targets. In this EEG experiment, a ball jumped across the screen in discrete steps before it disappeared behind an occluder. The participants' task was to discriminate the presence or absence of a small stimulus inside the target when it reappeared. Different types of expectation (spatiotemporal, temporal only, spatial only, and neutral) resulted from manipulating the spatial trajectory (linear or random) and/or rhythm (regular or random) of the ball. Both spatial and temporal expectations speeded reaction times, with an additive effect when both dimensions could be predicted. ERPs were recorded when the ball reappeared after occlusion—the target event in the task. Modulation of the earliest visual potential, P1, showed a striking interaction between temporal and spatial expectations. Whereas the EEG recordings showed no P1 enhancement by temporal expectation alone, the gain modulation of P1 by spatial expectation was significantly potentiated when temporal expectations were also present (spatiotemporal compared to spatial condition). Other, later, potentials (N1, P2, and P3) were also affected by temporal and spatial expectation.

van Ede and colleagues (2011) studied the influence of hazard rates on contralateral sensorimotor alpha and beta desynchronization in anticipation of lateralised and spatially-cued tactile stimuli. As I introduced in section 1.4, desynchronization of alpha and beta activity over task-relevant areas is often

linked to anticipation and preparation in the perceptual or motor domain. Across experimental blocks, tactile stimulation was differentially distributed over the course of single experimental trials, occurring at one of three (1, 2, or 3 seconds) or only at two intervals (1 and 3 seconds). The results showed that beta-band desynchronization (lower power contralateral relative to ipsilateral to the expected stimulation hand) clearly adapted to the block-specific hazard rate, with desynchronization being strongest just before possible times of stimulus presentation and relaxing in between. In this task, hazard rates thus influenced the time course of oscillatory activity related to spatiotemporal orienting in the tactile domain, which was associated with better performance.

Rohenkohl and colleagues (2014) tested whether perceptual effects of temporal cueing depended on spatial attention. Participants made difficult perceptual discriminations on peripheral grating stimuli. These targets appeared after a cue that predicted (with 80% validity) the side (left, right) and the interval (800, 2,000 ms) of the target. Results confirmed a synergistic interaction between temporal and spatial expectations. In this study, temporal expectation boosted the effects of spatial expectations on perceptual variables, resulting in enhanced visual discriminations. However, valid temporal cues combined with invalid spatial cues had no significant effect on performance.

The powerful effect of spatial-temporal expectations on behaviour has also been shown for spatial-temporal sequences, i.e. sequences of targets that contain a spatial-temporal structure (O'Reilly et al. 2008a; see also Chapter 4 in this thesis). In this study, participants acquired this sequence implicitly over time. The addition of a paired temporal sequence greatly improved reaction times,

compared to having a spatial sequence that was combined with random temporal intervals.

1.8 Overview of this thesis

As I introduced in the preceding overview, temporal orienting of attention is an important aspect of many human behaviours, especially when it can be integrated with predictions about space or upcoming actions. Our brain generates temporal predictions in a continuous, automatic fashion, and thereby ensures that we optimally prepare for upcoming interactions with the world. In this last section of this general introduction I will introduce the three experiments that form the core of this thesis. I first will provide a rationale for studying temporal orienting in ageing and neurodegeneration, as I did in Chapters 2 and 3 of the current thesis. Furthermore, I will discuss why it is important to investigate temporal expectations in more complex, implicitly acquired sequential behaviours, which is the topic of Chapter 4.

1.8.1 Chapter 2: Spatial-temporal orienting for perception in ageing

When studying cognitive processes like spatial-temporal orienting, and neural modulations that accompany such processes, it is important to study these processes not only in young participants, but to also consider how these processes change with normal, healthy ageing. A large body of studies has shown that changes in attentional processes with ageing are observed in a variety of

tasks and circumstances (see Zanto and Gazzaley, 2014 and Erel and Levy, 2016, for reviews).

Potential deterioration of spatial-temporal processing may have substantial deleterious consequences. For instance, in order to navigate through traffic, it is important to integrate temporal and spatial information about one's own location and movement speed, but also with respect to other vehicles. Older adults seem less able to use and integrate temporal information, which may form complications in such highly dynamic contexts (see e.g. Andersen et al., 2000).

Deterioration of interval timing with ageing has been reported in a number of studies (see Block et al., 1998; Lustig, 2003; Balci et al., 2009, for reviews). For temporal orienting tasks using temporal cues the picture is less clear. One study that investigated cue-based temporal orienting in perceptual detection, forced-choice discrimination and Go/NoGo discrimination, found that temporal orienting declined with ageing (Zanto et al., 2011). In this study, younger adults used temporal cues to improve their behavioural performance, while older adults did not perform better when cued with valid, compared to invalid temporal information. Similar effects were found in the EEG data. In younger adults, the time course of preparatory activity, expressed in the time course of the contingent negative variation and preparatory alpha desynchronisation, adjusted to the time course indicated by the temporal cue. In older adults these effects were largely reduced, suggesting that the effects of temporal cues diminish with age. Contrary to these findings, Chauvin and colleagues (2016) recently showed, using speeded and non-speeded behavioural tasks, that in some cases temporal orienting can be preserved in healthy ageing. However, both of these studies only

investigated the effects of temporal orienting, while the spatial location of targets was fixed. Whether and how ageing also affects behaviour and neural effects related to joint spatial-temporal orienting of attention has not yet been explored, while such expectations might be especially powerful in guiding attention (Rohenkohl et al., 2014).

Spatial orienting of attention is generally found to be preserved in ageing (see Zanto and Gazzaley, 2014; Erel and Levy, 2016), especially when other factors like declines in bottom up processing and general slowing are controlled. However, there is some evidence to suggest that neural modulations related to spatial orienting might be altered, or diminished (Deiber et al., 2013; Hong et al., 2015).

Rohenkohl et al. (2014), found a clear synergistic interaction between spatial and temporal expectations on behavioural performance in younger adults. In this study these joint spatial-temporal expectations were especially powerful, because the task involved a difficult perceptual discrimination. Having valid information in both modalities was therefore most beneficial for task performance. In Chapter 2, I used an adapted version of this task, to study cued spatial-temporal orienting in the visual domain in both younger and older adults. This allowed me not only to explore how such joint spatial-temporal expectations are expressed in younger adults, but also to assess how such processes change with ageing, at both the behavioural and the neural level.

1.8.2 Chapter 3: Temporal orienting and selective motor preparation in Parkinson's disease

Parkinson's disease (PD) was first described by James Parkinson in 1817 (republished in 2002, as a Neuropsychiatry Classic). In this fascinating read, Parkinson describes a set of "Illustrative cases" and outlined some of the most striking symptoms of this disease, with the most important being tremor. However, Parkinson's observational analysis failed to describe some of the additional cardinal symptoms of PD, like bradykineasia (slowness of movement), rigidity and postural instability, in addition to the cognitive, mood and sleep disturbances that are now considered part of the clinical manifestation of this disease (Jankovic, 2008). Parkinson's disease is associated with progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, and common treatments involve dopaminergic medication, or the more invasive option of deep brain stimulation in the subthalamic nucleus.

Research with PD patients has implicated dopaminergic functioning in the basal ganglia as a key process involved in temporal processing (see Jones and Jahanshahi, 2014, for a review), at least when this involves tasks that require explicit timing. Explicit timing tasks include tasks that require judgments about durations, require the reproduction of intervals, or involve synchronisation and continuation of an external rhythm. In such tasks, PD patients generally show impairments compared to healthy control participants, especially when "off" their dopaminergic medication (Artieda et al., 1992; Pastor et al., 1992; O'Boyle et al., 1996). In temporal orienting tasks (where temporal information can be utilised to achieve non-temporal task-goals, see Coull and Nobre, 2008), this

picture is less clear (Jahanshahi et al., 1992; Praamstra and Pope, 2007; de Hemptinne et al., 2013a). There is some evidence that temporal orienting is spared, at least at the behavioural level, although the time course of beta modulations in motor areas might be affected (Praamstra and Pope, 2007; te Woerd et al., 2014). However, whether similar behavioural benefits and neural modulations occur in the context of cue-based temporal orienting is still unknown. In Chapter 3 of this thesis I therefore investigated cued temporal orienting of attention and accompanying neural modulations in PD participants off dopaminergic medication and matched healthy control participants.

1.8.3 Chapter 4: Spatial-temporal orienting in complex sequences

In daily life, temporal associations often occur embedded within sequences of events. In 1951, Lashley wrote an influential chapter on "*The problem of serial order in behaviour*", addressing the integration of spatial and temporal structure in complex, sequential behaviours, of which he deemed language the most striking example. Other examples can be found in music, sports or when driving a car. Timing related to such predictable, but non-isochronous movement patterns is often acquired in an incidental manner, over long periods of time.

Studying these types of complex behaviours in the lab is a challenging endeavour, especially compared to tasks involving only one or two temporal intervals and simple responses. In 1987, Nissen and Bullemer invented the "serial-reaction-time task", or SRT task, to study the acquisition of ordinal sequences. In SRT tasks, stimuli are mapped to corresponding motor responses, and participants get faster over time when patterns repeat, even when they are

unaware that such patterns exist. Since this first study, SRT tasks have become a staple in the sequence learning literature. Interestingly, SRT tasks have more recently also been used to investigate the temporal aspects of such sequences as well (Buchner and Steffens, 2001; Salidis, 2001; Shin and Ivry, 2002; Ullen and Bengtsson, 2003; Karabanov and Ullen, 2008; O'Reilly et al., 2008a; Gobel et al., 2011; Kornysheva et al., 2013; Schultz et al., 2013; Kornysheva and Diedrichsen, 2014; Sanchez et al., 2015). Studies investigating combined spatial-temporal sequences have found that the addition of this temporal structure has a huge impact on performance, compared to having spatial structure alone (O'Reilly et al., 2008a).

Most previous SRT studies that involved an additional temporal component looked at the *acquisition* or learning of visual-motor sequences. However, this leaves unanswered questions about how we make use of such implicit information to perform the task at hand. In Chapter 4, I used an SRT task in MEG to look instead at the *utilisation* of expectations about individual learned spatial-temporal sequence elements, to investigate how implicit predictions about both space and time are used to anticipate upcoming targets and responses, and how these processes are reflected in temporally specific modulations in the alpha and beta band.

1.8.4 Implications

This thesis aims to explore the robustness and flexibility of behaviour and anticipatory neural modulations with spatial-temporal orienting of attention. This is done in Chapter 2 by investigating changes that occur in healthy ageing,

and in Chapter 3 by studying a group of patients that is known to exhibit deterioration of temporal processing, caused by progressive neurodegeneration. In Chapter 4 temporal expectations are explored in a more dynamic, complex setting, where spatial-temporal structure had been acquired over time.

Chapter 2 will show that the neural dynamics associated with spatial, temporal and spatial-temporal orienting are all associated with differential neural dynamics that are, moreover, differentially affected by ageing. Chapter 3 will show that the ability to use temporal cues and align anticipatory brain dynamics in time to guide adaptive motor behaviour is diminished (albeit not absent) in PD patients. Chapter 4 will show that learned spatial-temporal structure (to which participants remains largely unaware) affects both behaviour and oscillatory modulations in a similar fashion to temporal cues. These studies provide several new insights and open many interesting new questions that I discuss in Chapter 5, the general discussion.

Chapter 2: Anticipatory neural dynamics of spatial-temporal orienting in ageing

Spatial and temporal expectations act synergistically to facilitate visual perception. However, several reports indicate that behavioural and neural dynamics related attentional orienting diminish with ageing. In this experiment I investigated anticipatory neural dynamics associated with such joint spatial-temporal orienting of attention using MEG in both younger and older adults. Participants performed a cued covert spatial-temporal orienting task requiring the discrimination of a visual target. Cues indicated both where and when targets would appear. In both age groups, valid spatial-temporal cues significantly enhanced perceptual sensitivity and reduced reaction times. In the MEG data, the main effect of spatial orienting was the lateralised anticipatory modulation of posterior alpha and beta oscillations. In contrast to previous reports, this modulation was not attenuated in older adults; instead it was even more pronounced. The main effect of temporal orienting was a bilateral suppression of posterior alpha and beta oscillations. This effect was restricted to younger adults. The results also revealed a striking interaction between anticipatory spatial and temporal orienting in the gamma-band (60 – 75 Hz). When considering both age groups separately, this effect was only clearly evident and only survived statistical evaluation in the older adults. Together, these observations provide several new insights into the neural dynamics supporting separate as well as combined effects of spatial and temporal orienting of attention, and suggest that different neural dynamics associated with attentional orienting appear differentially sensitive to ageing.

I took over this project after the data collection was complete. All analyses and interpretations are mine. This chapter is the basis of a manuscript that will soon be submitted.

2.1 Introduction

Our interactions with the world are adaptively shaped by our ability to anticipate relevant sensory events and orient our attention towards them. While such attentional orienting is classically studied with regard to how we orient our attention in space (i.e. "spatial orienting"; Posner et al., 1980), the question of how we orient our attention in time (i.e. "temporal orienting") is equally relevant (Coull and Nobre, 1998; Nobre and Heideman, 2015, see also Chapter 1 in this thesis). Moreover, studies point to a synergistic interaction between spatial and temporal orienting in vision, whereby the influence of temporal expectations is particularly pronounced when combined with spatial expectations (Doherty et al., 2005; Rohenkohl et al., 2014). This indicates that knowing when a relevant visual event is going to happen, in addition to where, allows you to prepare optimally to perceive and act upon this event.

In human electrophysiology, considerable progress has been made in understanding the anticipatory neural dynamics that support attentional orienting in space. The preparatory attenuation of alpha (8 - 12 Hz) and beta (15 - 30 Hz) band oscillations in relevant sensory areas repeatedly come forward as a central substrate (Worden et al., 2000; Thut et al., 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Jensen and Mazaheri, 2010; Snyder and Foxe, 2010; Gould et al., 2011; Haegens et al., 2011; van Ede et al., 2011). However, a number of outstanding questions remain unaddressed. First, whereas spatial and temporal orienting have each received ample investigation on their own, the neural dynamics that occur when they join

forces remain largely unknown, despite good evidence for a synergistic relationship (O'Reilly et al., 2008a; Rohenkohl et al., 2014). Second, most previous studies investigating anticipatory neural dynamics in humans have focused on oscillations below 30 Hz. One study in non-human primates showed that temporal orienting of attention may additionally amplify higher-frequency gamma-band oscillations in visual cortex (Lima et al., 2011), which are suggested to reflect enhanced feedforward communication (Fries, 2015). It remains unclear whether visual gamma-band amplification can also be observed during temporal orienting in humans and, if so, whether such preparatory gamma modulations interact with spatial orienting.

Furthermore, recent studies have started exploring how attentional orienting and its neuronal underpinnings change over the lifespan (see Zanto and Gazzaley, 2014, and Erel and Levy, 2016, for reviews). One study in particular argued for diminished benefits of temporal information with ageing (Zanto et al., 2011), showing declines in both behavioural and neural markers of temporal orienting (but see also Chauvin et al., 2016). Diminished anticipatory alpha-band modulations in older adults have also been noted for orienting attention in space (Deiber et al., 2013; Hong et al., 2015; but see also Sander et al., 2012, Leenders et al., 2016 and Mok et al., 2016). Whether and how ageing also alters joint spatial-temporal orienting of attention, and the neural dynamics that support such orienting, remain unaddressed.

In the first experiment of this thesis, I sought to investigate the anticipatory oscillatory markers of combined spatial-temporal orienting and to test whether these decline with ageing. Younger and older adults engaged

in a joint spatial-temporal orienting task, requiring a difficult perceptual discrimination following a spatial-temporal cue (cf. Rohenkohl et al., 2014), while anticipatory neural dynamics were measured using MEG.

2.2 Methods

2.2.1 Participants

Twenty younger adults (13 males, 7 females; aged 24.1 ± 4.3 SD) and twenty-one older adults (9 males, 12 females; aged 66.9 ± 4.5 SD) completed the study. All but one participant were right-handed, according to self-report. All participants were healthy, had no history of neurological, psychiatric or vascular disease and had normal or corrected-to-normal vision. Data of three older adults had to be excluded due to large structural abnormalities visible on the structural magnetic resonance imaging (MRI) scan, technical problems during the recording and excessive artefacts in the MEG data, respectively. Data of two additional older adults had to be excluded because they performed below our cut-off threshold (<26) on the Montreal Cognitive Assessment (MoCA), which is indicative of a mild cognitive impairment (Nasreddine et al., 2005). A total of twenty younger adult datasets and sixteen older adult datasets (6 males, 10 females; aged 67.3 ± 5.0) remained for the analysis on which I report here. All participants gave informed consent, and the study was approved by the Central University Research Ethics Committee of the University of Oxford (MSD-IDREC-C1-2013-062 and MSD-IDREC-C1-2012-98) All participants were reimbursed for their time and travel expenses. The study

was run in three (younger adults) or four (older adults) separate sessions (see 2.2.4 Overview of sessions) on separate days. Sessions were completed in the following order: a training visit, an MEG session, an MRI session, and a clinical and neuropsychological evaluation (older adults only).

2.2.2 Clinical and neuropsychological evaluation

The older participants' data were collected as part of a larger "Cognitive Health in Ageing" research project. Therefore, in addition to the MEG study, older adults completed a set of demographic surveys, standardised clinical assessment questionnaires and neuropsychological tasks to assess psychological health and basic cognitive function (see Appendix 2.1). This session took approximately 90 minutes. After the exclusion of two older adults who scored below 26 on the Montreal Cognitive Assessment (MoCA; see Nasreddine et al., 2005), all participants in the final analysis were within two standard deviations of normative values across all clinical assessment and neuropsychological tests.

2.2.3 Experimental set-up

Whole-head MEG recordings were acquired at the Oxford Centre for Human Brain Activity using an Elekta NeuroMag (306 channel) MEG system. A magnetic Polhemus FastTrak 3D system (Vermont, United States) was used for head localisation. Relative positions of three anatomical landmarks (nasion, left and right auricular points) were measured in addition to relative positions of four head-position indicator coils.

MEG data were recorded in three (older adults) or four (younger adults) separate blocks of 12-15 minutes each, that were presented back to back with short breaks in between during which participants remained seated in the MEG chair. Data were sampled at 1000 Hz, and a bandpass filter between 0.03 and 300 Hz was applied during digitisation of the signal. ECG and horizontal and vertical EOG were recorded. In addition, eye movements were recorded with a video-based eye tracker with a sampling frequency of 1000 Hz (EyeLink 1000, SR Research, Ontario, Canada). Fiber-optic response pads (made at BRU, Aalto University, Helsinki) were used to collect manual responses.

Stimuli were presented using MATLAB (The MathWorks, Inc., Natick, MA) and Psychtoolbox v.3.0 for MATLAB (Kleiner et al., 2007). The stimuli were back projected (Panasonic PT D7700E, Panasonic, Osaka Japan) on a 58 x 46 cm screen placed 120 cm in front of the participant, with a spatial resolution of 1280 x 1024 and a refresh rate of 60 Hz.

2.2.4 Experimental procedure and stimuli

Overview of sessions

Both groups performed the same spatial-temporal orienting task, but there were some minor differences between the number of sessions and the type and amount of data collected for younger and older adults. Younger adults took part in three sessions: a behavioural training session, an MEG session involving 800 trials of the spatiotemporal orienting task (see MEG paradigm and procedure), and an MRI session in which an MRI T1 structural scan was obtained. Older adults took part in four sessions: a behavioural training visit,

a second session involving MEG with 600 trials[4] of the spatiotemporal orienting task and a resting-state recording (results of which will not be evaluated in this thesis), a third session including MRI T1 and T2 structural scans, a functional localiser scan, a resting-state scan and a diffusion tensor imaging scan (results of which will not be discussed in this thesis), and a fourth session involving an extensive clinical and neuropsychological evaluation (see 2.2.2 Clinical and neuropsychological evaluation).

MEG paradigm and procedure

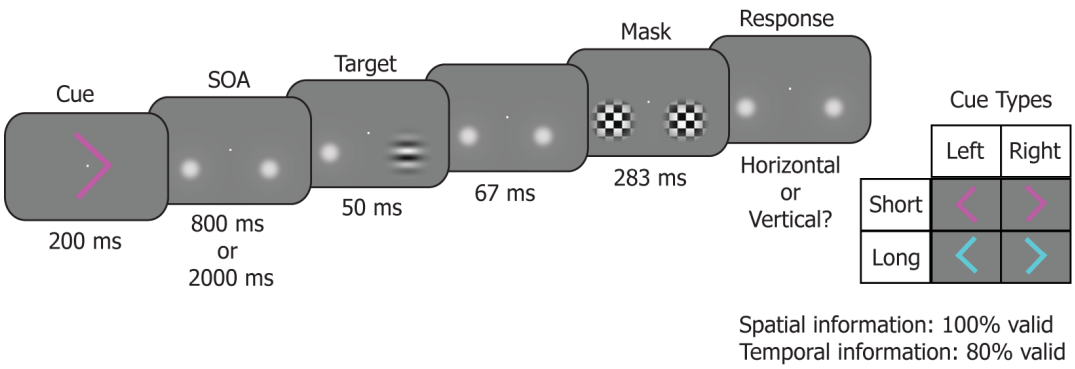


Figure 2.1 Experimental task. Coloured arrow cues predicted where (bottom left or right, 100% valid) and when (after a short or long interval: 800 or 2000 ms, 80% valid) subsequent targets were likely to occur. Targets consisted of horizontally or vertically oriented Gabor patches followed by a backwards mask. Target discrimination performance was equated across participants by means of an adaptive staircase procedure using only valid spatial-temporal cues. Participants responded to the orientation of the Gabor grating by making left and right index finger responses. Note that stimuli are shown larger than actual size on screen for display purposes.

4 Fewer trials were collected in older adults to reduce potential effects of fatigue. However, I note that the behavioural results do not change when the first 600 trials are included only.

The experimental task is depicted in Figure 2.1a. Participants had to discriminate the orientation (horizontal or vertical) of a peripherally presented target against a grey background while maintaining central fixation. Each trial started with a central fixation dot (diameter: 0.88° of visual angle) followed after 750 – 1200 ms by a foveally presented coloured arrow cue indicating where (left or right, 100% valid) and when (short cue/early: after 800 ms, or long cue/late: after 2000 ms, 80% valid) the upcoming target was likely to occur. Fully predictive spatial cues were used (100% valid) because Rohenkohl et al. (2014) showed that behavioural benefits of temporal expectation are restricted to targets occurring at attended spatial locations. Using only spatially valid cues enabled us to simplify the task and to focus on the neural dynamics of combined spatial-temporal attention.

Luminance pedestals positioned at 4.78° below the horizontal meridian and 3.38° from the vertical meridian (10% contrast) were presented throughout the experiment, indicating the two possible target positions. Cues were presented for 200 ms and consisted of blue or pink coloured arrows. Arrow direction indicated target location and the colour indicated when the target was most likely to appear. Colour-interval mappings were counterbalanced across participants. Both target locations and interval lengths were equiprobable and randomised across trials. Targets replaced the luminance pedestals for 50 ms. They were followed by a 283-ms backwards mask after an 117-ms target-mask SOA. Targets consisted of horizontally or vertically oriented Gabor patches with a diameter of 1.96° of visual angle and a spatial frequency of two cycles per degree of visual angle. The target contrast

was adjusted individually using the adaptive staircase procedure (see 2.2.4 MEG practice and staircase). Backward-mask stimuli were constructed by applying a Gaussian-vignette to the convolution of 100% square-wave gratings at the two possible target orientations. Responses were made with the left or right index finger, depending on target orientation. The response mapping was also counterbalanced across participants. A total of 800/600 (younger/older) trials were presented in randomised order (320/240 each for both the short and long valid temporal cues, and 80/60 each for the short and long invalid temporal cues), in three blocks of about 15 minutes each. Self-paced rest breaks were inserted every 20 trials.

MEG practice and staircase

The MEG session was preceded by a 90-minute practice and staircase session, taking place on a separate day (Kaernbach, 1991; see also Rohenkohl et al., 2014, for a full description of the procedure that was followed). The practice involved 5 blocks in which the task became increasingly difficult, by decreasing the time of target presentation up to the presentation time of 50 ms. Once participants were practised and comfortable with the task, an adaptive psychophysical staircase procedure was run to estimate the threshold contrast for each participant. Task difficulty was adjusted by titrating the Gabor patch contrast until discrimination was performed at 75% accuracy. The calibration was run over 120 trials. After the calibration, each participant's performance was inspected to see if a 75% asymptote was

reached. During the practice and staircase session, all intervals were cued with 100% validity.

During the MEG session, which took place within one week after the practice session, participants performed a second practice consisting of 50 trials, using similar cue probabilities as used in the main MEG task. Participants were told that timing cues would now be correct in the majority of trials, but that they should still try to use the cued spatial and temporal information to predict where and when targets would occur. The MEG session, including set up and practice, took approximately 100 minutes for each participant.

2.2.5 Behavioural analysis

The behavioural data were analysed using MATLAB, and statistics were performed in SPSS version 22 (IBM Corp. Armonk, NY). The MEG behavioural data were analysed with respect to perceptual sensitivity (*d'*)[5] values and reaction times (RTs). Perceptual sensitivity was calculated according to the following formula:

$$d' = z[PCH] + z[PCV]$$

z[PCH] and z[PCV] correspond to the inverse normal (z-score) transformations of the participants' proportions of correct responses to

[5] Although *d'* is generally used to reflect Z(Hits) - Z(False alarms), it can also be quantified in discrimination tasks (see Smith & Wolfgang, 2007; Macmillan & Crewman, 2005). *d'* has the benefit over regular accuracy that it also models response biases (e.g. being more likely to report horizontal irrespective of the actual target).

horizontal and vertical stimuli (see Rohenkohl et al., 2014). In cases where either of those values was equal to 0, the value was replaced with 0.5/N; and if the value was equal to 1, it was replaced by (N-0.5)/N, where N reflects the number of trials with a horizontal or vertical stimulus for that condition, thereby penalising for conditions with fewer trials (i.e. conditions with invalid temporal cues). Trials with RTs smaller or larger than a participant's mean RT ± 3 times the standard deviation were excluded from the behavioural analysis.

2.2.6 MEG analysis

Pre-processing and artefact rejection

MEG data analyses were performed using custom-written MATLAB code, the in-house OHBA Software Library (OSL) version 1.4 and Fieldtrip (Oostenveld et al., 2011). First, channels containing excessive noise were identified manually. Subsequently, spatiotemporal signal space separation (TSSS) and movement compensation were applied. Neuromag's MaxFilter software separates signals arising from inside and outside the helmet and thereby minimises extra-cranial noise (Taulu et al., 2004). The temporal extension of this signal space separation method removes interference from nearby sources (Taulu and Simola, 2006). In addition, MaxFilter compensates for the effects of head movement by using continuous head position measurements.

After using MaxFilter, the data were checked manually to ensure no problems occurred during the MaxFilter stage and down-sampled to 250 Hz. A 0.1-Hz high-pass filter was applied to the data to remove low-frequency drift. Because most datasets included periods with excessive noise recorded during

rest-periods, the data were epoched before Independent Component Analysis (ICA) was performed, thereby ensuring that these periods with excessive noise would not negatively impact the ICA. ICA was used to reject artefacts associated with eye blinks, eye movements and heartbeat. All components were inspected manually before removing them from the data. After ICA, the data were inspected manually to remove any remaining artefacts. Trials with eye blinks occurring during target presentation were excluded as well. On average 12% of trials were removed from the analysis. Trials with incorrect responses were not excluded from the MEG analysis because I was mainly interested in the anticipatory period before target appearance, i.e. before responses were being made[6]. Before analysis of high-frequency (gamma) oscillations, Fieldtrip's visual artefact rejection function showing summary statistics was run on data bandpass filtered between 40 - 100 Hz, to remove any remaining artefacts that were specific to the gamma-range.

Region-of-interest selection based on event-related fields

To avoid overlap with the main time period of interest (0 - 800 ms after cue onset) or main measure of interest (time-frequency data between 4 - 100 Hz), visual regions-of-interest (ROIs) were selected based on target-evoked ERFs. ERFs were calculated separately for all four combinations of target location and interval (left-short, right-short, left-long and right-long). ERFs were baseline-corrected with the average of the window 100 ms before target

[6] I have repeated the analysis using trials with correct responses only. Results were comparable to the results reported here for all trials.

presentation (700 - 800 ms after the cue for targets appearing after a short interval and 1900 - 2000 ms for targets appearing after a long interval). Data for the planar gradiometer pairs were combined, resulting in a 102-channel combined planar gradiometer map in sensor space. Subsequently, ERFs for short and long targets were aligned at target presentation and averaged separately for left and right targets. Finally, a left-right difference ERF was calculated for each participant and averaged across all participants. This difference ERF topography was plotted 200 - 400 ms after target presentation, where the difference was maximal. Based on the topography (see Figure 2.3) six (symmetric) channel pairs were selected on the left (MEG1632+1633; MEG1642+1643; MEG1912+1913; MEG1922+1923; MEG1942+1943; MEG2042+2043) and on the right (MEG2032+2033; MEG2312+2313; MEG2322+2323; MEG2342+2343; MEG2432+2433; MEG2442+2443). Channel pairs were selected based on the grand average of all participants, but are also shown separately for younger and older adults in Figure 2.3 to demonstrate that channels with maximum lateralised ERFs were the same for both groups.

Time-frequency analysis

Time-frequency analysis was performed using a short-time Fourier Transform, separately for lower (4 - 40 Hz) and higher (40 - 100 Hz) frequencies. For both analyses, I used a fixed sliding time window of 300 ms that was advanced over the data in steps of 25 ms. For the lower frequencies, I used a Hanning taper, and estimated power between 4 and 40 Hz, in 0.5 Hz

steps. For the higher frequencies, I used a multi-taper approach (Percival and Walden, 1993) using ± 8 Hz spectral smoothing, and estimated frequencies between 40 and 100 Hz, in steps of 1 Hz.

For both lower and higher frequencies, the power spectra were averaged separately over trials for each cue condition. The power time series in the planar gradiometer pairs were then combined (Cartesian sum), resulting in a 102-channel combined planar gradiometer map in sensor space. All relevant time-frequency contrasts were computed as the average of the selected ROI channels (see 2.2.6 Analysis of event-related fields for region of interest selection) and subsequently averaged for ROIs contralateral and ipsilateral to the cue direction. All contrasts were computed as relative contrasts. For example, the contrast between short vs. long cues was calculated as follows (separately for contralateral and ipsilateral channels):

$$((\text{Short Cue} - \text{Long Cue})/(\text{Short Cue} + \text{Long Cue})) \times 100$$

Contrasts of interest were evaluated during the early interval (0 - 800 ms). This is the time period during which temporal expectations differ between cueing conditions. After the first interval passes, it becomes evident that the target will appear after a long interval irrespective of the initial cue, so temporal cueing benefits dissipate. Differences between conditions were investigated by means of cluster-based non-parametric permutation testing in Fieldtrip using 1000 permutations with a cluster alpha of 0.05. This approach circumvents the multiple-comparisons problem (Maris and Oostenveld,

2007). The resulting one-sided p-values are reported as two-sided p-values (i.e. they were multiplied by a factor of 2).

2.2.7 Analysis of eye-tracking data

Eye-tracking data were absent or not usable for six younger adults and two older adults. Therefore, data from the remaining fourteen younger adults and fourteen older adults were included in the eye-tracking analysis. Eye-tracking analysis was performed on the x-position eye-tracker data (i.e. gaze in the horizontal plane) during the early interval, recorded in Volt as a separate channel on the MEG system. All trials that were rejected during pre-processing (see 2.2.6 Pre-processing and artefact rejection) were rejected from the eye-tracking analysis as well. Participant averages were calculated separately for all four combinations of cued target location and interval (left-short, right-short, left-long and right-long) and averaged separately for younger and older adults. Data were baselined using the 500-ms window before cue presentation.

2.3 Results

Magnetoencephalographic brain activity was recorded in healthy human volunteers, while they engaged in a joint spatial-temporal orienting task (see Figure 2.1). Coloured arrow cues indicated where (left or right, 100% valid) and when (after 800 ms/early or after 2000 ms/late, 80% valid) upcoming visual targets were most likely to be presented, and participants indicated the

orientation (horizontal or vertical) of this target by making a left or a right button press.

2.3.1 Behavioural results

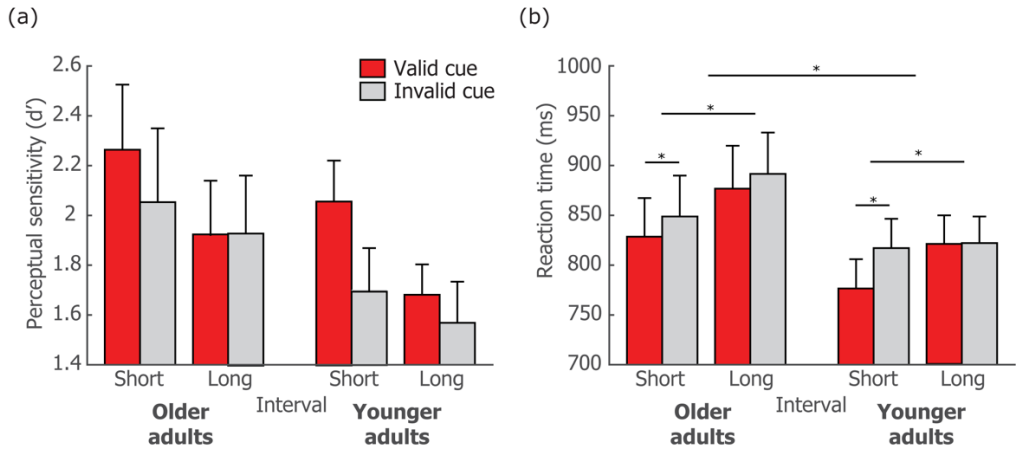


Figure 2.2 Behavioural results. Results are shown for (a) perceptual sensitivity (*d'*) and (b) reaction time (RT). Behavioural results are shown separately for older and younger adults, for each cue type (valid/invalid) and interval length (short/long). Error bars show standard error of measurement (SEM). Asterisks indicate statistically significant effects.

Behavioural results for perceptual sensitivity (*d'*) and reaction time (RT) are shown in Figure 2.2a and Figure 2.2b. To investigate the difference between valid and invalid temporal cues (spatial cues were always valid), i.e. the "temporal validity effect", a repeated-measures analysis of variance (ANOVA) was performed, with the within-subject factors Cued Interval (short or long: 800 or 2000 ms) and Validity (valid or invalid) and the between-subjects factor Age Group. For *d'*, a main effect of Cued Interval ($F(1,34) = 9.33$, $p = .004$, partial $\eta^2 = 0.22$) and a main effect of Validity ($F(1,34) = 7.39$, $p = .01$,

partial η^2 = 0.18) were found. The interaction between Cued Interval and Validity did not reach significance ($F(1,34) = 3.51$, $p = .07$, partial $\eta^2 = 0.09$). No main effect of Group ($F(1,34) = 1.36$, $p = .25$, partial $\eta^2 = 0.04$) or three-way interaction with Group ($F(1,34) = 0.02$, $p = .90$, partial $\eta^2 = 0.00$) was present.

For RT, I found a main effect of Cued Interval ($F(1,34) = 23.60$, $p < .0001$, partial $\eta^2 = 0.41$), a main effect of Validity ($F(1,34) = 19.77$, $p < .0001$, partial $\eta^2 = 0.37$) and an interaction between Cued Interval and Validity ($F(1,34) = 7.27$, $p = .011$, partial $\eta^2 = 0.18$). There was again no main effect of group[7] ($F(1,34) = 1.36$, $p = .25$, partial $\eta^2 = 0.04$), but there was a three-way interaction between Cued Interval, Validity and Group ($F(1,34) = 4.17$, $p = .049$, partial $\eta^2 = 0.11$). Pairwise t-tests revealed that for both older and younger adults a validity effect was present for the short (older: $t(15) = 2.54$, $p = .02$, Cohen's $d = -0.63$; younger: $t(19) = 6.13$, $p < .0001$, Cohen's $d = -1.37$), but not for the long interval (older: $t(15) = 1.73$, $p = .11$, Cohen's $d = -0.43$; younger: $t(19) = 0.17$, $p = .87$, Cohen's $d = -0.04$). An independent samples t-test showed that the magnitude of the temporal validity effect for short cues was larger in younger, than in older adults ($t(34) = 2.09$, $p = .045$, Cohen's $d = 0.70$).

To summarise, for both *d'* and RT, performance was better following valid, compared to invalid temporal cues. For RT, these performance benefits were present following short, but not following long intervals. Based on these findings, I expected the largest neural differences due to temporal

[7] Note that although no main effect of group was present for either *d'* or RT, both measures were numerically higher in older adults, which may hint at older adults possibly being more conservative and relying on a slightly different speed-accuracy trade-off.

expectations (i.e., in the contrast between short and long cues) to occur in the early interval, and therefore focused on this interval in the MEG analysis.

2.3.2 MEG results

Region-of-interest selection

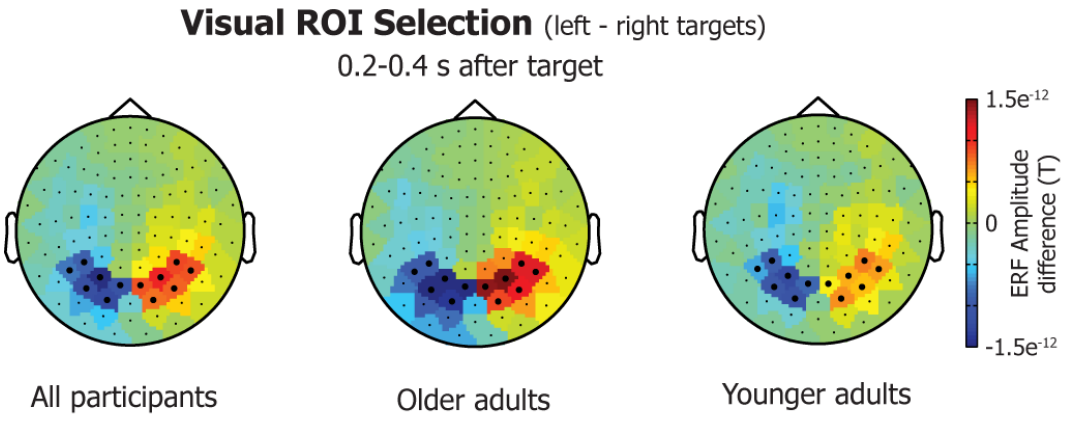


Figure 2.3 Region-of-interest selection. Topographies for the amplitude difference in the ERF 200 - 400 ms after target presentation in the left vs. right visual field (averaged over both short and long interval lengths). The six left and six right occipital-parietal channels that were used as ROIs throughout the subsequent MEG analysis are marked in black. Channels were selected based on visual inspection of the ERF grand average for all participants. Separate topographies for older and younger adults show that the largest ERF amplitude was found in the same channels for both groups.

Figure 2.3 shows the regions-of-interest (ROIs) that were used to extract left and right (and thus contra- and ipsilateral) visual activity. The left and right occipital-parietal ROIs were selected after visual inspection of event-related field (ERF) topographies for the difference between left and right targets in the interval between 200 and 400 ms post-target. ROI selection was

performed on the grand average across all participants. The same sensors would have been selected based on either the younger or older adult averages in isolation.

Spatial orienting effects

Before investigating temporal orienting effects, or the combined effects of spatial-temporal orienting of attention, I first wanted to ensure that I could replicate oscillatory effects that previously have been found for spatial orienting of attention in younger adults. For this purpose, I focused on lateralisation in the alpha and beta band in the period following the cue. ROIs that were used to extract left and right (and thus contra- and ipsilateral) visual activity are shown in Figure 2.3. Figure 2.4a zooms in on the spatial orienting effect by showing the difference in power (across time and frequency) between trials in which the cue was contralateral minus ipsilateral to the selected ROIs (collapsed across both ROIs and short and long temporal cues[8]). To stay consistent with all further analysis, I focused exclusively on the early preparatory interval (0 - 800 ms). Results are shown separately for older (top plot) and younger (middle plot) adults, as well as the difference between these groups (bottom plot). Significant clusters (outlined in white, corrected for multiple comparisons across time and frequency; Maris and Oostenveld, 2007) were found in these time-frequency plots for the anticipatory lateralisation for both older and younger adults (older adults: two-sided cluster p = .002;

[8] I collapsed across both cue types here, because I first wanted to establish a pure spatial orienting effect. However, I note that results look nearly identical for short and long cues.

younger adults: two-sided cluster p = .002), starting from approximately 300 ms after cue presentation, in a frequency band that spanned roughly from 5 to 25 Hz (i.e. encompassing both alpha and beta bands). These results replicate well known patterns previously reported for spatial orienting of attention in younger adults (Worden et al., 2000; Thut et al., 2006; Kelly et al., 2009; Gould et al., 2011; Händel et al., 2011; Deiber et al., 2013) and additionally demonstrate that this pattern is similar for older adults (see also Sander et al. 2012; Leenders et al., 2016). In fact, the bottom plot shows that, in this data, this lateralisation was even stronger in older than in younger adults (two-sided cluster p = .030), with a significant group-effect cluster that localises to the higher portion within this frequency range.

Associated topographies of the spatial lateralisation effect (i.e. left vs. right cues) are shown in Figure 2.4b, averaged over frequencies between 8 - 24 Hz and between 300 - 650 ms post-cue. Topographies are plotted up to 650 ms to reflect only the interval that is purely 'preparatory', provided our sliding time window of 300 ms (see 2.2.6 Time-frequency analysis). Note that topographies look highly similar in both groups and that the group difference (stronger lateralisation in older adults) also appears to originate, at least in large part, from the selected posterior channels.

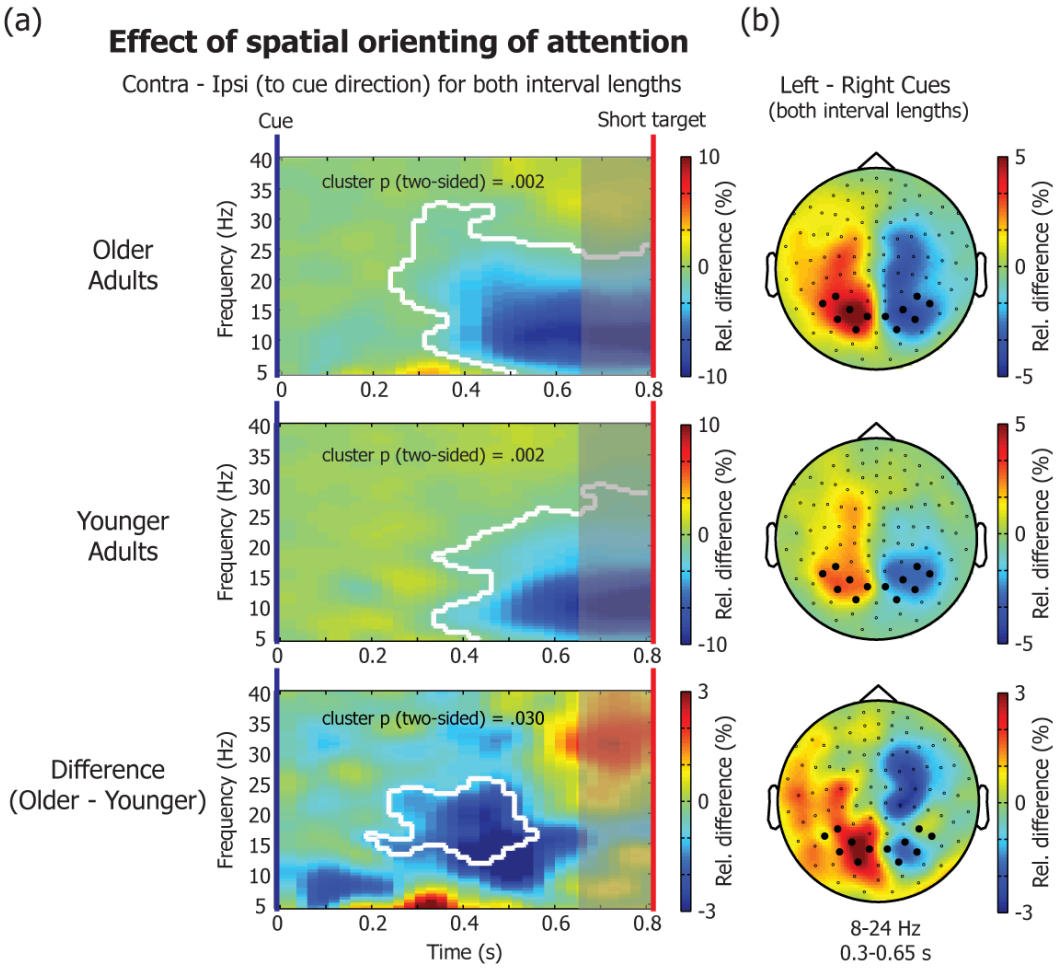


Figure 2.4 MEG results for the effect of spatial orienting of attention. Time-frequency representation (TFR) plots for older adults, younger adults and the difference between both groups (older-minus-younger), for contralateral ROI channels minus ipsilateral ROI channels (to the direction of the cue), averaged over both cue-target interval lengths. Results are shown for the short interval (0 - 800 ms) only. The colour scale indicates a relative increase or decrease. Significant clusters are outlined in white. The shaded area indicates a time period that cannot be considered purely 'preparatory' because target-evoked activity might bleed in. (c) Topographies for the left-minus-right cue contrast (averaged over both interval lengths), separately for older adults, younger adults and the difference between both groups (older-minus-younger). Topographies are averaged over frequencies between 8 - 24 Hz and for a time window between 300 - 650 ms.

Temporal and spatial-temporal orienting effects

I next separated the trials further by also separating "short" and "long" temporal cues. I again focused on the early interval (0 - 800 ms post-cue). Figure 2.5a shows the difference between short- and long-cue trials in this early interval, separately for contralateral and ipsilateral ROIs, as well as for their difference (i.e. contra (short – long) minus ipsi (short – long); i.e. the spatial-temporal interaction effect).

Focusing on the lower frequencies (bottom panels in Figure 2.5a) for the combined groups (top row), I observed an effect of temporal orienting of attention (i.e. short – long cues) for the ipsilateral ROI (two-sided cluster p = .022), with a contralateral effect going in the same direction, but not reaching significance. When comparing the effect for both groups, it becomes clear that this effect of temporal orienting was present in younger adults only, now reaching significance in both contralateral (two-sided cluster p = .026) and ipsilateral (two-sided cluster p = .010) ROIs. Younger adults showed a bilateral power decrease (desynchronization), while no significant effects were found in older adults. This difference between older and younger adults was also reflected in the older-minus-younger contrast over both contralateral (two-sided cluster p = .036) and ipsilateral (two-sided cluster p = .036) ROIs. These effects are also visible in the topographies for the short-minus-long cue contrast, as depicted in Figure 2.5b, averaged for frequencies between 8 - 28 Hz. The bilateral attenuation in low-frequencies found in younger adults is clearly reflected here, while this pattern again appeared to be absent in older adults A hint of a spatial-temporal interaction in the alpha-band (i.e. a stronger

lateralisation following short compared to long cues, or, analogously a stronger temporal modulation contralateral compared to ipsilateral) might be seen in younger adults, starting from 600 ms, but since this effect overlapped with the window which could be contaminated by target-evoked activity, we cannot be certain if this effect is truly anticipatory. Younger adults thus demonstrated a clear effect of temporal orienting in the lower frequencies. However, since this effect was largely independent of concurrent spatial expectations, it may not be key to explaining joint spatial-temporal orienting effects.

Interestingly, however, when focusing on the higher frequencies (upper panels in Figure 2.5a), I observed, across the whole group, a temporal attention modulation that appears specific in time as well as in space. I found significant short-minus-long clusters both for the ROI contralateral to the cue direction (two-sided cluster $p = .032$) and for the contra-minus-ipsi difference (two-sided cluster $p = .026$), indicating larger gamma power in this early interval following short, compared to long cues. When investigating this effect in both groups separately, this effect appeared largely exclusive to older adults. A significant cluster was found for this age group, for the ROI contralateral to the cue direction (two-sided cluster $p = .042$). The topographies (Figure 2.5b, upper topography plots) confirmed that the pattern of gamma amplification occurred most strongly in contralateral posterior channels (again in line with an interaction between temporal and spatial orienting). In younger adults no significant clusters were observed, and anticipatory gamma modulations were either much weaker, noisier, or not present at all. Nevertheless, while the time-

frequency plots revealed neither clear signs of anticipatory gamma modulations nor significant high-frequency clusters in this age group, it is still noteworthy that, when considering the topographies, the data in the younger adults appear to hint at a possible modulation with similar spatial-temporal nature as observed in the full group as well as in the older adults.

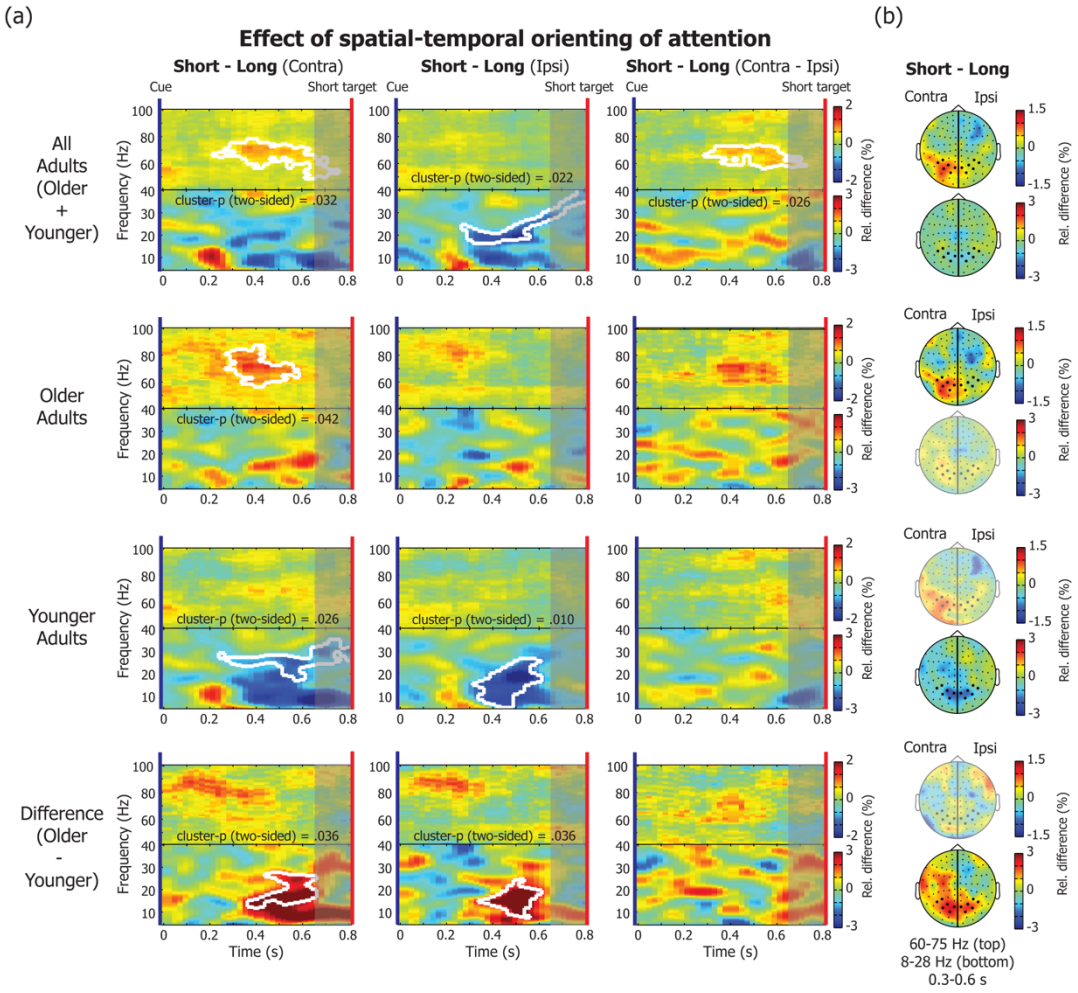


Figure 2.5 MEG results for the effect of spatial-temporal orienting of attention. (a) Time-frequency representation (TFR) plots showing the short-minus-long cue contrast for all participants (older-plus-younger), older adults, younger adults and the difference between groups (older-minus-younger), separately for ROI channels contralateral (first column) and ipsilateral (second column) to the cue direction and for the contra-minus-ipsi contrast (third column). Results are shown for the short interval (0 - 800 ms) only. The colour scale indicates

a relative increase or decrease. Significant clusters after nonparametric cluster-based permutation testing are outlined in white. The shaded area indicates a time period that cannot be considered purely 'preparatory' because target-evoked activity might bleed in. (b) Topographies for the same short-minus-long contrast, for contralateral (shown on left) and ipsilateral (shown on right) channels. Topographies display activity averaged over frequencies between 60 - 75 Hz (top) and 8 - 28 Hz (bottom) and for a time window between 300 - 600 ms after cue presentation.

2.3.3 Gaze analysis

I evaluated the eye-tracking data to investigate whether the spatial-temporal orienting effects may have been driven by gaze differences between conditions (or groups), i.e. by more gaze shifts in the direction of the cued target location after short, compared to long cues. The left graph in Figure 2.6a shows the average x-position over time for both older (top) and younger (bottom) adults over the course of the short interval, for all cue conditions, with the shaded area reflecting the 95% confidence interval. The graph on the right shows the average left-minus-right cue difference over time, presented separately for short and long cues. Although these graphs show a tendency for both younger and older adults to gaze toward the anticipated target location, this tendency was highly stereotyped and showed no difference between short and long cues (indeed, the 95% confidence interval for this difference always overlapped with the zero line; see Figure 2.6a, right panel). As such, these data suggest that, while I cannot exclude that differential gaze patterns may have accounted for some of the spatial orienting effects, they did not account for any of the

reported spatial-temporal orienting effects – which is a central point of the current study.

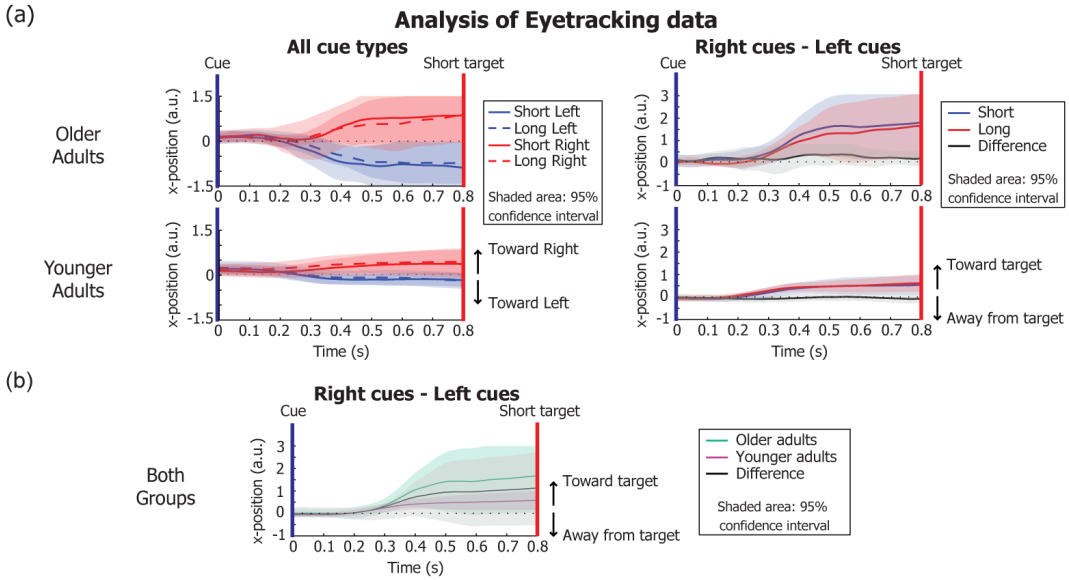


Figure 2.6 Analysis of eye-tracking data. (a) Data are shown for older (top) and younger (bottom) adults separately. The left side shows data for all cue types. The y-axis shows the x-position of the eye tracker, with 0 being completely centre. The right side shows data for the size of the difference in x position between left and right cues, for both the short and the long interval. All data are plotted with the 95% confidence interval (shaded area). Note that the (grey) confidence interval of the difference line overlaps with the zero crossing, indicating that there was no significant difference in the size of horizontal eye movements between short and long cues. (b) Results for older and younger participants, averaged across short and long cues, for the difference between left and right cues. Note that the (grey) confidence interval of the difference line overlaps with the zero crossing, indicating that there was no significant difference in the magnitude of horizontal eye movements between older and younger adults.

Returning to the spatial gaze shift, I was concerned that the stronger lower frequency lateralisation observed with spatial cueing in the older adults

may have been driven by a larger spatial gaze bias in this group. I therefore decided also to evaluate the difference in spatial gaze bias between older and younger adults (see Figure 2.6b). As before, although there seems to be an optical difference between younger and older adults, this difference never reached statistical significance (i.e. the confidence interval of this difference overlaps with 0 for all tested time points).

2.4 Discussion

In this experiment I investigated anticipatory neural dynamics related to spatial-temporal orienting of attention using MEG, in both younger and older adults. In both age groups, I replicated well known effects of spatial orienting by showing lateralisation of posterior alpha and beta oscillatory power (Worden et al., 2000; Thut et al., 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Jensen and Mazaheri, 2010; Snyder and Foxe, 2010; Gould et al., 2011; Haegens et al., 2011; van Ede et al., 2011). In contrast to several previous reports, which I discuss below, this spatial modulation was not attenuated but, instead, enhanced in the older adults. In contrast, a pure temporal orienting effect involving a bilateral suppression of alpha and beta oscillations appeared exclusive to younger adults. Finally, the joint forces of spatial and temporal expectations resulted in a temporally and spatially specific amplification of anticipatory gamma-band oscillations in the older adults.

2.4.1 Neurophysiology of spatial-temporal orienting

Spatial and temporal orienting of attention are typically studied in isolation and have each been associated with preparatory modulation of alpha and beta oscillations (spatial: Worden et al., 2000; Thut, 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Jensen and Mazaheri, 2010; Snyder and Foxe, 2010; Gould et al., 2011; Haegens et al., 2011; van Ede et al., 2011; temporal: Rohenkohl and Nobre, 2011; van Ede et al., 2011; Zanto et al., 2011). Such attenuations are generally attributed to a preparatory increase in neuronal excitability (Pfurtscheller and Lopes da Silva, 1999; Jensen and Mazaheri, 2010; Haegens et al., 2011; Jenkinson and Brown, 2011), and have also been proposed to relate to feedback processes (Buffalo et al., 2011; Bastos et al., 2015). In addition to replicating such anticipatory patterns by and large, one particular aim of this experiment was to investigate interactions between both forms of attentional orienting. Rohenkohl et al. (2014) showed a strong synergy at the behavioural level between temporal and spatial orienting (see also e.g. Doherty et al., 2005; O'Reilly et al., 2008a). Such a synergy must be supported by anticipatory neural modulations that are both spatially and temporally specific. To my surprise, modulations in the alpha and beta-bands did not show such clear interactions in the current study (in contrast to van Ede et al., 2011). Instead, I observed a complementary anticipatory modulation in the gamma-band in older adults that was both spatially and temporally specific, which I discuss further below.

2.4.2 Anticipatory gamma dynamics

The interaction between spatial and temporal orienting was found in the gamma band, expressed in a preparatory amplification of 60 - 75 Hz oscillations in contralateral parietal channels, with stronger gamma power in the early interval when targets were expected to occur early. When breaking this down by age group, this was only clearly evident and significant in the older adult group. Only the topographies hinted at a possibly similar (albeit much weaker) modulation in the younger adults.

Anticipatory modulations of gamma-band activity related to temporal orienting have previously been reported by Lima and colleagues (2011) in a study with non-human primates. They showed anticipatory enhancement of gamma in primary visual cortex (V1) following temporal cues when monkeys expected a task-relevant fixation cross change in time. In contrast to my study, however, Lima and colleagues investigated temporal gamma modulations without varying spatial expectations. The spatial specificity of the effect could not, therefore, be evaluated in their study.

In humans, reports of preparatory gamma modulations are rare (but see van Ede et al. 2014) and such modulations have not previously been reported in the context in which both temporal and spatial orienting are present concurrently. Van Ede and colleagues (2014) focused on spatial attention in the somatosensory modality in younger adults and found small but significant lateralised gamma-band power increase over somatosensory areas contralateral to the cued side, which was similar in range, although much weaker, than gamma modulations during sustained stimulus processing. Here

I report a similar effect in human visual cortex and, moreover, show that this is also temporally specific.

There are at least three possible reasons why most previous studies may not have found preparatory modulations of gamma-band activity. First, a constant, driving, visual input might be necessary for detectable gamma-band modulations to occur, like the continuously visible luminance pedestals in the current study, or the constant grating in Lima et al. (2011). Such an effect may reflect the pre-target instantiation (or amplification) of a feedforward communication channel (in line with e.g Fries, 2009, 2015; Bastos et al., 2015; possibly enabled through the driving input of the pedestal), such that when the target comes in, it can efficiently be broadcasted to downstream areas. Second, previous studies simply might not have looked at higher frequencies, either because they focused on well-described modulations of lower alpha and beta-band oscillations, or because they were based on electroencephalography (EEG) instead of MEG. Third, it might be the case that preparatory gamma modulations are strongest when information about both space and time can be used to guide attention to relevant perceptual events, while most previous studies focused on either spatial or temporal orienting alone. Moreover, given that the spatial-temporal gamma modulations were only clearly evident in the older adults, such a modulation may be missed or be absent in studies that focus exclusively on younger adults. Clearly, further research is necessary to elucidate the exact conditions under which preparatory effects of spatial-temporal orienting occur in the in gamma band. In future studies, it will be important to investigate if these spatial-temporal anticipatory gamma

modulations are truly limited to older adults (and therefore might reflect some form of compensatory activity with ageing), or whether these modulations can also be reliably revealed in younger adults, for example with larger sample sizes.

These results also highlight that when gamma oscillations are amplified, alpha and beta oscillations do not always concurrently decrease in power. This is also in line with research by Scheeringa and colleagues (2011), who showed in a combined EEG-fMRI study that gamma-band oscillations correlated with the BOLD signal independently of alpha- and beta-band oscillations. Other studies also suggest that alpha/beta and gamma modulations need not always go hand in hand, but may sometimes occur independently of each other (e.g., Bauer et al., 2014; van Ede et al., 2014; Shaw et al. 2017).

2.4.3 Spatial-temporal orienting and anticipatory brain dynamics in ageing

Older adults are usually found to maintain the ability to orient attention to specific spatial locations to improve performance (Zanto and Gazzaley, 2014; Erel and Levy, 2016). However, anticipatory alpha modulations with such attentional orienting are sometimes found to be reduced (Deiber et al., 2013), and some reports suggest that attentional deployment in older adults might not be reliant on alpha power lateralisation at all (Hong et al., 2015).

Contrary to these findings, and more in line with the current results, a recent study using a lateralised working-memory task (Leenders et al., 2016) showed similar alpha lateralisation in younger and older adults during the

attentional cue period preceding a to-be-remembered sample array. Likewise, Mok et al. (2016) recently found largely preserved alpha and beta lateralisation in older adults with a different working-memory paradigm that used retro-cues to orient attention to specific locations of items maintained in working memory. Sander et al. (2012) found lateralised alpha power in older adults for medium, but not high memory loads during a retention interval. These studies show that, under some circumstances, older adults show well preserved lateralised low-frequency (alpha and beta) activity when directing their attention to one cued hemifield, at least for short periods of time. The current study suggests that in some cases this lateralisation might be even stronger in older adults, at least in the beta band. There are at least two possible explanations for this effect. While this may reflect a true amplification of this modulation in older adults, an alternative explanation is that this modulation is more diffuse in its spectral distribution in older adults — consistent with the group difference peaking in the beta band range (see Figure 2.4).

The degree to which the benefits of temporal orienting are affected by ageing has also been a matter of recent debate. Zanto and colleagues (2011) have shown that beneficial effects of temporal information may decline with ageing, using a variety of cued temporal-orienting tasks. Both behavioural performance and preparatory EEG modulations were affected, suggesting that the effects of temporal cues diminish with ageing. Contrary to these findings, Chauvin and colleagues (2016) recently showed preserved temporal orienting abilities in healthy ageing using speeded and non-speeded behavioural tasks.

Both Zanto et al. (2011) and Chauvin et al. (2016) used central targets and central cues. However, as shown by Rohenkohl et al. (2014), the strongest effect of temporal expectations can be found when both space and time are relevant and interact, and the task to be performed is perceptually challenging. In this experiment, older adults were clearly able to benefit behaviourally from temporal cues. Moreover, when considering the joint spatial-temporal orienting effect (i.e. the gamma band modulation), this effect appeared restricted to older adults. It will be interesting to address in future research whether, for example, synergistic behavioural effects observed previously in young adults (Rohenkohl et al., 2014) are equally well preserved in ageing (as our MEG data suggest).

This study revealed that different neural dynamics associated with attentional orienting may be differentially sensitive to ageing, with some effects appearing exclusively in younger adults (bilateral alpha modulation with temporal orienting), whereas others appear most clearly or even exclusively in older adults (spatial-temporal gamma modulation). In future work it will be interesting to assess to what extent these changes with age must be attributed to changes in physiology, different strategies, or compensatory processes.

2.4.4 Conclusions

The main insights from this first study are threefold. First, when visual spatial and temporal attention joined forces, I found certain anticipatory neural dynamics (i.e. in the gamma band) that were sensitive to joint spatial-temporal

expectations, while others (i.e. in the alpha and beta bands) were mainly sensitive to spatial and temporal expectations by themselves, irrespective of concurrent expectations in the other dimension. Second, I demonstrated the involvement of anticipatory neural dynamics in the gamma band in older humans and showed that it is possible to study this non-invasively using MEG recordings. Finally, I found that different anticipatory neural dynamics are not always diminished, but sometimes are even more pronounced in older adults.

Chapter 3: Diminished behavioural facilitation and anticipatory neural dynamics of temporally cued motor preparation in Parkinson's disease

Patients with Parkinson's disease (PD) have been argued to suffer from deficits in temporal processing and in the anticipation and voluntary preparation of future actions. Based on this, I hypothesised that patients with PD may also have a diminished ability to use predictive temporal cues to voluntary prepare for actions at their anticipated times, and that this would be mediated by diminished neural signatures of temporal preparation for upcoming response signals and anticipated actions. To address this, I used MEG to investigate anticipatory neural dynamics in a temporally cued Go/NoGo task, in eighteen PD participants off dopaminergic medication and eighteen healthy control participants. Combined auditory-visual cues indicated with 80% validity when upcoming targets would appear (early: after 1.2 s, or late: after 2.2s). Participants had to respond to a majority of green "Go" targets (80% of trials), but to withhold their response when red "NoGo" targets would appear (20% of trials). The response hand was counterbalanced between blocks. The behavioural results show that while a benefit of valid, compared to invalid, temporal cues was present in both groups for the short interval, this temporal validity effect was significantly diminished in PD participants. Other measures of performance were equivalent between groups. For the MEG data I first investigated the frequency spectra for each group, independently of condition. This analysis indicated some potential peak frequency differences between the groups, whereby PD participants showed, on average, a lower alpha peak frequency. I therefore contrasted power following short vs. long cues across the whole frequency spectrum in a predefined anticipatory window of interest. In this window, control participants showed an anticipatory decrease of alpha- and beta-band power, which was stronger when targets were expected early, compared when targets were only expected later. This anticipatory modulation was significant in contra- and ipsilateral motor ROIs as well as in a visual ROI. In comparison, no significant differences were found in the PD participants. Moreover, when directly comparing groups, control participants showed a significantly stronger anticipatory alpha/beta decrease in the contralateral motor ROI and in the visual ROI. When subsequently evaluating these results also across time, there was also a significant anticipatory alpha/beta suppression in the PD group, which occurred relatively late in the anticipatory window of interest in the contralateral motor ROI. These results suggest that both behavioural effects of temporal orienting and concurrent anticipatory modulations of oscillatory brain dynamics are diminished, but not absent, in PD participants compared to healthy age-matched control participants.

3.1 Introduction

Temporal orienting of attention based on learned associations between temporally informative cues and targets is a key aspect of dynamic proactive cognition. Such learned associations allow us to prepare optimally to act upon anticipated events. Although the study of temporal and spatial-temporal orienting remains largely restricted to healthy humans (e.g. Doherty et al., 2005; Schoffelen et al., 2005; van Elswijk et al., 2007; van Ede et al., 2011; Zanto et al., 2011; Rohenkohl et al., 2014), it is also important to consider whether and how this key cognitive capacity might change with neurodegenerative diseases like Parkinson's disease (PD), in which it is potentially compromised.

Previous research suggests that PD patients are impaired in a range of explicit timing tasks (e.g. Artieda et al., 1992; Pastor et al., 1992; Freeman et al., 1993; Lange et al., 1995; O'Boyle et al., 1996; Harrington et al., 1998; see Almeida, 2012 and Jones and Jahanshahi, 2014 for reviews). Explicit timing tasks generally involve either perceptual or motor timing. In perceptual timing tasks, individuals estimate or compare temporal attributes of stimuli, such as when comparing stimulus durations. Motor timing tasks require performing actions according to temporal intervals, such as when reproducing a duration with a motor response or synchronising tapping to a rhythm and continuing to tap after the external stimuli stop (Coull et al. 2011, Jones & Jahanshahi, 2014). Impairments in these types of tasks are especially pronounced when tested "off" medication, and generally improve after dopaminergic treatment

(Artieda et al., 1992; Pastor et al., 1992; O'Boyle et al., 1996). Deficits in temporal processing in PD are therefore likely to be linked to dopamine depletion in the basal ganglia, which is a hallmark of the disease. Indeed, basal ganglia-cortical networks have been implicated in temporal processing (Buhusi and Meck, 2005; Grahn and Brett, 2009; Coull et al., 2011; Grahn and Rowe, 2013), and dopamine suppletion has been shown to correlate with temporal performance in PD patients (Rammsayer and Classen, 1997; Slagter et al., 2016). Complementing such observations, a recent study showed that in normal, healthy participants, dopamine blockade impaired the ability to extract and use temporal information to prepare motor responses (Tomassini et al., 2016).

However, thus far, temporal processing in PD has mainly been explored in the context of explicit timing tasks. In contrast, the ability to use temporal information implicitly to affect performance in non-temporal task goals has not been much investigated. Explicit and implicit timing functions are not only conceptually dissociable, but may also rely on non-overlapping brain systems and mechanisms (Coull and Nobre, 2008).

Temporal relations within the task influence performance, independently of whether the participant is aware of them or uses them deliberately or not. Temporal orienting tasks involving temporal cues are a good example of implicit timing. The participant's task is to detect of discriminate a target stimulus, but benefits in performance are carried by temporally informative cues. Some evidence suggests that temporal orienting may not affected in PD to the same extent as explicit timing judgements, at

least at the behavioural level (Jahanshahi et al., 1992; Praamstra and Pope, 2007; de Hemptinne et al., 2013a). The extent to which PD patients can actively use temporal information to orient their attention in time, and how these processes are reflected in neural modulations, is thus far not well understood. I sought to investigate these questions through two complementary measures: behavioural motor performance to visually cued targets and neural dynamics of temporal anticipation triggered by temporally informative cues, in the context of a cued visual Go/NoGo task.

Neural dynamics of attentional orienting involve modulations of alpha (8 - 12 Hz) and beta (15 - 28 Hz) oscillations in relevant sensory and motor areas (Pfurtscheller and Lopes da Silva, 1999; Worden et al., 2000; Sauseng et al., 2005; Alegre et al., 2006; Thut et al., 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Rihs et al., 2009; Jensen and Mazaheri, 2010; Snyder and Foxe, 2010; Gould et al., 2011; Haegens et al., 2011; van Ede et al., 2011). Studies specifically manipulating expectations about the time at which imperative stimuli will occur show that the time course of such power modulations can adapt to temporal expectations, so that participants are optimally prepared at moments when relevant events are anticipated (e.g. Schoffelen et al., 2005; Alegre et al., 2006; Rohenkohl and Nobre, 2011; van Ede et al., 2011).

Excessive oscillatory synchrony in the beta band in the basal ganglia is a hallmark of PD (see e.g. Hammond et al., 2007; Brittain and Brown, 2014). However, how this exaggerated beta in the basal ganglia affects beta activity in the motor cortex and the motor symptoms in Parkinson's disease is still

unclear (Hammond et al. 2007; Jenkinson and Brown, 2011). In fact, motor-cortical beta in PD patients is often reported as similar (e.g. de Hemptinne et al., 2013b), or even reduced compared to control participants (e.g. Bosboom et al., 2006; Stoffers et al. 2007; Vardy et al., 2011; Pollok et al., 2012). In addition, the extent to which such putative physiological changes might alter the cognitive modulations of cortical beta modulations (e.g., during cued motor preparation) remains unresolved.

A series of related studies suggests that in the context of a regular, rhythmic task structure (i.e. a task where timing is implicit in the structure of the task), the time course of beta modulations is affected in PD (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015, 2017), despite behavioural performance being similar to healthy control participants. However, it is unclear how anticipatory modulations based on learned associations between cues and target stimuli are affected when temporal cues are voluntarily used to orient attention to specific moments in time, instead of when attentional orienting is (involuntarily) captured by a rhythm. As I introduced in Chapter 1, temporal expectations induced by rhythm are automatic (see e.g. Sanabria et al., 2011; Breska and Deouell, 2014), and may rely on different neural and cognitive mechanisms from temporal cues (Rohenkohl et al., 2011, Nobre and Rohenkohl., 2014).

Based on the above, I hypothesised that PD participants would be less able than control participants to benefit from temporal cues to orient their attention in time, and that this smaller behavioural benefit would be mediated

by a reduced ability to dynamically modulate anticipatory beta dynamics in the motor cortex.

3.2 Methods

3.2.1 Participants

The study protocol was approved by the Oxfordshire Research Ethics Committee as part of the National Research Ethics Service (Reference number 12/SC/0650). Nineteen idiopathic PD patients (11 males, 8 females; aged 68.8 ± 6.4 SD) and twenty-one age- and education-matched healthy control participants (11 males, 10 females; aged 67.4 ± 4.9 SD) completed the study following a screening procedure. Participants gave informed consent, and were reimbursed for their time (£10 per hour) and travel expenses. PD participants were recruited via the Dementias and Neurodegeneration (DeNDRoN) Specialty. The following set of criteria were adopted: (a) having a diagnosis within 5 years of the participation date, (b) being able to understand instructions in written and spoken English, and (c) being above the age of 50. Healthy older adults were recruited from the Oxford Dementia and Ageing research database and were selected based on being similar in age and education to the PD participants.

The screening procedure established MEG and fMRI eligibility and ensured that participants fit our other inclusion criteria. Participants were excluded if they had any metal implants or implanted devices (including deep-brain stimulation devices) that would pose a safety risk or cause large artefacts

in the MEG and fMRI recordings; if they were taking part in a clinical drug trial; if they were taking prescription or non-prescription medications that would cross the blood-brain barrier (other than PD medications); or if they self-reported neurological, head injury or psychiatric history other than PD. In addition, PD participants were excluded if they could not tolerate coming off their PD medication. All but two patients and two healthy control participants were right handed, and all participants had normal or corrected-to-normal vision. Data from three control participants and one PD participant had to be excluded. Data from two control participants were excluded because of technical problems during data acquisition, resulting in the loss of trigger information. Data from one control participant and one PD patient were excluded because of their inability to comply with task instructions. The resulting analysis included data of eighteen PD participants (10 males, 8 females; aged 68.5 ± 6.5 SD) and eighteen matched control participants (9 males, 9 females; aged 67.3 ± 4.8 SD).

The study was completed over two separate sessions (see 3.2.4 Overview of sessions), either occurring on the same day or on two separate days, with the MEG session always preceding the MRI session. PD participants were asked to withdraw from their dopaminergic medication starting from 19:00hr the night before the experiment, and to refrain from taking their medication in the morning.

3.2.2 Neuropsychological evaluation and UPDRS

At the start of the MEG session, both PD and control participants underwent a neuropsychological evaluation to assess basic cognitive function (see Appendix 3.1). In addition to the neuropsychological evaluation, participants were examined by a trained clinician using the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008). The UPDRS-III motor examination was administered before the MEG session to evaluate PD symptoms, both in PD patients and control participants. As part of this rating, disease severity was evaluated using the Hoehn and Yahr (1967) scale. The Hoehn and Yahr scale ranks PD symptoms from 1 to 5, with 5 being most severe. PD patients often display symptoms asymmetrically (van der Hoorn et al., 2011, 2012); I therefore examined left or right dominance of symptoms using the UPDRS-III lateral scores. Symptom Asymmetry Scores (SAS) were calculated by summing scores on sections 3.3 - 3.8 and 3.15 - 3.17 of the UPDRS-III separately for the left and right side, subtracting left minus right scores and dividing by the sum of those, i.e. (Left - Right)/(Left + Right). UPDRS scores, lateralisation of symptoms and other patient details are summarised in Table 3.1 for PD participants and in Table 3.2 for control participants. Note that certain measures are not applicable (indicated as n.a.) for the control group. Also note that Appendix 3.2 shows the behavioural results for the PD group, testing for an interaction with the lateralisation of symptoms.

Table 3.1. *Clinical details of PD participants*

Nr.	Gender	Age	Education	Handedness	SAS	LS	HY	UPDRS-III	YSD	LEDD
1	F	68	10	R	-.29	L	3	49	2	400
2	M	67	13	R	.11	R	2	51	2	400
3	F	63	12	R	-.05	L	2	23	1	300
4	M	68	11	R	.38	R	1	43	2	400
5	M	73	17	R	.06	L	2	48	2	300
6	M	54	14	R	-1.0	L	1	15	2	n.a.
7	M	59	16	L	.54	R	1	17	2	400
8	M	67	11	R	-.2	L	2	48	4	900
9	M	72	23	R	.25	R	2	30	1	300
10	F	62	12	R	.33	R	3	37	4	380
11	M	74	11	R	-.24	L	2	27	4	900
12	F	73	12	R	-.39	L	2	23	4	887.5
13	F	77	17	R	-.06	L	1	30	4	750
14	F	65	14	R	-1.0	L	1	11	4	600
15	F	75	13	L	-.2	L	1	19	2	n.a.
16	F	66	17	R	-.31	R	2	32	2	320
17	M	79	10	R	.29	R	2	21	4	300
18	M	71	16	R	-.24	L	2	35	4	450

SAS: Symptom Asymmetry Score, negative values represent left lateralisation of symptoms and positive values represent right lateralisation of symptoms; LS: Lateralisation of symptoms, most affected side; HY: Hoehn & Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale; YSD: Years Since Diagnosis; LEDD: Levadopa Equivalent Daily Dose in mg/day. n.a.: measure not applicable.

Table 3.2. *Clinical details of control participants*

Nr.	Gender	Age	Education	Handedness	SAS	LS	HY	UPDRS-III	YSD	LEDD
1	F	70	10	R	n.a.	n.a.	0	3	n.a.	n.a.
2	F	74	20	R	n.a.	n.a.	0	4	n.a.	n.a.
3	F	67	16	L	n.a.	n.a.	0	1	n.a.	n.a.
4	M	63	17	R	n.a.	n.a.	0	4	n.a.	n.a.
5	M	68	10	R	n.a.	n.a.	0	0	n.a.	n.a.
6	M	69	20	R	n.a.	n.a.	0	0	n.a.	n.a.
7	M	72	13	R	n.a.	n.a.	0	4	n.a.	n.a.
8	F	60	16	R	n.a.	n.a.	0	0	n.a.	n.a.
9	F	62	11	R	n.a.	n.a.	0	1	n.a.	n.a.
10	F	66	12	R	n.a.	n.a.	0	0	n.a.	n.a.
11	F	60	11	R	n.a.	n.a.	0	0	n.a.	n.a.
12	F	68	19	R	n.a.	n.a.	0	1	n.a.	n.a.
13	M	74	18	R	n.a.	n.a.	0	1	n.a.	n.a.
14	M	76	12	R	n.a.	n.a.	0	0	n.a.	n.a.
15	F	63	13	R	n.a.	n.a.	0	1	n.a.	n.a.
16	M	64	17	R	n.a.	n.a.	0	1	n.a.	n.a.
17	M	68	17	R	n.a.	n.a.	0	0	n.a.	n.a.
18	M	67	20	L	n.a.	n.a.	0	1	n.a.	n.a.

SAS: Symptom Asymmetry Score, negative values represent left lateralisation of symptoms and positive values represent right lateralisation of symptoms; LS: Lateralisation of symptoms, most affected side; HY: Hoehn & Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale; YSD: Years Since Diagnosis; LEDD: Levadopa Equivalent Daily Dose in mg/day. n.a.: measure not applicable.

3.2.3 Experimental setup

All participants were tested with MEG at the Oxford Centre for Human Brain Activity (OHBA) using an Elekta NeuroMag (306 channel) MEG system. A magnetic Polhemus FastTrak 3D system (Vermont, United States) was used for head localisation. Relative positions of three anatomical landmarks (nasion, left and right auricular points) were measured in addition to relative positions of four head-position indicator coils.

MEG data were recorded in six separate blocks of 5-6 minutes each. In between blocks participants had a small break, during which they remained seated in the MEG chair. A bandpass filter between 0.03 and 300 Hz was applied during digitisation of the signal and data were sampled at 1000 Hz. ECG and horizontal and vertical EOG were recorded in addition to eye tracking data that were recorded with a video-based eye tracker (EyeLink 1000, SR Research, Ontario, Canada) with a sampling frequency of 1000 Hz. A fibre-optic response pad (made at BRU, Aalto University, Helsinki) was used to collect manual responses.

Stimuli were presented using MATLAB (The MathWorks, Inc., Natick, MA) and Psychtoolbox v.3.0 for MATLAB (Kleiner et al., 2007). The stimuli were back projected (Panasonic PT D7700E, Panasonic, Osaka Japan) on a 58 x 46 cm screen placed 120 cm in front of the participant, with a spatial resolution of 1280 x 1024 and a refresh rate of 60 Hz.

3.2.4 Experimental procedure and stimuli

Overview of sessions

Each participant took part in two experimental sessions that either occurred on the same day, or on two separate days. PD participants were scanned following overnight withdrawal of their PD medication. Each participant first completed the MEG session, which took place at OHBA. This session consisted of 45 minutes of standardised neuropsychological testing and administration of the UPDRS (see Neuropsychological evaluation and UPDRS and Appendix 3.2), followed by the MEG scan, which took approximately one hour. During

the MEG session I collected 10 minutes of resting-state data (eyes open), 45-minutes of task data (including breaks) and 5 minutes of data on an additional motor task using grip bars. In this thesis I will focus on the data from the first task only. The second session took place at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR), where participants went into the MRI scanner for 45 minutes to collect 20 minutes of functional task data, 10 minutes of resting-state data, and a T1 structural scan. Following this session, participants completed two computerised tasks. The data from the second, (MRI) session will not be discussed in the current thesis.

Experimental task

Participants performed a cued Go/NoGo task, that is shown in Figure 3.1. Participants had to respond as quickly as possible by pressing a button on a button box whenever a green target appeared (the "Go" target; present in 80% of trials) and to withhold responding whenever a red target was presented instead (the "NoGo" target; present in 20% of trials). A central fixation dot (diameter: 0.01° of visual angle) was present throughout the trial and was followed after a random interval between 3 and 5 seconds by a cue indicating when (early: 1 s cue-target ISI vs. late: 2 s cue-target ISI) the upcoming Go/NoGo target would appear. Temporal cues were valid 80% of the time and consisted of blue circles combined with auditory beeps. A smaller circle (diameter: 0.57° of visual angle) combined with a high pitched beep (880 Hz) predicted the short ISI, and a larger circle (diameter: 1.34° of visual angle) combined with a low pitched beep (440 Hz) predicted the long ISI. Visual cues

and targets were presented for 200 ms each, and auditory beeps were presented for 100 ms. After presentation of the "Go" target (diameter: 1.53° of visual angle) participants had 2 seconds to respond.

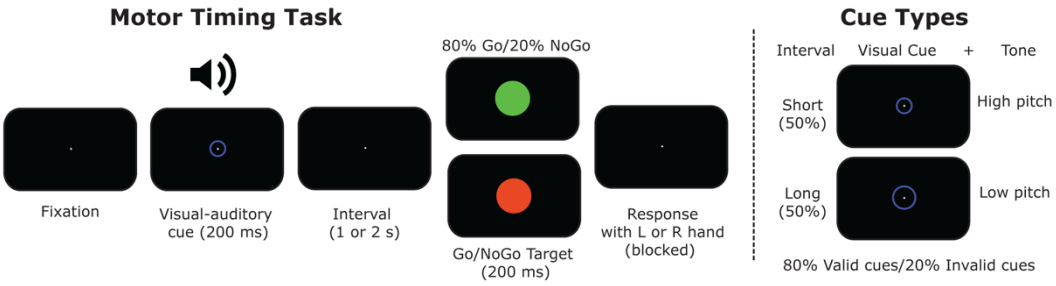


Figure 3.1. Experimental task. A combined auditory-visual cue, consisting of a blue circle and an auditory beep, predicted when (with 80% validity) a subsequent Go/NoGo target would occur. The small circle/high-pitched beep combination indicated that a short cue-target ISI (1 s) was likely to follow, while a larger circle/lower-pitched beep indicated a long ISI (2 s). "Go" targets consisted of a green circle, and were presented in 80% of trials; "NoGo" targets consisted of a red circle, and were presented in 20% of trials. Participants were instructed to respond as quickly as possible whenever a green target appeared, but to withhold responding to the red target.

Six blocks of 50 trials each were presented in total. Responses were made with the left or right index finger. The response hand alternated between blocks, and the order of left- and right-hand blocks was counterbalanced across participants. After each block there was a longer break, during which the MEG data were saved. Preceding the MEG recording, participants were instructed on the task. Participants were told the predictive nature of the cues and were encouraged to use this information to guide their behaviour.

Participants performed 30 practice trials whilst seated in the MEG chair before starting the main experiment.

3.2.5 Behavioural analysis

The behavioural data were analysed using MATLAB, and statistics were performed in SPSS version 22 (IBM Corp. Armonk, NY). The behavioural data were analysed with respect to reaction times (RTs) and percentage correct (PC). For the RT analysis, trials with RTs smaller or larger than a participant's mean RT ± 3 times the standard deviation were excluded from the behavioural analysis. On average 2.7 ± 0.2 trials were excluded this way. Only GO trials were included in the RT analysis. The analysis of PC was performed separately for Go and NoGo trials. Incorrect trials in the analysis of Go trials were trials where no response was given (on average 1.9 ± 0.7% of trials), while incorrect trials in the analysis of NoGo trials included trials in which participants did respond (on average 16.0 ± 2.3% of trials).

I also evaluated the relationship between clinical symptoms in the PD group and the obtained behavioural data, by calculating Pearson correlation coefficients between UPDRS-III scores and the behavioural results. I did this for both average RT scores (across all conditions) and the temporal validity effect at the short interval (relative difference in RTs following valid vs. invalid temporal cues).

3.2.6 MEG analysis

Pre-processing and artefact rejection

MEG data analyses were performed using MATLAB, OSL version 2.0, and Fieldtrip (Oostenveld et al., 2011). First, channels containing excessive noise were identified automatically using MaxFilter software (Neuromag). Subsequently, MaxFilter's spatiotemporal signal space separation (TSSS; Taulu et al., 2004; Taulu and Simola, 2006) and movement compensation were applied. The data were down-sampled to 250 Hz, and a 0.1 Hz high-pass filter was applied to remove low-frequency drift. Artefacts associated with eye blinks, eye movements, and heartbeat were rejected using independent-component analysis (ICA). All artefactual components were inspected visually before removing them from the data. OSL's variance-based automated artefact detection was applied after epoching of the data to exclude trials with excessive noise. This method works by estimating a linear model and down-weighting trials which are particular influential to the results. This robust regression is used to find the mean; any trials which are strongly down-weighted below a set threshold are subsequently rejected. Trials excluded during the behavioural analysis stage, were excluded from the MEG data as well. On average 5.2 ± 0.6% of trials per participant were excluded from the analysis (5.5 ± 0.9% from control participants; 5.0 ± 0.8% from PD participants).

Analysis of event-related fields for region-of-interest selection

Two motor and one visual regions-of-interest (ROIs) were selected based on event-related fields (ERFs) evoked by targets and motor responses. This way, I ensured that the ROI selection was independent of the main pre-target analysis period (the short cue-target ISI, i.e. the anticipatory period), was independent of the signal features of interest (time-frequency data), and was independent of condition (short or long ISI).

ERFs were calculated separately for left and right responses. Data for the planar gradiometer pairs were combined, resulting in a 102-channel combined planar gradiometer map in sensor space. A left vs. right difference ERF was calculated for each participant separately and subsequently averaged across participants. Motor ROIs were selected based on the left vs. right difference ERF topography in a ±150 ms window relative to the button press, from the grand average across all participants (see Figure 3.2). Based on the topography, six symmetric channel pairs were selected. Left sensors were MEG0412+0413, MEG0422+0423, MEG0432+0433, MEG0442+0443, MEG1812+1813 and MEG1822+1823; and right sensors were MEG1112+1113, MEG1122+1123, MEG1132+1133, MEG1142+1143, MEG2212+2213 and MEG2222+2223. The distribution of response-related ERFs was similar for both groups, so that similar channels would have been selected based on the averages for each group separately. Visual ROIs were similarly selected based on the average ERF topography in a window of 100 - 200 ms after target presentation (see Figure 3.3). I selected six central posterior channel pairs (MEG1922+1923, MEG1932+1933, MEG2112+2113,

MEG2122+2123, MEG2332+2333, MEG2342+2343) based on the grand average across all participants. Again, similar channels would have been selected for each participant group separately.

Selection of anticipatory time-window-of-interest

Because of possible differences in the frequency spectrum between groups (see 3.3.2 Frequency analysis), I decided to evaluate modulations for the whole frequency spectrum, averaged across a predefined time-window-of-interest (TWOI). In Chapter 2 we saw that anticipatory modulations (both spatial and temporal) were already very prominent around 400 - 500 ms after cue onset. Similar results for anticipatory modulations were obtained for example in van Ede et al. (2011; 2012) and Wildegger et al. (2017). In this study, I therefore defined the anticipatory TWOI as the 700-ms time period that started 500 ms after cue onset and lasted until the time at which a short target would be presented (at 1200 ms).

Frequency and time-frequency analysis

To compare the dominant frequencies in the MEG signals between groups, I first performed a frequency analysis using a Fast Fourier Transform (FFT) and a Hanning taper for frequencies between 1 and 45 Hz in 0.5 Hz steps. The frequency analysis was performed across all trials, for one single time window with a length of 2 s, ranging from 0 – 2 s after cue onset. This analysis was first performed on the raw data and subsequently repeated on normalised data to be able to compare the shape of the power spectrum between participants.

Data were normalised by z-scoring the time-domain data (for each trial and channel, across the time dimension), before performing the analysis.

Power values were combined for all planar gradiometer pairs (Cartesian sum), resulting in a 102-channel combined planar gradiometer map in sensor space. For the motor ROIs (see 3.3.6 Analysis of event-related fields for region-of-interest selection), the power was averaged for the selected ROI channels and subsequently averaged for ROIs contralateral and ipsilateral to the response hand. Because detection of clear beta peaks was difficult, and in some participants may have reflected the alpha tail instead (see 3.3.2 Frequency analysis), this analysis was repeated a second time after taking the time-domain derivative of the signal before z-scoring the data and performing the frequency analysis. This procedure was aimed at attenuating the contribution of the 1/F noise present in the signal (while preserving oscillatory components), thereby increasing the relative contribution of higher frequencies in the signal.

To evaluate the main contrast of interest (the relative power difference between short vs. long cues), I averaged across the predefined time-window-of-interest (TWOI; see previous section), for each of the contra- and ipsilateral motor and the visual ROIs. I performed a frequency analysis using a multi-taper approach (Percival and Walden, 1993) using ± 3 Hz spectral smoothing[9] (3 tapers) to estimate frequencies between 4 and 45 Hz in 0.5 Hz steps in a single time window (the TWOI), which had a length of 700 ms. Importantly,

[9] I performed some smoothing on the data to minimise the contribution of (potential) small peak-frequency differences between groups to the results for the contrast of interest (anticipatory modulations following short vs. long cues).

for this analysis, I did not z-score the time-domain data first, since I wished to compare both "shape" of the spectra (i.e., in the relative contributions of the difference frequencies) and the potential amplitude differences (as a function of frequency) between conditions and groups. I again combined power values for planar gradiometer pairs to get a 102-channel combined planar gradiometer map in sensor space. As in Chapter 2, the short vs. long contrast was computed as a relative contrast:

$$((Short\ Cue - Long\ Cue)/(Short\ Cue + Long\ Cue)) \times 100$$

This contrast was evaluated by means of cluster-based non-parametric permutation testing in Fieldtrip (circumventing the multiple-comparisons problem; Maris and Oostenveld, 2007). I used 1000 permutations with a cluster alpha of 0.05 and multiplied the resulting p-values by 2, to obtain two-sided p-values.

Finally, to evaluate the results across both frequency and time, I performed a time-frequency analysis using a short-time Fourier Transform and a Hanning taper for frequencies between 4 and 45 Hz (in 0.5 Hz steps). A fixed sliding time window of 300 ms was advanced over the data in steps of 50 ms. Again, after performing the analysis, time-frequency power values were combined for planar gradiometer pairs to get a 102-channel combined planar gradiometer map. Using a similar method to Chapter 2, I compared contrasts of interest separately for each ROI, again during the early interval (0 - 1.2 s; i.e. the time period where temporal expectations were expected to differ between

cue types), by means of cluster-based non-parametric permutation testing. Note that for this analysis, the last 150 ms preceding the target cannot be considered purely anticipatory, because target-induced activity may have contributed to the signal.

Analysis of correlation with behavioural performance

To assess correlations between behavioural performance and MEG data, I calculated the Pearson correlation coefficient between the relative temporal validity effect for the short ISI (i.e. the relative RT difference between valid vs. invalid temporal cues), and the relative anticipatory beta power difference following short vs. long cues. For this analysis I took the average of beta (15 - 28 Hz) power per participant in the anticipatory TWOI, separately for each ROI.

3.3 Results

3.3.1 Behavioural results

The RT distribution for each participant (collapsed across conditions) is plotted in Figure 3.2a. This distribution shows the proportion of responses that fell within each of 22 non-overlapping 50 ms bins between 0 and 1.1 seconds, with control participants plotted in red (top panel) and PD participants plotted in blue (middle panel). The thick lines in the bottom panel show the group averages. This figure shows that the mean RT distributions are very similar between groups.

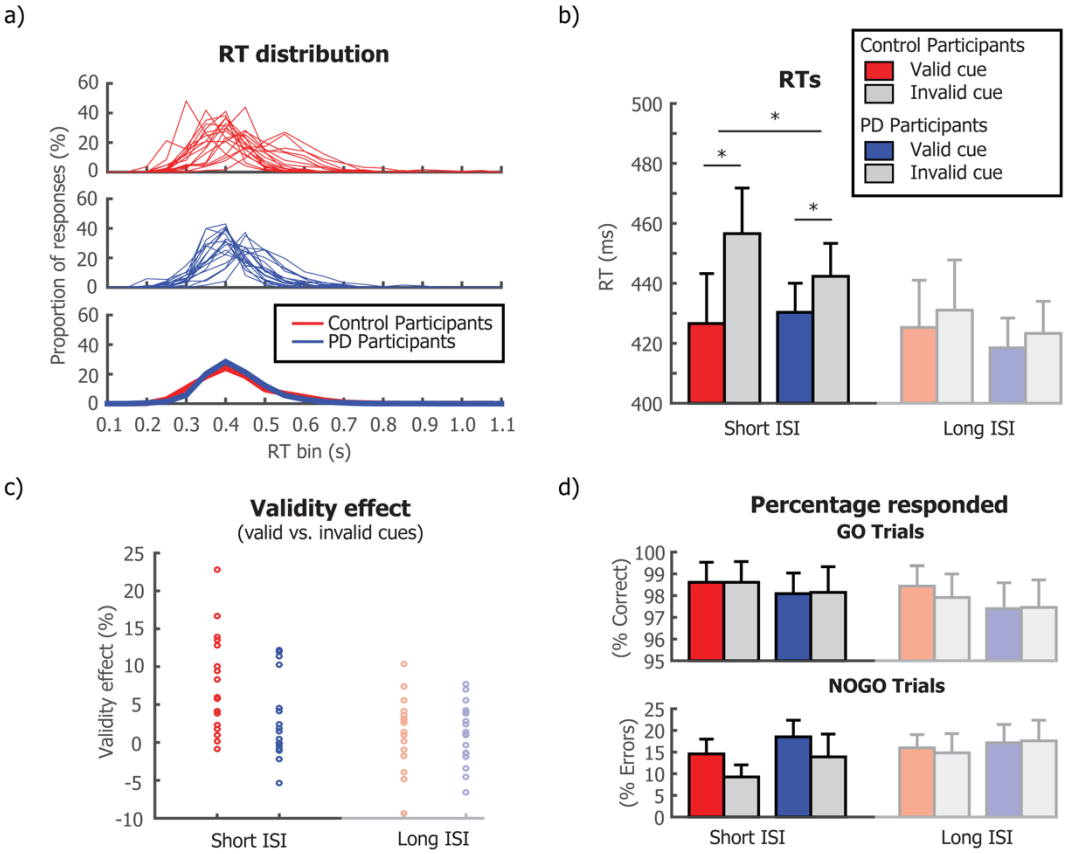


Figure 3.2 Behavioural results. (a) Reaction time (RT) distributions for each participant, with control participants in red and PD participants in blue, displayed as the proportion of responses within each of 22 50-ms bins between 0 and 1.1 s. Solid lines indicate group averages. (b) RT results shown separately for healthy control participants and PD participants, for each temporal cue type (valid vs. invalid) and each cue-target inter-stimulus-interval (ISI; short or long: 1 or 2 s). Error bars show standard error of measurement (SEM). Asterisk indicate statistically significant effects. (c) The size of the temporal validity effect (relative difference in RT following a valid vs. invalid cue) for each individual, shown separately for both groups and for both cue-target ISI lengths. (d) The percentage of trials in which participants responded, shown separately for Go trials (where responses indicate correct trials) and NoGo trials (where responses should have been withheld and therefore indicate errors). Results are shown separately for both groups, for each temporal cue type (valid and invalid) and each cue-target ISI.

RTs as a function of attentional condition are shown in Figure 3.2b. To assess the difference between valid and invalid temporal cues (the "temporal validity effect", see also Experiment 1), I performed a repeated-measures ANOVA with the within subject factor Cue Validity (valid or invalid) and the between-subjects factor Group (control or PD participants). I focused this analysis on the short ISI trials only, as temporal cueing effects are known to be largely exclusive to the short interval (see e.g. Coull and Nobre 1998; Miniussi et al. 1999; Nobre 2010; Rohenkohl et al. 2014, and the results obtained in Chapter 2 in this thesis). This analysis showed a main effect of Cue Validity ($F(1,34) = 29.86$, $p < .0001$, partial $\eta^2 = 0.47$) and a significant interaction between Group and Validity ($F(1,34) = 5.46$, $p = .026$, partial $\eta^2 = 0.14$). There was no main effect of Group ($F(1,34) = 0.08$, $p = .78$, partial $\eta^2 = 0.002$). Post-hoc pairwise t-tests revealed that for both groups a validity effect was present (control participants: $t(17) = 5.35$, $p < .0001$, Cohen's $d = 1.78$; PD participants: $t(17) = 2.29$, $p = .035$, Cohen's $d = 0.76$), and that this effect was larger in control participants than in PD participants: $t(34) = 2.42$, $p = .021$, Cohen's $d = 0.81$ (see also Figure 3.2c). I subsequently performed a similar analysis for the PD group only, with the added factor of Lateralisation of symptoms (least or most affected side). The results of this analysis showed that there was no main effect of Lateralisation of Symptoms and no interaction of Lateralisation of Symptoms with Cue Validity, and can be found in Appendix 3.2.

Similar statistical analyses were performed for the percentage of responses that were made in Go trials (where responses should be made and indicated correct trials) and NoGo trials (where participants should not

respond and responses therefore indicated errors). These results are displayed in Figure 3.2d. For Go trials, this analysis showed no main effect of Cue Validity ($F(1,34) = 0.01$, $p = .93$, partial $\eta^2 < 0.001$), no main effect of Group ($F(1,34) = 0.13$, $p = .73$, partial $\eta^2 = 0.004$), and no interaction between Cue Validity and Group ($F(1,34) = 0.01$, $p = .93$, partial $\eta^2 < 0.001$). For NoGo trials, this analysis showed no main effect of Cue Validity: $F(1,34) = 2.56$, $p = .12$, partial $\eta^2 = 0.07$), no main effect of Group ($F(1,34) = 0.87$, $p = .36$, partial $\eta^2 = 0.03$), and the interaction between Group and Cue Validity ($F(1,34) = 0.01$, $p = .91$, partial $\eta^2 < 0.001$) was again not significant.

To evaluate the relationship between clinical scores (total UPDRS-III score) of the PD group and the behavioural results, I calculated Pearson correlations between UPDRS scores and both the mean RT scores (across all conditions) and the relative temporal validity effect at the short interval. This analysis showed no significant correlations (Mean RT: $R = 0.23$, $p = .37$; Cue Validity: $R = 0.14$, $p = .59$). Because behaviour did not differ based on disease severity, I did not further evaluate relationships between UPDRS scores and MEG results.

3.3.2 MEG results

Region-of-interest selection

Figure 3.3a depicts the symmetrical left and right ROIs that were used to extract motor cortical activity, contralateral and ipsilateral to the response hands. Left and right ROIs were selected after visual inspection of ERF topographies for the difference between left vs. right responses in a ± 150 ms

window centred at the button press (collapsed over responses following short and long targets). ROI selection was performed on the grand average across all participants. Importantly, however, as shown in Figure 3.3a, the same sensors would have been selected based on either the control or PD group in isolation.

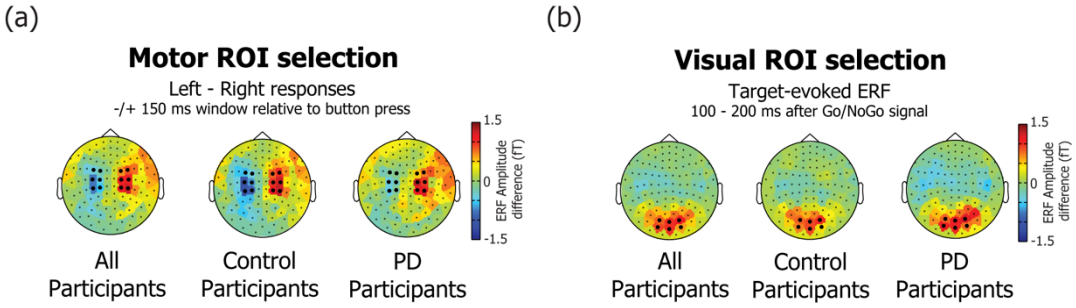


Figure 3.3 Region-of-interest selection. (a) Topographies for the left-minus-right response amplitude difference in the ERF in a ± 150-ms window relative to the button press (averaged over short and long interval lengths). The six left and six right central-motor channels that were used as ROIs throughout the subsequent MEG analyses are marked in black. Channels were selected based on visual inspection of the ERF grand average for all participants. Separate topographies for control and PD participants show that the largest ERF amplitudes were found in the same channels for both groups. (b) Topographies for the amplitude of the target-evoked ERF 100 - 200 ms after target presentation. The six posterior visual channels that were used as a ROI throughout the subsequent analyses are marked in black. Channels were selected based on visual inspection of the ERF grand average for all participants. Separate topographies for control and PD participants show that the largest ERF amplitudes were found in the same channels for both groups.

In a similar vein, I also determined a visual ROI, which is depicted in Figure 3.3b. This ROI was selected based on visual inspection of the ERF topography for the target-evoked ERF (averaged for targets following short and long intervals) in a window 100 - 200 ms after the visual Go/NoGo target.

ROI selection was again performed on the grand average across all participants, but would have been equivalent if performed on control or PD group averages in isolation.

Frequency analysis

Before evaluating the task-related temporal-orienting contrasts of interest, I investigated whether the characteristic frequencies in the measured brain activity were actually comparable between both groups to begin with. The relevant frequency spectra are shown in Figure 3.4a, with activity in the first column averaged across both motor ROIs, for each individual participant and the group average in the second column. The third column shows the individual data for the visual ROI, with the group average presented in the fourth column. Control participants are plotted in red and PD participants are shown in blue. When investigating the individual participant data in the first and third column, it becomes clear that there was a lot of individual variability in global power, which makes it difficult to compare the shape of the frequency distributions between groups. I therefore performed this analysis a second time, on data that was normalised (z-scored in the time domain) before performing the frequency analysis. These data are shown in Figure 3.4b.

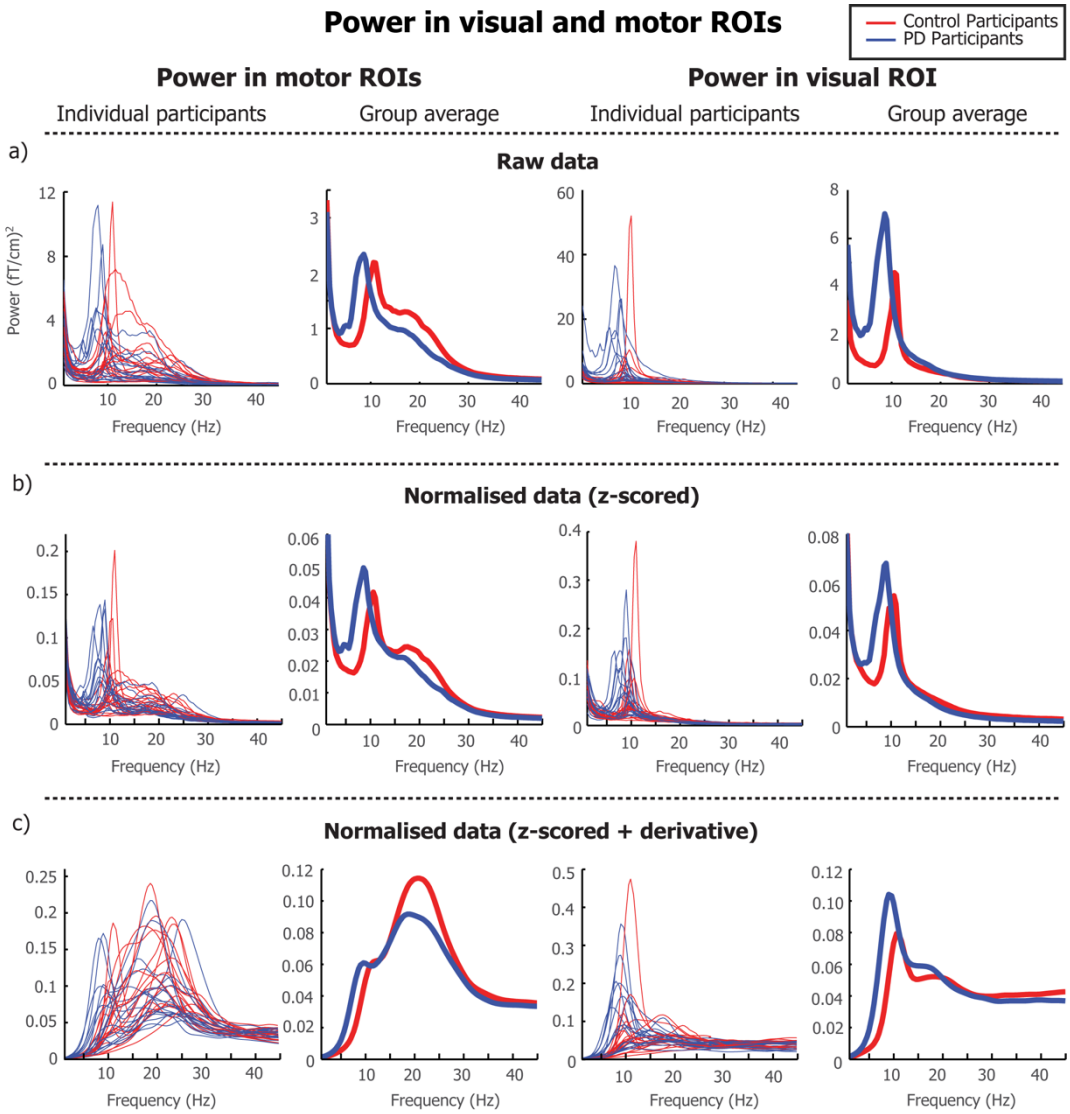


Figure 3.4 Frequency power spectrum. The first column reflects activity averaged across both motor ROIs, for a time window ranging from 0 to 2 s after cue onset, for each individual participant. The second column shows the group average. The third column shows the individual data for the visual ROI, with the group average presented in the fourth column. Control participants are plotted in red and PD participants are shown in blue. Power spectra are shown for (a) the raw power spectra; (b) data that were z-scored before performing the frequency analysis; and (c) data where the derivative of the signal was taken before z-scoring and performing the frequency analysis (see 3.2.6 Frequency and time-frequency analysis).

Figure 3.4a (raw spectrum) and b (z-scored spectrum) reveal that the PD group potentially showed a downwards shift in both alpha and beta peak frequencies. The significance of these observations was tested by performing independent sample t-tests for the peak frequency for alpha (motor and visual ROIs) and beta (motor ROIs), between groups. Peak frequencies were determined from the raw data[10], by taking the frequency with the maximum amplitude between 6 and 14 Hz (alpha) and 15 and 28 Hz (beta). This analysis showed that the beta peak frequency in the motor ROIs was significantly lower in PD participants (control vs. PD participants: 18.7±0.6 Hz vs. 16.7±0.6 Hz; $t(34) = 2.30$, $p = .027$, Cohen's $d = 0.767$), while the alpha peak shift showed a similar trend for both the motor (control vs. PD participants: 9.5±0.5 Hz vs. 8.7±0.6 Hz, $t(34) = 1.82$, $p = .077$, Cohen's $d = 0.61$) and the visual ROIs (control vs. PD participants: 9.5±0.6 Hz vs. 8.7±0.7 Hz; $t(34) = 1.70$, $p = .10$, Cohen's $d = 0.57$).

After visual inspection of the individual participant peaks, I was concerned that for some participants the detected beta peak frequency might reflect the tail of the alpha peak, instead of a "true" beta peak, which could possibly have exaggerated differences between groups. To reduce this problem, I performed a second analysis, in which I took the derivative of the time-domain signal before performing the frequency analysis (on z-scored data to normalise across participants; see 3.2.6 Frequency and time-frequency analysis). This procedure was performed to attenuate 1/F noise, resulting in a

[10] Note that I did not perform this analysis on the z-scored data because peak frequencies found in the raw data and z-scored data were nearly identical (mean R across the three ROIs = 0.993; $p < .0001$ for all ROIs).

greater sensitivity to higher frequencies. As we can see in Figure 3.4c and d, this procedure worked as intended, with now a much clearer beta peak showing for the motor channels. Results for the peak detection on these data show no difference in beta (control vs. PD participants: 21.4±0.6 Hz vs. 20.3±0.8 Hz; $t(34) = 1.07$, $p = .29$, Cohen's d'= 0.36) or alpha (control vs. PD participants: 13.0±0.4 Hz vs. 12.3±0.6 Hz; $t(34) = 0.89$, $p = .38$, Cohens d' = 0.30) peak frequencies in the averaged motor ROIs, but there was a significant reduction in PD participants in the peak alpha frequency in the visual ROI (control vs. PD participants: 12.2±0.4 Hz vs. 10.6±0.5 Hz; $t(34) = 2.25$, $p = .031$, Cohen's d = 0.75). Although together these results do not provide a definitive answer (for example, the answer appears to depend on chosen methodology), they strongly hint at putative spectral differences between both groups, when considering beta oscillations in the combined motor ROIs and alpha oscillations in the visual ROI. These potential differences are important to take into account when evaluating the MEG data with respect to the main measure of interest, which involve anticipatory modulations in these frequency bands and ROIs following short vs. long cues.

Because the data did not only seem to show a frequency shift, but also potential differences in the absolute power in both the alpha and beta frequency ranges (potentially as a result of, or at least related to, the peak-frequency shift), I also statistically evaluated potential differences in power.

I performed this analysis by comparing the raw power at each individual peak between groups. This analysis showed no power differences between groups (beta power in motor ROI: $t(34) = 1.18$, $p = .25$, Cohen's d = 0.39; alpha

power in motor ROI: t(34) = -0.25, p = .81, Cohen's d = -0.08; alpha power in visual ROI: t(34) = -0.95 p = .35, Cohen's d = -0.32). Similarly, for the peaks detected in the data where the derivative was taken before normalisation, this analysis (again performed on amplitude values taken from the raw data) showed no differences (beta in motor ROI: t(34) = 0.96, p = 0.34, Cohen's d = 0.32; alpha power in motor ROI: t(34) = 0.23, p = .82, Cohen's d = 0.08; alpha power in visual ROI: t(34) = -0.74, p = .46, Cohen's d = -0.25).

Despite these analyses not indicating any significant differences, I was still concerned that there might be overall power differences in the frequency ranges of interest. I therefore compared amplitudes a third time, but now for the full alpha and beta frequency ranges. For this analysis I took the mean (raw) power for each participant, separately for beta (14-28 Hz) in the motor ROIs, alpha (8 - 12 Hz) in the motor ROIs and alpha (8 - 12 Hz) in the visual ROI. These values were evaluated statistically by means of an independent-samples t-test. This analysis again showed no differences in beta power (t(34) = 1.41, p = .17, Cohen's d = 0.47) or alpha power (t(34) = 0.07, p = .95, Cohen's d = 0.02) in the motor ROIs, as well as no difference in the alpha power (t(34) = 1.09, p = .28, Cohen's d = 0.37) in the visual ROI.

These results are in line with some previous studies where slowing of cortical activity in Parkinson's disease has been reported for both resting-state (e.g. Bosboom et al., 2006; Stoffers et al., 2007; Moazami-Goudarzi et al., 2008) and task data (Vardy et al., 2011). It seems to be largely unrelated to disease stage, duration, or severity; and only slightly affected by dopaminergic treatment (Stoffers et al., 2007). These data also make clear that, in contrasts

to excessive beta oscillations observed in invasive recordings from basal ganglia structures such as the sub-thalamic nucleus (see e.g. Hammond et al., 2007; Brittain and Brown, 2014), MEG recordings do not reveal similarly excessive beta oscillations (if anything, the difference goes in the opposite direction, with less beta power in PD patients than in control participants).

Frequency-resolved anticipatory modulations in the time-window of interest (TWOI)

In all MEG analyses, I focused on the early interval (0 - 1.2 s post cue onset), because this is the interval in which modulations were expected to differ following short vs. long cues (i.e. with different temporal expectations; see also Chapter 2). To maximise sensitivity, I first analysed this contrast without time-resolution, using the a-priori defined anticipatory time-window-of-interest (TWOI), starting 500 ms after the cue (to allow some time to initiate attentional modulations) and lasting up to 1200 ms (the time of a short response cue; see also 3.2.6 Selection of anticipatory time-window-of-interest). Because the previous analysis indicated a possible frequency shift between groups, I started by evaluating this cue-short vs. cue-long contrast across the whole frequency range, averaged over this anticipatory TWOI.

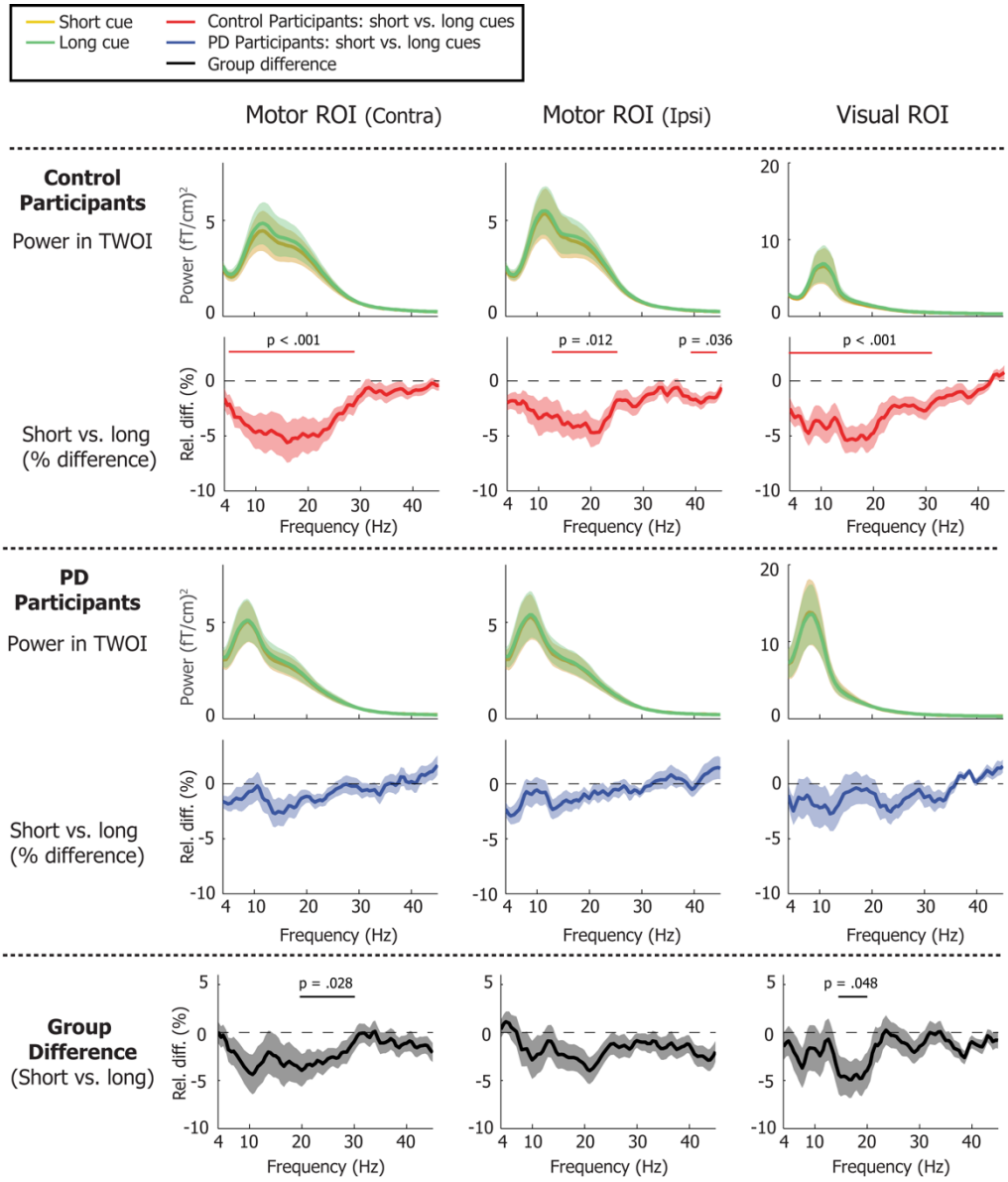


Figure 3.5 MEG results for the effect of temporal orienting of attention across the whole frequency spectrum. The frequency power spectrum, shown separately for short (yellow) and long (green) cues, for the contralateral (left) and ipsilateral (middle) motor ROIs, and the visual ROI (right), for the anticipatory time-window-of-interest (TWOI; 500 to 1200 ms after cue onset). The red and blue lines reflect relative power differences following short vs. long cues, for control participants (red) and PD participants (blue). The black lines indicate the group differences. Horizontal lines indicate significant clusters after cluster-based non-parametric permutation testing. Shaded areas reflect the standard error of the mean (SEM). p-values reflect two-sided cluster p-values.

Figure 3.5 shows the raw power[11] between 4 and 45 Hz in the anticipatory TWOI, following both short (yellow) and long (green) cues, separately for control participants (top and second row) and PD participants (third and fourth row), separately for the motor ROI contralateral to the anticipated response hand (left), the motor ROI ipsilateral to the response hand (middle), and the visual ROI (right; note that the visual ROI is not lateralised as visual response signals were always presented centrally). The relative difference between short- vs. long-cue trials for control and PD participants are shown in red and blue respectively. The bottom row shows the group difference of this temporal modulation in black. Horizontal lines indicate significant clusters after cluster-based non-parametric permutation testing, to deal with multiple comparisons along the frequency axis (Maris and Oostenveld, 2011).

In the control group, one significant cluster was found for the contralateral motor ROI (4.5 - 28.5 Hz; two-sided cluster $p < .001$), two clusters were found for the ipsilateral ROI (12 – 24.5 Hz and 39 – 44 Hz; two-sided cluster $p = .012$ and $p = .036$, respectively), and one cluster was found for the visual ROI (4 – 31.5 Hz; two-sided cluster $p < .001$). In the PD group no significant clusters were present. The group difference was significant between 19.5 and 30 Hz in the contralateral motor ROI (two-sided cluster p =

[11] Note that these data now reflect raw power (instead of z-scored data and/or data where the derivative was taken, like was shown in Figure 3.4b and c). I have also tried the analysis presented here for data where the derivative was taken before performing the frequency analysis. The results for the contrast of interest (relative difference following short vs. long cues) are equivalent to the results presented here, indicating that this procedure did not remove any task-relevant modulations.

.028) and between 14.5 and 20 Hz in the visual ROI (two-sided cluster p = .048).

These results show that, while in control participants a clear modulation with temporal expectation was visible across all three ROIs, in PD participants no such modulation was visible. Furthermore, this modulation was significantly stronger in the control group in both the contralateral motor and the visual ROI. By investigating these differences across all frequencies, and for both groups separately, this analysis strongly suggests that these group differences are not due to group differences in the peak-frequencies of the temporal modulations, but instead by group differences in the presence and/or magnitude of these modulations.

Anticipatory modulations across time and frequency and space

In the previous section we saw that significant modulations with temporal orienting were present in the control group, while such modulations seemed absent in the PD group. In the next part of the analysis, I broadened the analysis to include the spatial and the temporal dimension. This is important, as the observed group differences may potentially also be due to differential localisation of the reported effects in both space and time.

Figure 3.6a shows the topographies for the modulations in the anticipatory TWOI, for both alpha (8 - 14 Hz; top) and beta (15 - 28 Hz; bottom). From the topographies it is clear that in control participants, as well as in the group comparison, the anticipatory alpha and beta modulations occurred in both posterior (putatively visual) sites as well as bilateral central

(putatively, motor) sites. In PD participants no clear modulation in the alpha band was visible, while for beta there was a hint of a temporal modulation in contralateral motor channels.

Figure 3.6b shows the difference between short- and long-cue trials as a function of both time and frequency, again in the early interval, for frequencies between 4 - 45 Hz. This is depicted for control participants (first row), PD participants (middle row) and the difference between control and PD participants (bottom row). Results are shown separately for contra- (left) and ipsilateral (middle) motor ROIs, and the visual ROI (right). For the control group, a significant effect of temporal orienting of attention was again present for alpha and beta. Similar to Figure 3.5, a bilateral desynchronization with temporal orienting was found for the motor ROIs (contralateral: two-sided cluster $p < .001$; ipsilateral: two-sided cluster $p = .014$), as well as a large anticipatory modulation in the visual ROI (two-sided cluster $p < .001$). In line with the small contralateral beta modulation visible in the topography plot, in the PD group, a similar anticipatory cluster was now also found in the PD participants, for the contralateral ROI only[12] (two-sided cluster $p = .004$). No effect was found for the ipsilateral motor ROI, nor for the visual ROI. Contrary to the control participants, in this group there also was an early visual cluster that showed more power following long than short cues, that reached significance in this group (two-sided cluster $p = .004$). This early cluster likely

[12] Note that topographies plotted for a more restricted — but still purely anticipatory — time window (e.g. 300 - 150 ms pre target) look qualitatively similar to Figure 3.5a. It therefore does not seem to be the case that the slightly larger time window chosen for the TWOI influenced the results for the topographical distribution of this effect.

reflects a difference in the physical features (size) of the cues. Note that that there are two possible explanations for this stronger cue-induced effect in PD participants. It could be the case that this effect was indeed larger in the PD group, or, perhaps more likely, because in the control group the differential effect was (partially) overridden by the strong desynchronization in anticipation of the target, that seemed absent in the PD group. In future studies this cue-induced difference should be avoided by using similarly sized cues for both conditions.

When comparing PD participants to control participants, while correcting for multiple comparisons across time and frequency, I only found a significant difference cluster in the visual ROI, where control participants showed significantly stronger temporal suppression of alpha oscillations than PD participants. In both motor ROIs, qualitatively similar differences did not survive similar correction. Note that I performed an additional analysis in which I examined line plots of alpha and beta band modulations over time, for the short vs. long cue contrast. This analysis gave qualitatively similar results to the analysis described above and is included in Appendix 3.3.

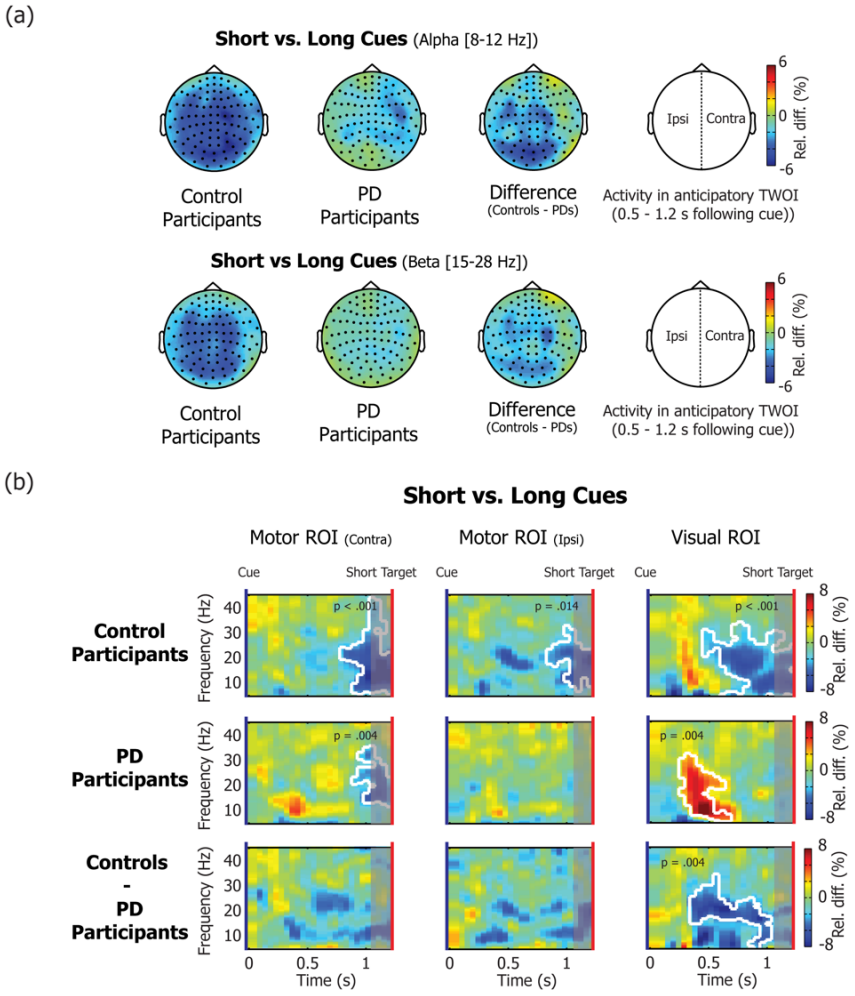


Figure 3.6 MEG results for the effect of temporal orienting of attention across time and frequency and space. (a) Topographies for the short-minus-long contrast, for contra- (shown in the right half of each plot) and ipsilateral (shown in the left half of each plot) channels. Topographies display activity averaged over frequencies between 8 - 12 Hz (top) and 15 - 28 Hz (bottom) in the anticipatory TWOI. (b) Time-frequency representation (TFR) plots showing the short-minus-long cue contrast for control participants (first row), PD participants (second row) and the difference between groups (control-minus-PD; third row), separately for the motor ROI contralateral (first column) and ipsilateral (second column) to the response hand, and the visual ROI (third column). The colour scale indicates a relative increase or decrease. Significant clusters after nonparametric cluster-based permutation testing are outlined in white. p-values reflect two-sided cluster p-values. The shaded area indicates a time period that cannot be considered purely "anticipatory" because target-evoked activity might bleed in.

Correlations between MEG data and behavioural performance

PD participants showed a weaker temporal orienting effect in behaviour, as well as in their anticipatory neural modulations, suggesting that the latter may mediate the former. To establish a link between beta modulations and performance, I correlated the magnitudes of the behavioural and the MEG results across both groups. Figure 3.7 shows time-and frequency-resolved correlations between the temporal validity effect in short interval (relative difference between RTs for validly vs. invalidly cued short targets[13]) and the short-minus-long contrast in the MEG data, calculated using the variability across participants.

Figure 3.7a shows the scatter plots of the individual participant scores, with control participants plotted in red and PD participants plotted in blue. On the x-axis the size of the behavioural validity effect (relative difference between valid vs. invalid cues) is plotted, while the y-axis shows the difference in beta (15 - 28 Hz) band activity following short vs. long cues, in the pre-defined anticipatory TWOI. For the control group, significant correlations were found for the contralateral motor ROI ($R = -0.76$, $p < .001$) and the ipsilateral motor ROI ($R = -0.68$, $p = .002$). The correlation in the visual ROI showed a non-significant trend ($R = -0.44$, $p = .07$). These results indicate that control participants with a larger RT difference between short vs. long temporal cues also showed a larger difference in beta band activity between expecting a target early (i.e. after a short cue) vs. expecting a target only later

[13] Note that invalidly cued short targets represent targets where a long cue was given (i.e. a short vs. long cue contrast for responses given after the short interval), and therefore was expected to correlate with the short vs. long cue difference in the MEG data.

(i.e. following a long cue). The PD group showed a non-significant trend in the contralateral motor ROI ($R = -0.42$, $p = .08$), and the correlations in the ipsilateral motor ROI ($R = -0.36$, $p = .14$) and visual ROI ($R = -0.10$, $p = .70$) were also found to be not significant. The Fisher r-to-z transformation was applied to assess the difference in the correlation values between both groups. This difference was not significant for any of the three ROIs (contralateral motor: $z = -1.49$, $p = 0.07$; ipsilateral motor: $z = -1.25$, $p = .11$; visual: $z = -1.02$, $p = .15$).

To probe the nature of these correlations, I also investigated these correlations across time and frequency, and plotted the topographical distribution of the effect. When considering the control group (top row in Figure 3.7b), a strong negative correlation was most prominent in the beta band, starting in the purely anticipatory period, but extending towards the target. This effect appeared slightly stronger in the contralateral than the ipsilateral motor ROI, and a small effect in the same direction also seemed to be present in the visual ROI. The topographies, shown in Figure 3.7c, with contralateral channels plotted on the right and ipsilateral channels plotted on the left, confirm the predominant motoric localisation of this effect[14]. In the PD group, correlations again seem largely absent. This absence of a correlation in the PD group is possibly due to reduced variability of interest as a result of the smaller behavioural effect and less anticipatory modulations with temporal orienting in this group.

[14] Note that in Fieldtrip it is not possible to perform cluster-based statistics on across subject correlations.

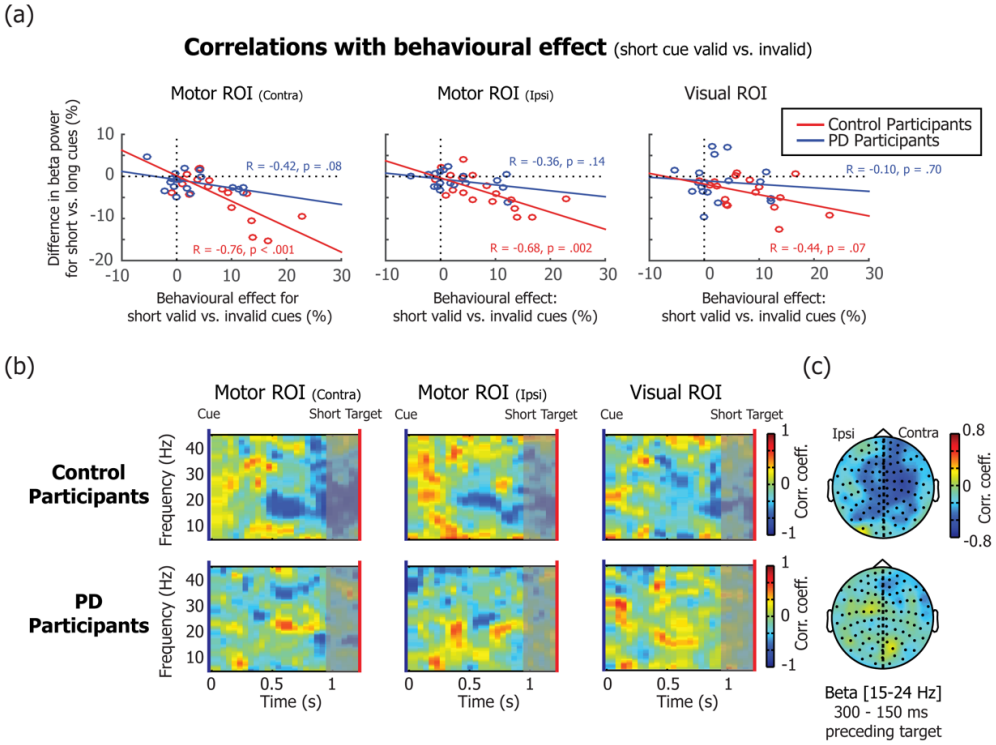


Figure 3.7 Correlations between temporal orienting effects in behavioural performance and anticipatory neural modulations. (a) Scatter plots and Pearson correlation coefficients for the relationship between the beta power difference between short vs. long cues in the anticipatory TWOI and the behavioural validity effect for short cues (relative difference between RTs following validly vs. invalidly cued short targets). Results are shown separately for the contralateral motor ROI (left), ipsilateral motor ROI (middle) and the visual ROI (right), and are shown separately for control participants (red) and PD participants (blue). Least squares lines are fitted to the data of both groups separately. (b) Correlation coefficients were calculated between the power for each time-frequency voxel and the behavioural validity effect for the short interval. Results are shown for frequencies between 5 and 45 Hz, for the early interval (0 - 1.2) only. Control participants are shown at the top and PD participants are shown at the bottom. The shaded area indicates a time period that cannot be considered purely 'anticipatory because target-evoked activity might bleed in. (c) Topographies of the effects shown in b) for contralateral (right) and ipsilateral (left) channels. Topographies display correlation coefficients between average beta band (15 - 28 Hz) activity and the behavioural validity effect for short cues in a window 300 - 150 ms preceding the target.

3.4 Discussion

In this chapter I investigated behavioural and neural dynamics of temporal orienting of attention in the context of a cued Go/NoGo task and asked whether and how this might be compromised in PD participants "off" dopaminergic medication. Behaviourally, both control and PD participants showed a benefit of valid temporal cues, but this effect was smaller in PD participants, compared to control participants. Moreover, for the control group, the effect of temporal orienting involved a desynchronization of alpha and beta band activity in bilateral motor ROIs as well as a central visual ROI. In the PD group, a similar (albeit weaker) modulation was observed, appearing only in the contralateral motor ROI and only in a relatively late part of the anticipatory time window of interest. Only the effect of temporal orienting in the visual ROI survived statistical comparison between groups, showing a decrease of alpha and beta band activity in the control group, while this effect was absent in the PD group.

3.4.1 Temporal orienting and timing deficits in PD

In cued temporal orienting tasks, like the one used in this experiment, cueing benefits are typically only observed at the short interval, as temporal expectations can be updated once the short interval has passed (see also Chapters 1 and 2 in this thesis). Focusing on the short interval, I observed that both groups showed a behavioural benefit of valid, compared to invalid temporal cues. This effect was stronger in the control group. This reduced temporal orienting effect in PD was unlikely to be mediated by differences in

general task performance, as RT distributions and performance accuracy were similar between groups.

Timing deficits in PD have previously been demonstrated in a range of different motor and perceptual timing tasks (see Jones and Jahanshahi, 2014 for a review). Most of these studies concerned explicit, rather than more implicit forms of timing[15]. For example, PD patients have previously been shown to be deficient in temporal discrimination in the tactile, auditory and visual modality (Artieda et al., 1992) and to exhibit impairments in both the estimation and reproduction of time intervals (Pastor et al., 1992; Lange et al., 1995; Harrington et al., 1998). Others have shown that PD patients are less able to synchronise to external rhythms, and show even stronger impairments when they have to maintain this rhythm when the extrinsic timing cues stop, suggesting a great reliance on external cues (Freeman et al., 1993; O'Boyle et al., 1996; Harrington et al., 1998). It is interesting to note that Jurkowski and colleagues (2005) found that PD patients showed deficits for voluntary, but not reflexive interval timing, suggesting that reflexive behaviours are spared in this condition.

In contrast to studies in which the time has to be tracked, or durations or rhythms have to be reproduced, implicit forms of timing are more often shown to be intact. A study by Jahanshahi and colleagues (1992) found that PD patients were able to benefit from warning signals when a foreperiod was

[15] Note that (as mentioned in the introduction) in explicit timing tasks measuring or keeping track of time is the end goal, while implicit timing involves tasks where temporal information is used to reach other task goals (which, in this experiment, is the goal of responding as fast as possible whenever a green target appears).

stable for a block of trials. Another study looking at anticipatory pursuit eye movements found no impairment in implicit temporal predictions in PD (de Hemptinne et al., 2013a). Here, I show that, although PD participants indeed benefitted from temporal cues, these temporal orienting effects were weaker than in control participants, both in behaviour and in anticipatory neural modulations.

3.4.2 Beta modulations in PD

In addition to measures of behavioural performance, I also investigated anticipatory neural dynamics associated with temporal orienting of attention. In the healthy sensorimotor system, such dynamics are associated with attenuated alpha and beta-band oscillations at times at which perceptual and motor events are expected (e.g. Doherty et al., 2005; Schoffelen et al., 2005; van Elswijk et al., 2007; van Ede et al., 2011; Zanto et al., 2011; Rohenkohl et al., 2011). In PD patients, it is well established that these oscillations show excessive synchrony, at least in basal ganglia-cortical circuits (see e.g. Hammond et al., 2007; Brittain and Brown, 2014). This may bear consequences for their ability to flexibly modulate these oscillations as a function of ongoing task demands. Interestingly, the MEG data (which is most sensitive to cortical sources) did not reveal excessive beta power in PD participants compared to control participants. Thus, increased beta synchrony in the basal ganglia is not reflected in cortical activity as detected in MEG.

Spectral analysis did, however, indicate peak frequency shifts in the PD group, compared to the control group (see also Bosboom et al., 2006; Stoffers

et al., 2007; Moazami-Goudarzi et al., 2008; Vardy et al., 2011). The exact nature of the results was dependent on analysis parameters, but overall the results were suggestive of a downwards shift of both alpha and beta peak frequencies. This is in line with reported shifts toward lower-frequency activity in PD (Bosboom et al., 2006; Stoffers et al., 2007; Moazami-Goudarzi et al., 2008; Vardy et al., 2011) as well as other neurodegenerative conditions (de Haan et al. 2008; Uhlhaas et al. 2017). Yet, despite this apparent shift, the group difference was not due to the PD group showing the same modulations in different frequency ranges. Moreover, the observed modulation in the contralateral motor ROI seemed to occupy a qualitatively similar frequency band as in the control group. It was therefore not the case that PD patients showed a similar modulation, but in a slightly different frequency range.

The MEG data showed that, in the control group, the effect of temporal orienting of attention appeared as a bilateral decrease in the alpha and beta band, while a significant cluster was only found for the contralateral ROI in the PD group. This effect in the PD group was less robust than the effect in control participants; it was not found when tested across frequency for the anticipatory TWOI, but only appeared when tested across time and frequency.

A series of related studies suggests that in the context of a regular, rhythmic task structure (i.e. a task where timing is implicit in the structure of the task), the time course of beta modulations is affected in PD (Praamstra and Pope, 2007; te Woerd et al., 2014, 2015, 2017), with beta desynchronisation in PD patients being more reactive, or target-induced (instead of anticipatory), compared to healthy control participants. In line with this, I also found that PD

patients showed less prominent anticipatory beta modulations when voluntarily orienting their attention in time following temporal cues.

Finally, it is worth pointing out that only for the control group I found a significant correlation between the temporal orienting effect in the behavioral data and the anticipatory modulations shown in the MEG data, showing that beta modulations are relevant for behaviour in this task. It is likely that this correlation did not reach significance in the PD group because both the behavioural and neural effects were smaller in size in this group.

3.4.3 Deficiencies in visual anticipation in PD

Although I was particularly interested in motor preparation, the visually guided motor task also involved a visual component, and therefore allowed me to look at neural dynamics associated with visual anticipation as well. In the visual ROI, I also found a significant group difference for the short vs. long cue contrast. The control group showed a clear anticipatory power decrease that was modulated by temporal expectation (i.e., stronger decrease when targets were expected early, similar to the modulation found for the motor ROI). Such a modulation with temporal orienting of attention appeared absent in the PD group, with the group difference also being significant.

Interestingly, Chauvin et al. (in preparation) performed a behavioural study in nearly the same group of participants using blocked temporal cues in both a speeded response (motor) task and a rapid serial visual presentation (RSVP) task. It was found that PD patients benefitted from temporal cues in the motor task, but not in the visual task. These data show that deficiencies in

temporal orienting in PD are not restricted to motor tasks, but may sometimes be even more pronounced in the visual domain, which is also in line with the current MEG results. In contrast, in my task, the visual aspects of the task were not very demanding, and yet I observed clear anticipatory modulations in control participants that were absent in PD. This calls for further research to map out in what contexts and modalities temporal orienting is particularly spared or impaired in PD.

Noteworthy, deficits in visual perception are often reported in PD (see Weil et al., 2016, for a review), and seem to occur across retinal, early visual, and higher cortical areas. How these reported deficits tie in with the apparent deficit in temporal orienting of visual attention also remains an interesting question for future studies.

3.4.4 Limitations and future directions

One limitation of the current study is that, as was shown by the frequency analysis of raw power, there were some physiological differences between the two groups to begin with, especially with respect to the alpha peak frequency. Such differences make it difficult to interpret task-related modulations between groups. I therefore focused my main analyses in a frequency-resolved fashion to reveal potential differences in the frequencies that were modulated during temporal orienting. In future research it may be useful to adopt a more individualised approach, where aspects of the individual participant signal are taken into account when evaluating contrasts of interest. As part of this more individualised approach, it may be important to perform more sophisticated

source analyses to determine the sources of the effects in the brain. The topographical distributions of alpha- and beta-band activity in the current study were relatively broad. Although (pre-)motor and visual areas are likely sources of anticipatory modulations with temporal orienting, this still needs to be confirmed in future research.

In this study, PD patients were tested off dopaminergic medication. While testing off medication allowed me to test for a specific effect of this disease on temporal orienting (instead of testing for such effects, mediated by variable doses of dopaminergic medication), it remains unclear whether the same results would have been obtained on medication. Studies differ in whether patients are tested "on" or "off", it is therefore difficult to compare these results with previous studies that only tested patients "on" medication.

In the current study, I considered the PD patients as one homogeneous group. Merchant and colleagues (2007) clustered PD patients into two subgroups, based on their performance on a temporal task. Whether such sub-classifications are associated with differences in behavioural and neural modulations remains another interesting target for future research.

Although the presence of qualitatively similar temporal orienting effects in PD and control participants suggests that PD patients understood task instructions well, I cannot rule out that the groups may have relied on different strategies. This may explain, for example, the distinct modulations observed over more posterior sites that I attributed to visual anticipation.

In future studies it is also important to jointly consider deficiencies in timing, problems in motor behaviour, and changes in beta oscillatory brain

dynamics that occur in PD patients, and how each of these variables are influenced by dopaminergic treatment and techniques like deep brain stimulation. Although these variables are difficult to tease apart and are likely to interact, it will be important to investigate the contribution of each of these factors to elucidate the precise mechanisms by which particular aspects of temporal orienting are diminished in PD.

3.4.5 Conclusions

I showed that PD participants off dopaminergic medication benefit less than control participants from valid temporal information to facilitate motor performance. Furthermore, I found that, in control participants, temporally anticipated targets and motor responses were accompanied by anticipatory decreases in the alpha and beta oscillations, occurring over task relevant, motor and visual cortical areas. Such modulations were largely reduced in PD participants who only revealed a qualitatively similar (albeit weaker) modulation in contralateral motor areas. I showed that in control participants the size of these anticipatory neural modulations correlated with behavioural performance benefits, suggesting that these neural modulations may mediate the behavioural benefit of valid temporal cues. These results suggest a graded temporal orienting deficit in PD in which that the use of temporal cues to prepare for upcoming actions is not abolished, but is attenuated in PD.

Chapter 4: Anticipatory cognitive and neural dynamics in hidden visual-motor sequences

In daily life, temporal expectations may derive from incidental learning of recurring patterns of intervals. Likewise, it has been shown in the lab that performance improves when participants respond to events that are structured in repeating sequences, suggesting that learning can lead to proactive anticipatory preparation. Whereas most sequence-learning studies have emphasised spatial structure, most sequences that we encounter in daily life also contain a prominent temporal structure. In Chapter 4, I used MEG to investigate spatial and temporal anticipatory neural dynamics in a modified serial reaction-time (SRT) task. In this experiment I compared performance and brain activity between blocks with learned spatial-temporal sequences and blocks where new sequences were presented instead (probe blocks). In the behavioural analysis I first confirmed a strong behavioural benefit of spatial-temporal predictability. Participants did not only get faster over time, but were also slower and less accurate during probe blocks, indicating that they learned the hidden sequence structure. I then addressed the hypothesis that implicit temporal orienting (evoked by the learned temporal structure) would have the largest influence on performance for targets following short (as opposed to longer) intervals between temporally structured sequence elements, paralleling classical observations in tasks using temporal cues. I found that, in line with this hypothesis, reaction time differences between new and repeated sequences were largest for the short interval, compared to the medium and long intervals, and that this was the case, even when comparing late blocks of the repeated sequence (where the sequence had been incidentally learned), to early blocks (where this sequence was still unfamiliar). For the MEG data, I show lateralisation of beta oscillations in anticipation of the response associated with the upcoming target location. In line with the behavioural results, this anticipatory beta lateralisation aligned to the expected timing of these forthcoming events. A stronger beta lateralisation was found at times that targets were expected, both when comparing between repeated (learned) and new (unlearned) sequences, as well as when comparing targets that were expected after short vs. long intervals within the repeated (learned) sequence. These findings suggest that learning of spatial-temporal structure leads to proactive and dynamic modulation of motor cortical excitability in anticipation of both the location and timing of events that are relevant to guide action.

The behavioural data presented in this chapter have been published as Heideman et al. (2017a). The MEG data presented in this chapter have been published as Heideman et al. (2017b).

4.1 Introduction

Many actions in daily life consist of structured sequences. Examples can be found in speech, driving a car, performing sports, or playing the piano. As sequences are repeated, performance improves. In the laboratory, sequence learning is typically studied using the serial reaction-time (SRT) task. In classic SRT tasks (see Nissen and Bullemer, 1987, for a first description of the task), participants have to follow the order of targets presented at four different locations on the screen by pressing the corresponding button whenever a target is presented. The button press either triggers the presentation of the next target, or alternatively, a fixed stimulus onset asynchrony (SOA) is used. Unknown to participants, the targets follow a repeating sequence, usually of length 8-12. In such tasks participants generally get faster over the course of the experiment, while it is unknown to them that they learned something. When 'probe blocks' — blocks containing a random or novel sequence — are presented, reaction times are much slower, indicating that these effects are caused by the incidental learning of the sequence, instead of a general effect of training.

The vast majority of SRT studies to date have focused on the learning about the spatial structure of events (see Abrahamse et al., 2010 and Schwarb and Schumacher, 2012, for reviews). They show that performance improves over the course of the experiment, while the precise sequence information (and the fact that elements are repeated) often remains implicit. Moreover, naturally occurring sequences often also contain temporal structure.

Accordingly, sequence-learning paradigms have been used to investigate not only the acquisition of spatial visual-motor sequences, but also how temporal aspects of such sequences are acquired (Buchner and Steffens, 2001; Salidis, 2001; Shin and Ivry, 2002; Ullen and Bengtsson, 2003; Karabanov and Ullen, 2008; O'Reilly et al., 2008a; Gobel et al., 2011; Kornysheva et al., 2013; Schultz et al., 2013; Kornysheva and Diedrichsen, 2014; Sanchez et al., 2015). Temporal learning in this type of task is said to be implicit, or 'incidental'. Incidental learning occurs as a by-product of non-temporal task goals, when stimuli or motor responses adhere to a strict temporal framework (see Coull and Nobre, 2008, for the proposed distinction between implicit and explicit timing). In such a situation, participants are not asked to time or recall the different intervals used in the task, but the temporal structure influences performance measures. Such incidental learning can be shown in the pattern of reaction times, which decrease over time in a manner consistently related to the temporal structure inherent to the task. SRT tasks containing a recurring sequence of temporal intervals show that learning of temporal sequences affects behavioural measures like reaction times, at least when they are combined with a stable spatial sequence. However, it is not yet clear how the influence of learned temporal structure on behaviour and neural processing develops over time.

From research on temporal orienting following informative temporal cues, we know that temporal cueing is most effective at short, compared to long intervals that are cued in the same task (e.g. 300 vs. 1500 ms in Coull and Nobre, 1998; see also Miniussi et al., 1999; Correa et al., 2006a; Nobre, 2010;

Rohenkohl et al., 2014 and Chapters 2 and 3 in this thesis). This can elegantly be explained by the notion of hazard rates, as is explained in the General Introduction. Whereas at short intervals participants will be most engaged following cues that predict short intervals, at long intervals their engagement will have become largely independent of the cue, because once the early interval has passed, it is certain that the stimulus will thus occur late (thus superseding the cue information). In other words, for events that are due to happen, knowledge about their expected timing will be most beneficial at early intervals. Based on this literature on temporal orienting following explicit cues, my first hypothesis is that incidentally learned temporal structure will also have the strongest impact on performance for targets that occur following short (as opposed to longer) intervals (with intervals referring to the intervals between the targets that comprise the sequence).

Furthermore, studies to date largely overlook a fundamental complementary question about sequence learning: How are learned spatial and temporal sequences utilised by the brain to improve performance? Learned sequences afford spatial and temporal predictions about the locations and timings of upcoming elements, which in principle could be used to modulate preparatory neural activity to enhance performance.

Studies in which predictions regarding upcoming sensory input or required motor responses are cued typically show anticipatory power decreases of alpha and beta oscillations over relevant (contralateral) sensory and/or motor areas (e.g. Pfurtscheller and Lopes da Silva, 1999; Sauseng et al., 2005; Schoffelen et al., 2005; Alegre et al., 2006; Thut et al., 2006; Kelly et al.,

2009; Rihs et al., 2009; Gould et al., 2011; Jenkinson and Brown, 2011; van Ede et al., 2011). Anticipatory decreases over sensory areas are thought to reflect increased excitability states that benefit the processing of the anticipated stimuli, while power decreases over motor areas are thought to reflect enhanced motor readiness (see also Chapter 1). Studies investigating the additional influence of temporal expectations further show that the time course of such power modulations in the alpha and beta frequency bands adapts to the timings used in the task, thereby ensuring optimal preparation for the moment when targets are expected (e.g. Schoffelen et al., 2005; Alegre et al., 2006; Rohenkohl and Nobre, 2011; van Ede et al., 2011).

My second hypothesis is therefore that the hidden spatial and temporal predictions within complex visual-motor sequences in an SRT setting will support similar anticipatory changes in oscillatory power. In SRT settings that manipulate spatial and temporal sequences, there is evidence for a strong behavioural interaction between space and time for improving performance (O'Reilly et al., 2008a; for further evidence for such spatial-temporal 'synergies', see also Doherty et al., 2005; Rohenkohl et al., 2014). I thus expected that anticipatory changes in oscillatory power would adhere to both the learned spatial and temporal aspects of the sequence, i.e. would not only lateralise depending on the predicted target/response, but also adapt to its expected timing, with the largest benefits occurring for short intervals.

In this experiment, I used magnetoencephalography (MEG) to investigate these neural dynamics within visually guided action sequences. Whole-head MEG measurements enabled me to additionally evaluate the respective

contributions of anticipatory neural dynamics in sensory and motor cortices. This is of interest, as both perceptual and motor preparation have been argued to contribute to performance improvements in SRT tasks (Howard et al., 1992; Willingham, 1999; Hoffmann et al., 2003; Clegg, 2005; Deroost and Soetens, 2006; Song et al., 2008; Schwarb and Schumacher, 2012)

4.2 Methods - Task development and pilot study

In this study I used an adapted version of the SRT task used by O'Reilly et al. (2008a) that contained blocks with either learned or pseudorandom sequences. O'Reilly and colleagues exposed participants to blocks of trials that had a repeating spatial sequence, a repeated temporal sequence, or both. However, because I aimed to use this task in MEG and fMRI, it was necessary to make some changes with respect to the O'Reilly et al. (2008a) task, which I will discuss below.

In total, I conducted 4 behavioural pilot studies to assess whether the task worked as expected and whether the behavioural results showed the predicted patterns. Results for one pilot study are included here. Other pilot studies (not shown in the current thesis) included two preceding pilot studies involving slightly altered versions of the task discussed here and a pilot study of the final task that was used in the main experiment.

4.2.1 Changes with respect to previous SRT studies

Because this experiment was designed for subsequent use with MEG, several changes were made with respect to previous SRT studies. In MEG we know that blinking and eye movements highly disturb the signal. In this pilot study, I therefore tested whether participants could do the task while keeping fixation and trying to minimize blinking. I included regular blinking breaks to limit blinking during task performance. To test for saccades, binocular eye movements were monitored during the experiment with a desktop mount video based eye tracker at 1000 Hz (EyeLink 1000, SR Research, Ontario, Canada). The eye tracking data were monitored throughout the study to determine whether participants managed to comply with the instructions, but these data were not subsequently analysed.

Other adjustments to make this more task suitable for MEG was the use of slightly longer intervals, to provide long enough time windows for MEG analysis and to ensure reliable hazard rate effects and the use of both hands for delivering responses, which would allow me to look at lateralised motor-related activity. It is important to note that although switch costs between fingers of different hands are generally found to be larger than between fingers of the same hand, bimanual SRT tasks have also been found to produce reliable sequence learning effects (see e.g. Trapp et al. 2012; Bhakuni et al. 2015; Hoff et al. 2015). Meier and Cock (2014) directly compared bimanual and unimanual responses and found no difference in performance. Importantly, in the current experiment I equated the number of hand-switches between conditions, which therefore will not have influenced the effects of interest.

Finally, I used intervals between responses and subsequent stimuli (response-to-stimulus intervals; RSIs) as opposed to between stimuli intervals (stimulus onset asynchronies; SOAs) in order to avoid contamination of stimulus-induced effects by response-related processes and to manipulate the temporal regularity of events within sequences. This latter adaptation was also justified by Shin and Ivry (2002), who previously reported comparable learning effects for SOA and RSI manipulations in a spatial-temporal RT task.

4.2.2 Experimental task and procedure

This behavioural pilot was approved by the Central University Research Ethics Committee of the University of Oxford (MSD-IDREC-C1-2012-98). Fourteen University of Oxford students participated. The experimental task is depicted in Figure 4.1. Series of targets were presented in blue on a grey background, next to a small fixation square (0.17° x 0.17°of visual angle), at four locations on the screen, indicated by a permanent white square outline (2.12° x 2.12° of visual angle for each square, total width of all stimuli: 11.66° x 2.12° of visual angle). Participants had to follow the order of targets by pressing corresponding keys on a computer keyboard. Unknown to the participants, the positions of the targets (and thus the pattern of responses) followed a 12-element cycle: ABACDBCADCBD, where A was the first position/left middle finger; B the second position/left index finger, C the third position/right index finger and D the fourth position/right middle finger. The response stimulus interval (RSI) was 667, 1000, or 1500 ms. The RSI factors were related by a scalar factor of 1.5. Like the spatial responses, the RSIs followed a repeating

12-element cycle: ABCABACBACBC. The spatial and temporal sequences were thus linked at the level of the 12-element cycle.

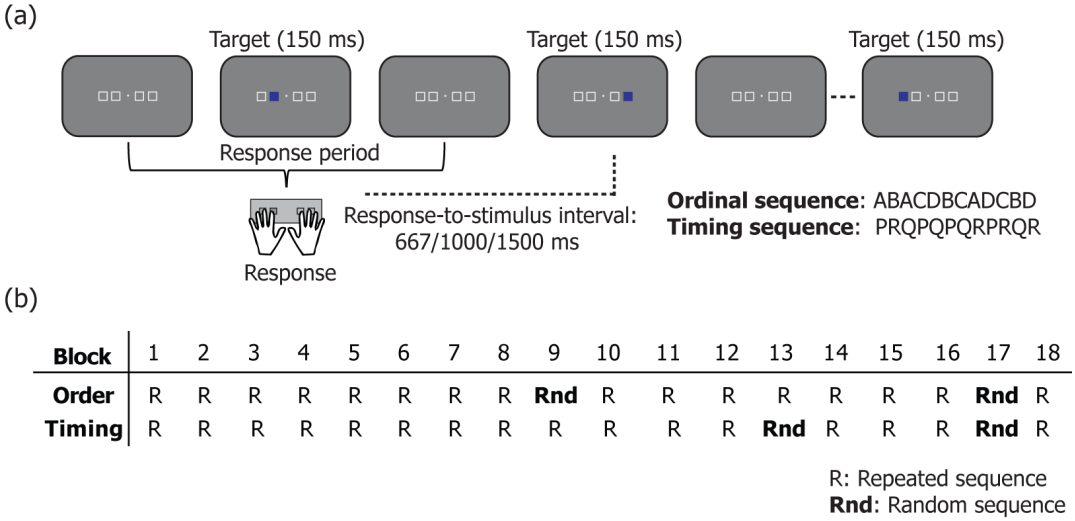


Figure 4.1 Pilot task. (a) Targets were presented in blue on a grey background. Four possible target locations on the screen corresponded to four button locations, to be pressed with the left and right middle and index fingers. Whenever a target appeared participants had to press the corresponding button. Unknown to participants, the order of the targets followed a repeating twelve-element cycle. The response-to-stimulus interval (RSI) preceding each target was one of three possible lengths: 667, 1000 or 1500 ms. In addition to the spatial sequence, the order of RSIs used in this study also followed a repeating twelve-element cycle. (b) Eighteen blocks of 96 trials each were presented in total. Fifteen of these blocks contained the repeated sequence ("R" blocks). Block 9, 13 and 17 were probe blocksi in which the order, timing, or both the timing and order were replaced by a pseudorandom order ("Rnd" blocks). The order of the three different types of Rnd blocks was counterbalanced across participants.

The experiment consisted of 18 blocks of approximately 2.5 minutes each. Fifteen blocks contained the repeating sequence (denoted "R" blocks in Figure 4.1). Three of the blocks (block 9, 13 and 17) were probe blocks, in which the spatial or timing sequence (or both) was replaced by a

pseudorandom sequence (counterbalanced across participants). The order of the three types of probe blocks (timing random: T, order random: O, and both timing and order random: TO) was counterbalanced between participants. Each block consisted of 96 trials, and contained an equal number of trials of each of the possible intervals, and of each possible target position and response. The total number of trials was 1728. Pseudorandom blocks were equated to sequenced blocks for simple event frequencies (see Reed and Johnson, 1994). Subsequent presentations of the same spatial stimulus were never more than 4 stimuli apart. Subsequent presentations of the same RSI were never more than 3 stimuli apart. Specific stimulus locations or RSIs were never presented twice in a row.

4.2.3 Behavioural analysis

Behavioural data were analysed using MATLAB (The MathWorks, Inc., Natick, MA) and statistics were performed in SPSS version 22 (IBM Corp. Armonk, NY). Separate averages were calculated per participant, per block. Only correct responses were included in the RT analysis. The first two trials after each break were excluded from the analysis because subsequent targets and intervals could only be anticipated when at least two preceding stimuli were present. In addition, trials with an RT shorter and larger than the mean plus or minus three times the standard deviation across participants were excluded.

4.3 Results - Task development and pilot study

4.3.1 Behavioural results

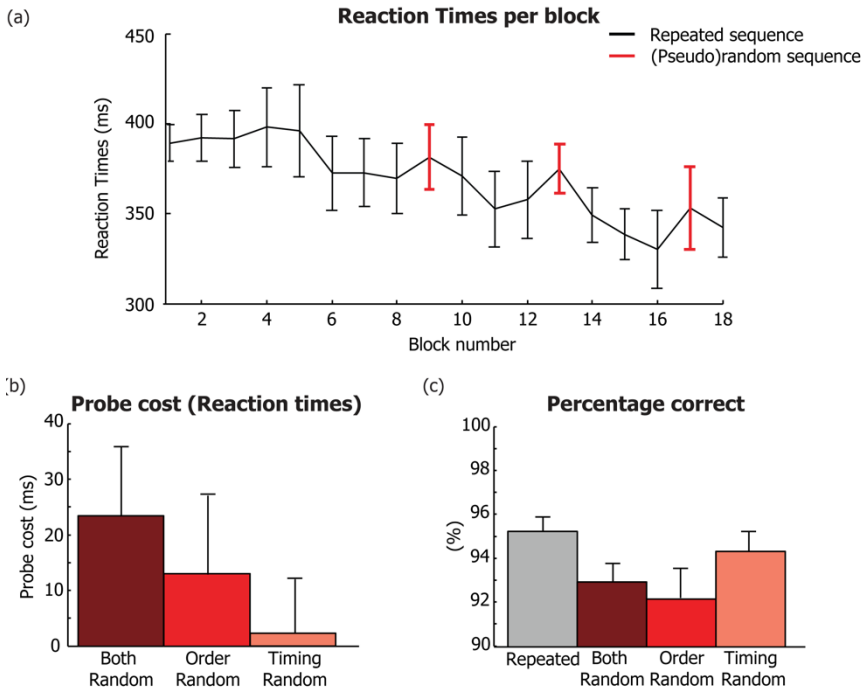


Figure 4.2 Behavioural results of pilot task. Results are shown for (a/b) reaction times (RTs) and (c) percentage of correct trials (PCs). Results for blocks with a repeated sequence are shown in grey, while results for blocks in which a (pseudo)random sequence was presented are shown in red. Error bars present standard error of means (SEM), calculated using the variance across participants.

RTs per block over the course of the pilot session are shown in Figure 4.2a. If implicit learning took place, RTs in repeated-sequence (R) blocks should decrease over the course of the experimental session. I tested this by pooling the R blocks in three groups of five blocks and comparing mean RT values in a repeated-measures ANOVA. This analysis showed that RTs indeed decreased over the course of the session ($F(2,12) = 19.06$, $p = .0001$, partial η^2

= 0.76). Follow up t-tests showed a decrease in RT between the first five blocks compared to the middle five blocks ($t(13) = 3.27$, $p = .006$, Cohen's $d = 0.95$) and a subsequent decrease between the middle five blocks and the last five blocks ($t(13) = 3.18$, $p = .007$, Cohen's $d = 0.91$).

Another way of assessing implicit learning is the introduction of probe blocks. RT differences between probe and sequenced blocks are shown in Figure 4.2b. Here I compared the mean reaction time during probe blocks with the mean RT during the two preceding repeated sequence blocks (R). I first performed a paired samples t-test between the average RT across all three probe blocks (O, T and TO) and the average RT in all preceding R blocks. This analysis revealed a significant difference between repeated sequence blocks and probe blocks ($t(13) = 2.19$, $p = .047$, Cohen's $d = 0.759$). To assess if the probe cost differed between the different types of probe blocks, I performed a repeated-measures ANOVA with the factor Probe Block Type (O, T or TO). Contrary to my hypothesis, there was no main effect of Probe Block Type ($F(2,12) = 0.80$, $p = .47$, partial $\eta^2 = 0.12$), indicating that the probe costs were similar for each type of probe block.

Percentage correct (PC) for each block type is shown in Figure 4.2c. The average percentage correct over the whole experiment was 94.8%. I performed a paired samples t-test between the average PC across all three probe blocks (O, T and TO) and the average PC in all preceding R blocks. This analysis revealed a significant difference ($t(13) = 2.87$, $p = .013$, Cohen's $d = 0.768$). To assess if the probe cost differed between the different types of probe blocks, I performed a repeated-measures ANOVA with the factor Probe

Block Type (O, T or TO). There was again no main effect of Probe Block Type $F(2,12) = 1.58$, $p = .25$, partial $\eta^2 = 0.21$), indicating that the probe costs were again similar for each type of probe block.

After the pilot, I asked participants if they noticed the repeating pattern. Most participants initially reported they did not notice the repeating spatial pattern, but after further questioning almost all of them said that at some point during the experiment they felt they could 'predict' what the next stimulus would be. Most of them also mentioned that these predictions however turned out to be wrong and that they did not try to detect patterns afterwards. Five participants reported that they sometimes responded prematurely and therefore had to respond twice. One participant explicitly learned the spatial pattern and used this to predict his subsequent responses. This participant was the only one who noticed that I included probe blocks. None of the participants noticed the temporal pattern, although after further questioning half of the participants reported to have noticed that the intervals were not always the same.

4.3.2 Evaluation and final MEG design

After this experimental pilot, I made additional changes to improve the task for the main experiment. First, I decided to include an initial behavioural session, taking place one day before the MEG session, to increase the chance that the pattern could be incidentally acquired before, and therefore used during the MEG session. Second, to maximise behavioural effects and to ensure enough trials for the MEG analysis, I decided to include only conditions in

which both temporal and spatial information followed the learned sequence, or in which both types of information were changed. Conditions in which both order and time repeated vs. conditions where both order and time were new was the comparison yielding the largest behavioural difference in a related previous study (O'Reilly et al. 2008a), and should therefore likely also show the strongest effects in the neural data. This was also the condition showing the numerically largest difference in this behavioural pilot study (see Figure 4.2), although the difference relative to the other types of probe blocks did not reach significance. Third, I decided to use three fully controlled new sequences that would be repeated within a specific probe block, instead of the pseudorandom sequences that were used in the pilot, to be able to control second-order conditional probabilities between blocks even better (see Reed and Johnson, 1994). Reed and Johnson showed that it is important to keep a number of parameters the same between repeated and probe sequences. These parameters are A) location frequency: how often each location occurs within the sequence; B) transition frequency, how often each possible transition between locations occurs; C) reversal frequency: how often back and forth movements occur (e.g. Position 1 - Position 2 - Position 1, see also Vaquero et al., 2006); D) rate of full coverage: how many targets occur before each location has at least occurred once; E) rate of complete transition usage: average number of targets before each possible location transition has occurred at least once. In addition to these constraints, I ensured that each of the three RSIs occurred once with every location, with the same RSI never occurring twice in a row. Finally, I developed a more thorough way of assessing

explicit awareness, instead of only informally asking participants if they noticed anything about the task (see main experiment). This new version of the study was piloted to ensure the effect would now indeed appear more strongly[16].

4.4 Methods - Main experiment

4.4.1 Participants

Twenty-one young, healthy volunteers (aged 24.7 ± 3.9 (SD), 9 males, 12 females) participated in this study. All were right handed according to self-report and all had normal or corrected-to-normal vision. All participants gave written informed consent and the study was approved by the Central University Research Ethics Committee of the University of Oxford (MSD-IDREC-C2-2014-036). Participants received money for their participation (£10 per hour). Each participant completed three experimental sessions: a behavioural session followed by an MEG and an fMRI session, all taking place on separate days (see 4.4.3 Overview of sessions). In this Chapter, I will describe the behavioural results from all three sessions, in addition to the MEG results from session 2. One participant was excluded from all analyses because of extreme fatigue during all three experimental sessions, causing a high number of mistakes and long gaps where the sequence was interrupted, especially during the second session (percentage correct was lower than the

[16] Results for this subsequent pilot are not included in the current thesis, but the behavioural patterns looked similar to the results reported for the main experiment.

mean minus 3 times the standard deviation across participants). Another participant was excluded from all analyses because of a very slow mean reaction time (larger than the mean plus 3 times the standard deviation across participants). One participant was excluded from the analysis of MEG data only, because technical difficulties during the recording unfortunately resulted in the loss of trigger information. I included the results of nineteen participants (aged 22.6 ± 4.0 (SD), 9 males, 10 females) in the behavioural analysis, and results of eighteen participants (aged 24.7 ± 4.0 SD, 8 males, 10 females) in the MEG analysis[17].

4.4.2 Experimental setup

All sessions were run in rooms with similar (normal) illumination. Stimuli were created with MATLAB (The MathWorks, Inc., Natick, MA) and presented using Psychtoolbox version 3.0 (Kleiner et al., 2007). During the first session stimuli were displayed on a 24-inch Viewsonic display with a spatial resolution of 1280 x 720 pixels and a refresh rate of 60 Hz at a viewing distance of 80 cm. Responses were collected via the computer keyboard, using the 'A', 'D', 'J' and 'L' keys.

Data collected during the second session were part of a whole-head MEG recording, acquired using an Elekta NeuroMag MEG System (Elekta, Stockholm, Sweden) in a magnetically shielded room at the Oxford Centre for Human Brain Activity. A magnetic Polhemus FastTrak 3D system (Vermont,

[17] I performed the behavioural analysis both with and without this last participant and note that the pattern of behavioural results does not change (and looks nearly identical) when this additional participant is excluded.

United States) was used for head localisation. Relative positions of three anatomical landmarks (nasion, left and right auricular points) were measured in addition to relative positions of four head-position indicator coils.

MEG data were collected in three separate recordings of 10-12 minutes each. In between the recordings the data were saved while participants remained seated in the MEG chair. MEG data were sampled at 1000 Hz using a 0.03 - 300 Hz bandpass filter during digitisation of the signal. ECG and horizontal and vertical EOG were recorded. Eye movements were additionally recorded with a video-based eye tracker at 1000 Hz (EyeLink 1000, SR Research, Ontario, Canada). A 4-button bimanual fibre-optic response device was used to collect manual responses. Stimuli were created with MATLAB (MathWorks, Natick, MA) and presented using Psychtoolbox version 3.0 (Kleiner et al., 2007). Stimuli were back projected (Panasonic PT D7700E, Panasonic, Osaka, Japan) on a 43 x 54.5 cm translucent screen placed 120 cm in front of the participant, with a spatial resolution of 1280 x 1024 and a refresh rate of 60 Hz.

Data collected during the third, final session were part of a functional magnetic resonance imaging (fMRI) session, acquired on a 3T Siemens TIM Trio scanner (Siemens AG, Erlangen, Germany) at the University of Oxford Centre for Clinical Magnetic Resonance Research. Stimuli were back projected onto a translucent screen that participants viewed through a mirror placed on the head coil. Responses were collected using a single 4-button fibre-optic response device held with both hands.

Both the short behavioural practice session preceding the final session and the assessment of explicit awareness following the final session were presented on a 15.6-inch Dell laptop with a spatial resolution of 1280 x 1024 pixels and a refresh rate of 60 Hz at a viewing distance of 60 cm. Responses were collected via the laptop keyboard, using the 'A, 'D', 'J' and 'L' keys.

4.4.3 Experimental procedure and stimuli

Overview of sessions

Each participant completed three experimental sessions. The first, behavioural, session lasted approximately 30 minutes and involved the participant giving informed consent, followed by task instructions and twelve blocks of the repeated sequence (see 4.4.3 Experimental task). The aim of this first session was to train participant on the task and on the spatial-temporal sequences, in order to ensure that the effects of learned sequence structure would be well established in the MEG session the next day.

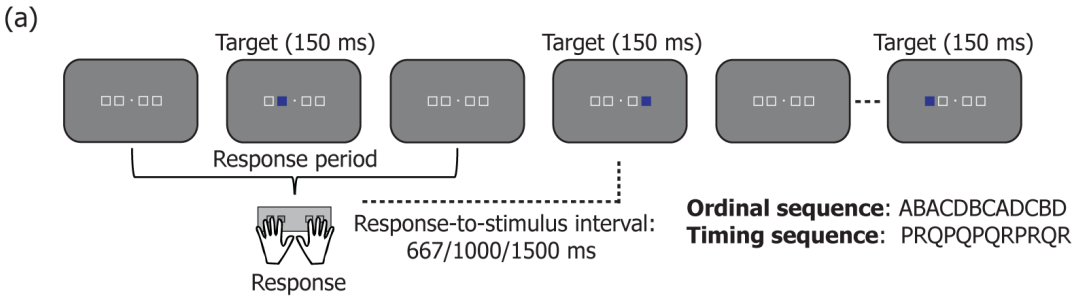
The second session took place one day later and lasted approximately 45 minutes, excluding MEG setup time. In this session participants again performed twelve blocks of the task, but now occasionally blocks with new sequences were inserted (see 4.4.3 Experimental task).

The final, fMRI, session took place one or two weeks later and lasted approximately 60 minutes. This session included a short practice to re-familiarise participants with the task, seven blocks of the task inside the scanner, a T1 structural scan, and the assessment of explicit awareness (see 4.4.3 Assessment of explicit awareness of spatial and temporal task features).

Experimental task

Participants performed a modified version of a serial reaction time (SRT) task (see Figure 4.3a). Four locations on the screen were permanently indicated by white square outlines (2.12° x 2.12° of visual angle for each square, total width of all stimuli: 11.66° x 2.12° of visual angle) to the left and right of a small fixation square (0.17° x 0.17°of visual angle) against a grey background. Within these outlines, series of targets were presented in blue. Participants had to follow the order of targets by pressing corresponding keys on the keyboard. Participants used the middle and index finger of the left and right hand to respond in a corresponding layout to the four designated buttons of the response device (see 4.4.2 Experimental Setup).

Unknown to participants, the positions of the targets (and therefore the pattern of responses) followed a twelve-element cycle: ABACDBCADCBD, where A was the first position/left middle finger; B the second position/left index finger, C the third position/right index finger and D the fourth position/right middle finger. The next target was only displayed after a correct button press was made, i.e. participants had to correct themselves whenever they made a mistake. The response-to-stimulus interval (RSI) was either 667, 1000 or 1500 ms. The RSI factors were related by a scalar factor of 1.5. Like the spatial responses, the RSIs followed a repeating twelve-element cycle: PRQPQPQRPRQR. The spatial and temporal sequences were thus only linked at the level of the twelve-element cycle. Each eight repetitions of the twelve-element sequences constituted one block of trials used for analysis.



(b)

Block	1	2	3	4	5	6	7	8	9	10	11	12
Behavioural session	R	R	R	R	R	R	R	R	R	R	R	R
MEG session	R	R	R	**N**	R	R	R	**N**	R	R	R	**N**
fMRI session	R	**N**	R	**N**	R	**N**	R					

R: Repeated sequence
N: New sequence

Figure 4.3 Task and overview of sessions. (a) Experimental task. Four white squares displayed on a grey background outlined four possible target locations. Each target location corresponded to one of four buttons, to be pressed with the left and right middle and index fingers. Every time a blue target appeared in one of the four target locations, the corresponding button had to be pressed. Unknown to participants, both the order of targets and the order of response-to-stimulus intervals (RSIs) followed a repeating twelve-element cycle. Three different RSI lengths were used: 667, 1000 and 1500 ms. Two different block types were presented: repeated sequence (R) blocks, containing eight repetitions of the twelve-element cycle, and new sequence (N) blocks in which a new spatial-temporal sequence was presented. (b) Overview of sessions. Participants took part in three experimental sessions: a behavioural session containing only R blocks, and an MEG and an fMRI session where R and N blocks alternated.

The first (behavioural) session consisted of twelve repeated (R) blocks (see Figure 4.3b). Each block consisted of 96 trials, and contained an equal number of trials of each of the possible combinations between interval and target position (and therefore response). The total number of trials in this session was 1152. Self-paced brakes were inserted every three blocks.

In the second (MEG) session, three blocks containing the repeated sequence (R blocks) were alternated with probe blocks containing a new, unlearned sequence (N blocks), for a total of twelve blocks, i.e. the experiment consisted of nine R and three N blocks (see Figure 4.3b). The new sequence was repeated eight times within a N block, but a different sequence was used for each N block. Unlearned sequences were used instead of pseudorandom sequences, which are often used in SRT tasks, to ensure that sequence characteristics would be as similar as possible between R and N blocks, with the only difference being whether participants previously had been exposed to the sequence or not. Short eight-second blinking breaks were inserted every 32 trials; a longer break occurred after every four blocks, during which the data were saved. This second session contained a total of 864 R and 288 N trials. Because the first two trials after each break were excluded from the analysis (see 4.4.4 Behavioural Analysis), each block started at a different (random) point within the repeated sequence, to ensure that approximately equal numbers of trials were excluded for each interval-position combination.

Before the third (fMRI) session one to two weeks later, participants completed a short behavioural practice session containing three R blocks interleaved by two self-paced breaks, to refamiliarise themselves with the task. The task design in the third session was adapted for fMRI; four R blocks alternated with three N blocks (see Figure 4.3b). After every 24 trials, there was a 16-second break, to allow the haemodynamic response to go back to baseline. The time spent inside the scanner was approximately 25 minutes. After being in the scanner I assessed participants' explicit awareness of the

sequence structure (see 4.4.3 Assessment of explicit awareness of spatial and temporal task features). The full session lasted around 60 minutes, including practice and assessment of explicit awareness. Similar to the second session, each block started at a different (random) point within the repeated sequence.

Assessment of explicit awareness of spatial and temporal task features

After the final session, I assessed explicit awareness of both the spatial and temporal features of the task. I first asked participants verbally about their awareness of the repeated spatial sequence: *'Did you notice there was a repeated sequence?'*, *'How confident, on a scale from 1-5, would you be that you could type out the sequence?'*. After answering these two questions I asked each participant to give this a try. Participants were presented with four empty squares, and I asked them to type out a sequence with a length of twelve, starting at any location, with targets showing up immediately when buttons were pressed. Subsequently, I asked them about the temporal features of the task: *'Did you notice anything about the timings in the experiment?'*, *'How confident, on a scale from 1-5, would you be that you could type out the sequence, also taking the temporal information into account?'* After answering these questions I asked participants to type out the remembered sequence for a second time, this time also taking the temporal information into account, as they remembered it. As each combination of three subsequent targets (i.e. each triplet) presented in the repeated sequence was unique, in a final assessment I presented participants with twelve combinations of two targets, as they appeared in the task, and asked them to press a button for the target they

predicted to appear next. These twelve combinations were presented in random order.

4.4.4 Behavioural analysis

Behavioural data were analysed using MATLAB (The MathWorks, Inc., Natick, MA) and statistics were performed in SPSS version 22 (IBM Corp. Armonk, NY). Since only combinations of three or more stimuli (triplets) were unique and allowed for preparation for the next, upcoming stimulus, I excluded the first two trials after each break from the analysis. In addition, I discarded trials with an RT shorter and larger than the mean plus or minus 3 times the standard deviation of the participant's mean reaction time in an experimental session. On average, 1.1 ± 0.5% (SD) of trials were rejected based on reaction times, with the maximum being 2.2% for one participant. Only correct responses were included in all RT analyses. When anticipatory responses (occurring during the RSI interval before target presentation) were made with the correct button, I included them in the RT analysis because excluding them might artificially mask the learning effect[18]. Premature responses occurred in 0.5 ± 1.1% (SD) of trials, with the maximum being 5% of trials for one participant.

Analysis of the assessment of awareness of order was performed by dividing both typed-out sequences into 12 triplets, and calculating how many of these triplets also occurred in the repeated sequence. In addition, I

[18] Note, however, that the pattern of results does not change when I exclude premature responses.

determined how many of the twelve combinations of two targets shown in the final task were finished correctly. These numbers were statistically tested against chance.

Analysis of the assessment of awareness of temporal information was performed for both typed out sequences separately by marking the four shortest RTs within a produced sequence as 'short interval', the four medium RTs as 'medium interval' and the four longest RTs as 'long interval'. I compared this produced sequence of short, medium and long intervals with the real sequence of short, medium and long intervals to establish, per participant, the longest temporal sequence that corresponded to the repeated sequence of short, medium and long RSIs used in the task. The same comparison was done with the three sequences that appeared in the new sequence blocks; I then compared the number corresponding to the maximum overlap with the repeated sequence statistically with the average maximum overlap with the three new sequence blocks.

4.4.5 MEG Analysis

Pre-processing and artefact rejection

MEG data analyses were performed using the in-house OHBA Software Library (OSL) version 2.0, Fieldtrip (Oostenveld et al., 2011), and custom-written MATLAB code. Using Maxfilter, MEG data from each participant were subjected to noise reduction using spatiotemporal signal space separation (TSSS). Neuromag's MaxFilter software minimises extra-cranial noise by separating signals arising from inside and outside the helmet (Taulu et al.,

2004), with the temporal extension method additionally removing interference from nearby sources (Taulu and Simola, 2006). MaxFilter also compensates for the effect of head movement by using continuous head position measurements. After using MaxFilter, the data were down-sampled to 250 Hz. A 0.1-Hz high-pass filter was applied to the data to remove low-frequency drift. Independent Component Analysis (ICA) was performed to reject artefacts associated with eye blinks, eye movements, and heartbeat. I inspected all artifactual components visually before removing them from the data. After epoching the data OSL's variance-based automated artefact detection was applied. Trials excluded during the behavioural analysis stage, including the first two trials after each break (see 4.4.4 Behavioural analysis), were excluded from the MEG data as well. On average 19.6 ± 4.6% of trials were excluded.

Region-of-interest selection based on event-related fields

Bilateral motor and visual regions-of-interest (ROIs) were selected based on event-related fields (ERFs) evoked by motor responses and targets, thereby ensuring that ROI selection was independent of the main analysis period and signal features of interest (anticipatory time-frequency data). Moreover, channel selection was performed independently of condition.

ERFs were calculated separately for left (position 1 and 2) and right (position 3 and 4) targets. Data for the planar gradiometer pairs were combined, resulting in a 102-channel combined planar gradiometer map in sensor space. A left vs. right difference ERF was calculated for each participant

separately and subsequently averaged across participants. Motor ROIs were selected based on the average left vs. right difference ERF topography in a window of 300 ms centred on the button press (see Figure 4.7a). Based on the topography, six (symmetric) channel pairs were selected on the left (MEG0412+0413, MEG0422+0423, MEG0432+0433, MEG0442+0443, MEG1812+1813, MEG1822+1823) and on the right (MEG1112+1113, MEG1122+1123, MEG1132+1133, MEG1142+1143, MEG2212+2213, MEG2222+2223). Visual ROIs were similarly selected based on the average left - right difference ERF topography in a window of 100 - 200 ms after target presentation (see Figure 4.7b). I again selected six (symmetric) channel pairs on the left (MEG1632+1633, MEG1642+1643, MEG1912+1913, MEG1922+1923, MEG1942+1943, MEG2042+2043) and on the right (MEG2032+2033, MEG2312+2313, MEG2322+2323, MEG2342+2343, MEG2432+2433, MEG2442+2443).

Time-frequency analysis

Time-frequency analysis was performed on Hanning-tapered data using a short-time Fourier Transform for frequencies between 4 and 45 Hz (in 0.5 Hz steps). A fixed sliding time window of 300 ms was advanced over the data in steps of 67 ms. Power time series in planar gradiometer pairs were combined (Cartesian sum), resulting in a 102-channel combined planer gradiometer map in sensor space.

Because each button press was immediately followed by the start of the following trial, no clean baseline period was present in the data. To sidestep

this problem, all data were therefore explored by looking at power differences between contralateral and ipsilateral ROIs only. For each ROI I computed relative contrasts between contralateral and ipsilateral expected visual targets ([[contra - ipsi] / [contra + ipsi]] *100), and subsequently averaged across both ROIs. I also calculated this contra vs. ipsi contrast for each symmetrical channel pair (symmetrical along the midline) to obtain the corresponding contra vs. ipsi topography plots.

I took particular care to equate the influence of previous button presses on the current trial between conditions. Because of the nature of spatial-temporal sequence learning, conditions differed with regard to the proportion of trials in which the previous response was made with the same or the opposite hand, and differed with regard to the RSI on the previous trial. Effects relating to previous trials can influence both behaviour and brain activity (see e.g. Van der Lubbe et al., 2004 and Los, 2010, and can in principle introduce spurious findings. In order to avoid any effects related to different proportions of preceding responses or RSIs, I limited the initial analysis to a subset of trials in which all relevant parameters were equated. I therefore only analysed trials in which the previous response (depicted at time point 0 in Figure 4.8 and Figure 4.9) was on the opposite hand. In addition, I only analysed short and long RSI trials (667 and 1500 ms), in which the RSI on the previous trial was of intermediate length (1000 ms). For R blocks, on average 118 ± 2 (SE) trials per RSI per participant were included, for N blocks this was 20 ± 0.4 trials per RSI per participant.

The main period of interest was the first 667 ms after the button press to the previous target (i.e. the time period corresponding to the short RSI). This is the time period during which spatial-temporal expectations (induced by the sequence structure) differ between repeated and new sequences, and between short and long RSIs in repeated blocks. I evaluated differences between conditions by using Fieldtrip's non-parametric cluster-based permutation tests, which circumvent the multiple comparisons problem by testing the full time-frequency space under a single permutation distribution of the largest cluster (Maris and Oostenveld, 2007). I used 1000 permutations with a two-tailed alpha level of 0.05.

Post-hoc analyses

In addition to the main analysis described above, I performed two post-hoc analyses on the data. First, I evaluated the relation between contra vs. ipsi beta power differences and our behavioural results (RTs) by investigating trial-by-trial Pearson's correlations for the short interval in the repeated condition for each time-frequency point. I limited the analysis to the same subset of trials as described above. These results were evaluated using Fieldtrip's non-parametric cluster-based permutation tests on the correlation values.

Secondly, to evaluate whether the beta suppression showed a parametric effect, I conducted an additional analysis for the repeated sequence condition using all thee RSI lengths. I again only included trials in which the previous response was on the opposite hand. For this analysis, it was necessary to relax the criterion that the previous RSI had to be of intermediate length. Contrasts

were again calculated as relative contrasts (see above) and evaluated using Fieldtrip's non-parametric cluster-based permutation tests. To quantify the influence of temporal expectations, I investigated magnitude (power) differences in the early interval after the previous sequence element, with the rationale that when targets are expected early (as compared to later), power modulations should be more pronounced in the early interval. Therefore, in addition, I extracted the data of interest in an a-priori defined pre-target window (i.e., beta band activity [15-28 Hz] in the window immediately preceding the first possible target [400 – 667 ms after the previous response]) to directly compare contra vs. ipsi differences between conditions in a repeated-measures ANOVA.

4.5 Results - Main experiment

Participants took part in a multi-session experiment involving a spatial-temporal SRT task. I will first describe the behavioural results reflecting learning and utilisation of spatial-temporal sequence structure. I will show that there was a robust facilitatory influence on behavioural responses, and that this effect was most pronounced for sequence elements that were expected at short inter-element intervals. When describing the MEG results I will focus on anticipatory neural dynamics related to the utilisation of the learned sequence structure, and show that beta lateralisation in anticipation of the response associated with the upcoming target location aligned to the expected timing of this event.

4.5.1 Behavioural results

Temporal-spatial learning effects

Since the task involved speeded responses to clearly visible targets, the main dependent variable of interest in the behavioural analysis was reaction time (RT). However, for completeness, I also report results for percentage correct (PC). RTs for all three sessions are shown in Figure 4.4. Learning in SRT tasks is generally shown by a decrease in RTs over the course of the experimental session. I expected that RTs would decrease most strongly during the first session, since this session only contained blocks with the repeated sequence, without interference from any new-sequence blocks. A repeated-measures analysis of variance (ANOVA) was performed with the mean RTs during block 1-4, block 5-8, and block 9-12 of the first session as the within-subjects variable. There was a main effect of Block: $F(2,17) = 17.39$, $p = < .0001$, partial $\eta^2 = 0.67$. RTs non-significantly decreased from block 1-4 to block 5-8 (M±SE = 388±15ms vs. 374±14ms; $t(18) = 1.94$, $p = .069$, Cohen's $d = 0.45$), and significantly decreased from block 5-8 to block 9-12 (M±SE = 374±14ms vs. 352±15ms; $t(18) = 5.469$, $p < .0001$, Cohen's $d = 1.27$). I performed a similar ANOVA for the mean PC during block 1-4, block 5-8 and block 9-12, which also showed a main effect of Block: $F(2,17) = 4.28$, $p = .031$, partial $\eta^2 = 0.34$), caused by a slightly larger PC for block 1-4 compared to block 5-8 (M±SE = 96.0±0.6% vs. 95.3±0.7%; $t(18) = 2.77$, $p = .013$, Cohen's $d = 0.66$), with no significant difference between block 5-8 and block 9-12 (M±SE = 95.3±0.7% vs. 95.3±0.6%; $t(18) = -0.12$, $p = .903$, Cohen's $d = 0.01$).

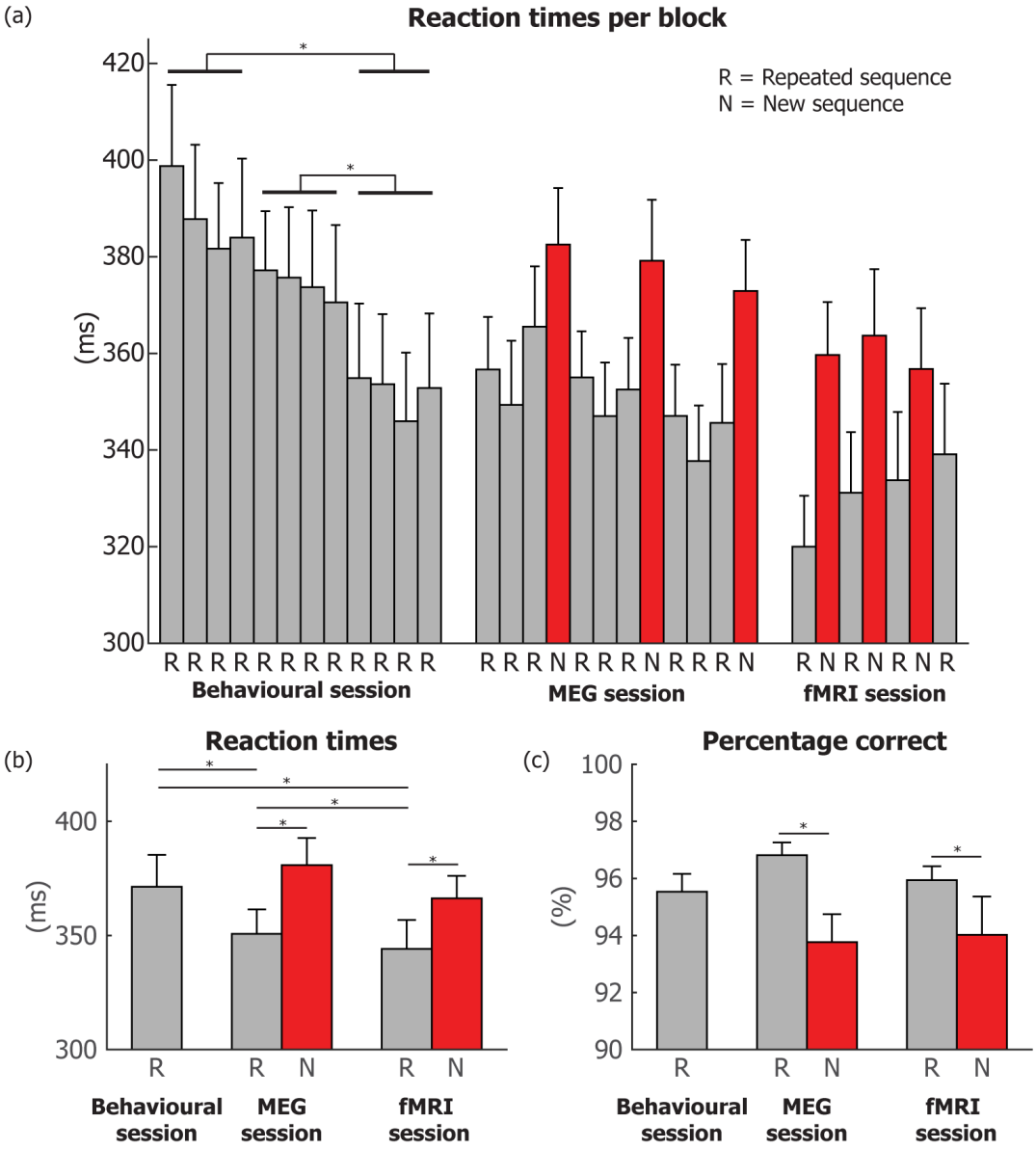


Figure 4.4 Behavioural results. Results are shown for (a/b) reaction times (RTs) and (c) percentage of correct trials (PCs) for the first, second and third sessions. Results for blocks with a repeated sequence (R) are shown in grey, while results for blocks where a new sequence (N) was presented are shown in red. Error bars present standard error of means (SEM), calculated using the variance across participants. Asterisks indicate statistically significant effects.

Since it was possible that RTs would continue to decrease over the course of the next two sessions, I performed a repeated-measures ANOVA on the

average RTs in repeated sequence (R) blocks during the first, second and third session (see Figure 4.4b). This indeed showed a main effect of Session: $F(2,17) = 8.77$, $p = .002$, partial $\eta^2 = 0.51$. Subsequent paired t-tests showed that RTs decreased significantly both from the first to the second session (M±SE = 371±14 vs. M±SE = 350±11; $t(18) = 3.21$, $p = .005$, Cohen's $d = 0.82$), and from the second to the third session (M±SE = 350±11 vs. M±SE = 329±13; $t(18) = 3.55$, $p = .002$, Cohen's $d = 0.86$). I performed a similar ANOVA for the percentage of correct trials (PCs; see Figure 4.4c), showing a main effect of Session: $F(2,17) = 15.54$, $p = .0001$, partial $\eta^2 = 0.65$. Mean performance was lower for session 1, compared to session 2 (M±SE = 95.5±0.6% vs. 96.8±0.4%, $t(18) = 3.71$, $p = .002$, Cohen's $d = -0.98$), but did not differ between session 2 and session 3 (96.8±0.4% vs. 97.2±0.5%; $t(18) = 0.86$, $p = .40$, Cohen's $d = -0.20$).

A second, more convincing, way of showing sequence-specific (compared to more general) learning in SRT tasks is the increase in RT and decrease in PC when a block containing a new sequence (denoted 'N') is presented instead of the learned, repeated sequence (denoted 'R'). During both the MEG and the fMRI session, three such 'probe blocks' were presented (see Figure 4.3b). The 'probe cost' is the increase in RT or decrease in PC when a new, unlearned sequence is presented. Therefore, a repeated measures ANOVA was performed with the factors Block Type (R or N) and Session (second or third). For this analysis I took separate averages across all repeated (R) and new (N) blocks within a session. This analysis confirmed a main effect of Block Type ($F(1,18) = 29.21$, $p < .0001$, partial $\eta^2 = 0.62$), and showed a main effect of

Session ($F(1,18) = 11.76$, $p = .003$, partial $\eta^2 = 0.40$), but no interaction between both variables ($F(1,18) = 0.68$, $p = .419$, partial $\eta^2 = 0.04$). For PC, a main effect of Block type was present ($F(1,18) = 16.83$, $p = .0006$, partial $\eta^2 = 0.48$), but no main effect of Session ($F(1,18) = 0.75$, $p = .40$, partial $\eta^2 = 0.04$) or interaction ($F(1,18) = 0.75$, $p = .40$, partial $\eta^2 = 0.04$) was found.

Temporal orienting effects across intervals

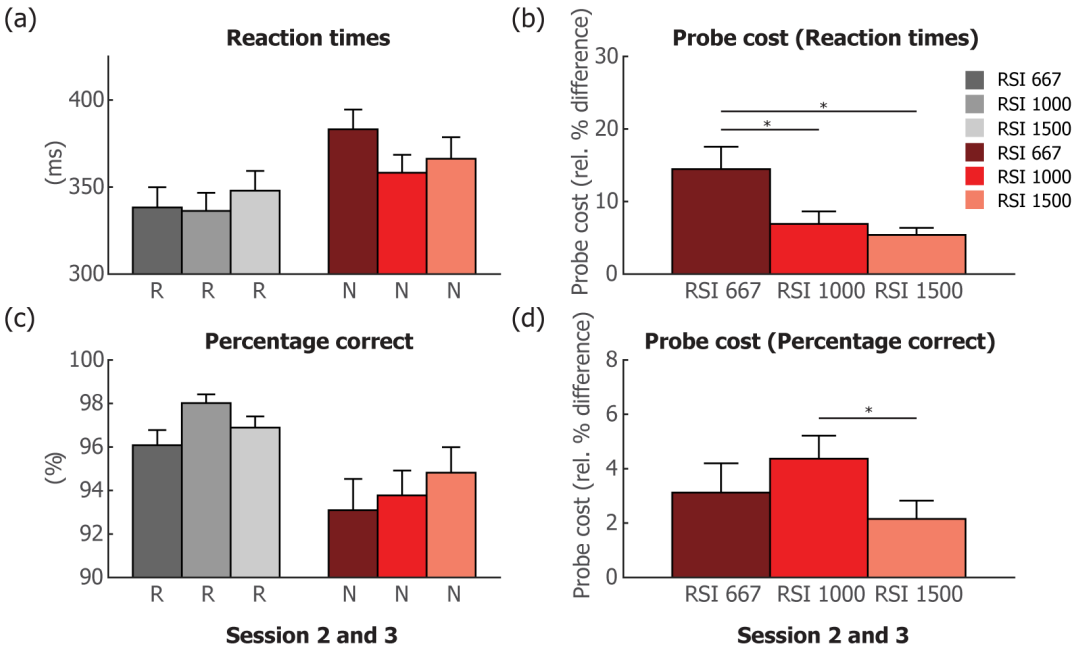


Figure 4.5 Behavioural results for the different RSIs. Results are shown for (a and b) RT and (c and d) PC for each of the three response-to-stimulus intervals (RSIs, 667/1000/1500ms), separate for repeated sequence (R) and new sequence (N) blocks, averaged across all R or N blocks of the session. The probe cost, shown in (b) and (d) for RT and PC was calculated as the relative difference between the average of all repeated sequence (R) and all new sequence (N) blocks across both sessions, for each RSI length. Error bars present SEM. Asterisks indicate statistically significant effects.

Both the decrease of RTs over the course of the experiment and the increase in RTs and decrease in PC when probe blocks were presented, indicated that participants learned the repeated spatial-temporal sequence. To investigate specifically the utilisation of the learned temporal structure in the sequences, I further investigated the difference in probe costs for the different response-to-stimulus intervals (RSIs) that were used in the task (667, 1000 and 1500 ms). Figure 4.5 shows the RT (a and b) and PC (c and d) results for the different RSIs.

To establish if the three RSIs indeed showed different RT patterns when comparing repeated (R) versus new (N) sequences, I performed a repeated-measures ANOVA with the factors RSI (667/1000/1500ms), Block Type (R or N) and Session (two or three). This analysis showed a main effect of RSI ($F(2,17) = 12.23$, $p = .001$, partial $\eta^2 = 0.59$), Block Type ($F(1,18) = 40.51$, $p < .0001$, partial $\eta^2 = 0.69$) and Session ($F(1,18) = 10.61$, $p = .004$, partial $\eta^2 = 0.37$; see Figure 4.4 for the main effect of Session). Critically, there was also an interaction between RSI and Block Type ($F(2,17) = 19.42$, $p < .0001$, partial $\eta^2 = 0.70$), but no interaction between RSI and Session ($F(2,17) = 1.35$, $p = .29$, partial $\eta^2 = 0.14$), no interaction between Block Type and Session ($F(1,18) = 0.46$, $p = .51$, partial $\eta^2 = 0.03$) and no three way interaction ($F(2,17) = 0.43$, $p = .66$, partial $\eta^2 = 0.05$). This interaction between RSI and Block Type can be evaluated by looking at the probe cost as a function of the different RSIs. However, before I could statistically compare the probe costs for the different RSIs, I first aimed to establish that there were indeed 'costs' for each RSI, i.e. that the difference between new and repeated blocks was present for each of

the three RSIs. I therefore performed pairwise t-tests between the average of all repeated sequence (R) blocks and all new sequence (N) blocks of the second and third session (collapsed across sessions because I found no three-way interaction with session; and not using the first session because it did not contain any probe blocks). Results show that there were indeed significant probe costs on RT for each of the three RSIs (short RSI: M±SE = 337±13ms vs. 383±12ms; $t(18) = 5.53$ $p < .0001$, Cohen's $d = 1.29$; medium RSI: M±SE = 333±11ms vs. 358±10ms; $t(18) = 3.90$ $p = .001$, Cohen's $d = 0.91$; long RSI: M±SE = 347±11ms vs. 366±12ms;$t(18) = 5.24$ $p < .0001$, Cohen's $d = 1.22$). I then investigated probe costs across the different RSIs (collapsed across sessions 2 and 3; see Figure 4.5b). A repeated-measures ANOVA showed a main effect of RSI ($F(2,17) = 21.26$, $p < .0001$, partial $\eta^2 = 0.71$). Pairwise t-tests showed that probe costs for the short RSI were larger than probe costs for the medium RSI (M±SE = 46±8ms vs. 24±6ms; $t(18) = 6.53$, $p < .0001$, Cohen's $d = 1.90$) and also larger for the short RSI than for the long RSI (M±SE = 46±8ms vs. 18±3ms; $t(18) = 3.76$, $p = .001$, Cohen's $d = 1.04$, but did not differ between the medium and long RSI (M±SE = 24±6ms vs. 18±3ms; $t(18) = 1.12$, $p = .276$, Cohen's $d = 0.29$).

I performed the same analysis for PC values (see Figure 4.5c and d). First, I performed a repeated-measures ANOVA with the factors RSI (667/1000/1500ms), Block Type (R or N) and Session (two or three). This analysis showed a main effect of Block Type ($F(1,18) = 22.84$, $p < .0001$, partial $\eta^2 = 0.56$), a trend towards a main effect of RSI ($F(2,17) = 3.55$, $p = .051$, partial $\eta^2 = 0.30$), but no effect of Session ($F(1,18) = 0.36$, $p = .56$, partial $\eta^2 = 0.02$).

Critically, there was again an interaction between Block Type and RSI ($F(2,17) = 8.11$, $p = .003$, partial $\eta^2 = 0.49$), but no interaction between RSI and Session ($F(2,17) = 2.44$, $p = .12$, partial $\eta^2 = 0.22$), no interaction between Block Type and Session ($F(1,18) = 0.033$, $p = .86$, partial $\eta^2 = 0.002$) and no three way interaction ($F(2,17) = 1.21$, $p = .32$, partial $\eta^2 = 0.13$). Since there was a main effect of Block Type, and an interaction between Block Type and RSI, I again evaluated if there were significant probe costs for each of the three RSIs (collapsed across sessions, because there was no main effect of session, or interaction with session). This was indeed the case (short RSI: M±SE = 96.08±0.63% vs. 93.09±1.30%; $t(18) = 2.90$ $p = .010$, Cohen's $d = 0.82$; medium RSI: M±SE = 98.01±0.39% vs. 93.78±1.12%; $t(18) = 5.20$ $p < .0001$, Cohen's $d = 2.35$; long RSI: M±SE = 96.89±0.50% vs. 94.82±0.93%; $t(18) = 3.23$ $p = .005$, Cohen's $d = 0.10$). Subsequently, a repeated-measures ANOVA on probe costs showed a main effect of RSI ($F(2,17) = 8.11$, $p = .003$, partial $\eta^2 = 0.49$). Subsequent pairwise t-tests showed that for PC, probe costs were larger for the medium RSI than for the long RSI (M±SE = 4.24±0.82% vs.2.07±0.65%; $t(18) = 3.12$, $p = .006$, Cohen's $d = 0.735$). But did not differ between the short and medium RSI (M±SE = 2.99±1.03% vs. 4.24±0.82%; $t(18) = 1.55$, $p = .138$, Cohen's $d = 0.37$) or the short and the long RSI (M±SE = 2.99±1.03% vs. 2.07±0.65%; $t(18) = 0.75$, $p = .463$, Cohen's $d = 0.18$).

After establishing a main effect of RSI when comparing new and repeated blocks, I hypothesised that it might be the case that a similar pattern of RT results could be found when comparing the first two and the last two blocks of the first session. During the first two blocks of this session, the standard

sequence was still unlearned and therefore one would expect the pattern of RTs to be similar to the pattern shown in new (N) blocks in session two and three, while in the last two blocks of the first session the sequence was learned (shown by the decrease in RTs over the course of the first session), and therefore would likely be similar to the pattern showed in repeated (R) blocks in session two and three. Relevant data are depicted in Figure 4.6. Before comparing the size of learning effects between the different RSIs, I first established if learning effects in the first session were indeed present for each RSI. Pairwise t-tests show that RTs indeed decreased significantly between the first and last two blocks of session 1 for each RSI (short RSI: M±SE = 347±16ms vs. 405±15ms; $t(18) = 4.62$, $p = .0002$, Cohen's $d = 1.06$; medium RSI: M±SE = 347±14ms vs. 385±16ms; $t(18) = 3.28$, $p = .004$, Cohen's $d = 0.76$; long RSI: M±SE = 355±14ms vs. 390±16ms; $t(18) = 4.20$, $p = .001$, Cohen's $d = 1.00$). For PC there was a difference between the first and last two blocks for the medium RSI (M±SE = 97.78±0.60% vs. 95.81±0.86%; $t(18) = 2.52$, $p = .021$, Cohen's $d = 0.61$) but not for the short or long RSI (short RSI: M±SE = 95.31±1.01% vs. 95.81±0.75%; $t(18) = -0.52$, $p = .61$, Cohen's $d = 0.12$; long RSI: M±SE = 96.05±0.70% vs. 95.31±1.01%; $t(18) = 0.78$, $p = .45$, Cohen's $d = 0.50$). Because RTs decreased significantly between the first two and the last two blocks of the first session for all intervals, I tested for potential differences in the size of this decrease between the different RSIs (see Figure 4.6b) with a repeated measures ANOVA, which showed that there was indeed a main effect of RSI ($F(2,17) = 8.36$ $p = .003$, partial $\eta^2 = 0.50$). The decrease in RT was larger for the short RSI than for the medium RSI (M±SE = 57±12ms vs. 39±12ms; $t(18) =$

4.16 p = .001, Cohen's d = 0.96) and larger for the short RSI than for the long RSI (M±SE = 57±12ms vs. 36±9ms; t(18) = 3.05, p = .007, Cohen's d = 0.83), but did not differ between the medium and long RSIs (M±SE = 39±12ms vs. 36±9ms; t(18) = 0.51, p = .62, Cohen's d = 0.11). This pattern of results is therefore similar to the pattern of results found for the probe costs for the different RSIs.

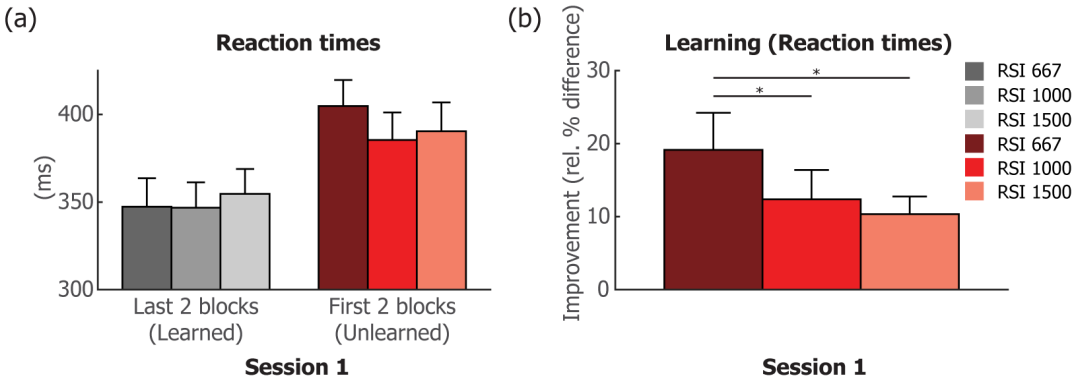


Figure 4.6 Behavioural results for the different RSIs in the first session. (a) RTs for each of the three response-to-stimulus intervals (RSIs, 667/1000/1500ms), separate for the first two and last two blocks of the first session. The learning effect, shown in (b) was calculated as the relative difference between the first two and the last two blocks, for each RSI length. Error bars present SEM. Asterisks indicate statistically significant effects.

Assessment of awareness of spatial sequence

After the last experimental session, I asked participants verbally if they noticed anything about the experiment. Nine participants answered that they did not notice anything in particular, while ten participants mentioned that they noticed there was a repeating pattern. After being told about the repeated sequence, fifteen participants mentioned they did indeed notice that the order sometimes repeated. However, most participants also mentioned that they

had not actively tried to learn the sequence when they realised this, it was more a feeling of occasionally noticing being able to predict the next target. In line with this result, participants were not very confident they would be able to type out the sequence; when asked to rate on a scale from 1-5 how confident they were they could type out the sequence the average rating was 1.74±0.25 (SE).

I also asked participants to generate the remembered sequence from memory (see 4.4.3 Experimental procedure and stimuli). Unfortunately, results of five participants had to be excluded from the analysis of these data, because of a mistake in the stimulus presentation script that caused some responses not to be recorded. Results of fourteen participants were therefore included in this analysis. Results for the spatial sequence showed that participants were consistent across both times they were asked to type out the sequence and on average produced 5.3±0.6 (M±SE; out of twelve) correct triplets during their first try (one-sample t-test against 4 expected by chance: $t(13) = 2.22$, $p = 0.045$, Cohen's $d = 1.23$) and 5.2±0.3 correct triplets during their second try (one-sample t-test against 4: $t(13) = 4.66$, $p < .001$, Cohen's $d = 2.58$).

The results for the final task, including results for all nineteen participants, in which participants were presented with twelve combinations of two targets (as they appeared in the task) and had to predict the next target, showed that on average 5.3±0.4 (M±SE) triplets were finished correctly (t-test against 4 correct to be expected by chance: $t(18) = 2.84$, $p = .011$, Cohen's $d = 1.57$). Results were therefore very similar to the results for the self-generated

sequences, and these results together suggest that, while participants were not very confident in their explicit knowledge of the spatial structure of the repeated sequence, they gained at least some intuition for the spatial aspects of the sequence, as they were able to perform the generation and prediction task slightly above chance.

Because the average performance was above chance when reproducing the sequence, I assessed if the main behavioural interaction of interest (i.e. the interaction between RSI and Block Type) would still hold when excluding the ten participants that initially said they noticed there might have been repeating pattern. This was indeed the case: $F(2,7) = 8.81$, $p = .012$, partial $\eta^2 = 0.72$). The main effects of RSI and Block Type were also still present (RSI: $F(2,7) = 9.67$, $p = .01$, partial $\eta^2 = 0.73$; Block Type: ($F(1,8) = 13.89$, $p = .006$, partial $\eta^2 = 0.64$), while there again was no two-way or three-way interaction with session (RSI and session: $p = .79$, Block Type and Session: $p = .95$, Block Type, RSI and Session: $p = .31$).

Assessment of awareness of temporal sequence

After asking about the spatial sequence, I asked participants about the temporal features of the task. When asked about the repeating temporal sequence, seven participants mentioned that they noticed that timings were not always the same (no one, however, mentioned noticing a repeated temporal structure). Six of these seven participants were part of the ten participants that mentioned noticing there might have been a repeated pattern, see above. No one was confident they would remember the timings

when typing out the sequence; only two participants rated their confidence as 2, while everyone else rated their confidence as 1 for this question (M±SE =1.11±0.07).

Because the temporal sequence only contained three different RSIs, and therefore, unlike the spatial sequence, did not contain unique triplets, I followed a different procedure for establishing awareness (see 4.4.4 Behavioural analysis). The length of the produced sequence of short, medium and long intervals that matched with the sequence of intervals in the repeated sequence was compared against the (mean) length that matched with the three new sequences. The correctly produced sequence of short, medium and long intervals that matched with repeated (R) blocks had an average length of 2.79±0.47 (M±SE) for the first try (i.e. before they were informed about the temporal sequence) and 2.07±0.27 for the second try (i.e. after they were informed about the temporal sequence). For new (N) blocks this was an average of 2.40±0.29(M±SE) for the first try (average across the scores for the three separate blocks) and 2.17±0.27 for the second try. Because there was no indication that being informed about the temporal sequence made a difference to these scores (scores for the second attempt were numerically lower, rather than higher) a pairwise t-test was performed between the average of the first and second try for the results for R and N blocks, showing no difference in average produced length between both conditions ($t(13) = 0.69$, $p = .50$, Cohen's $d = 0.38$). This shows that, as already suggested by the low confidence ratings, participants were not able to reproduce the temporal structure of the

task, and that participants thus gained no explicit knowledge of the temporal structure in the repeated sequences[19].

4.5.2 MEG results

Region-of-interest selection

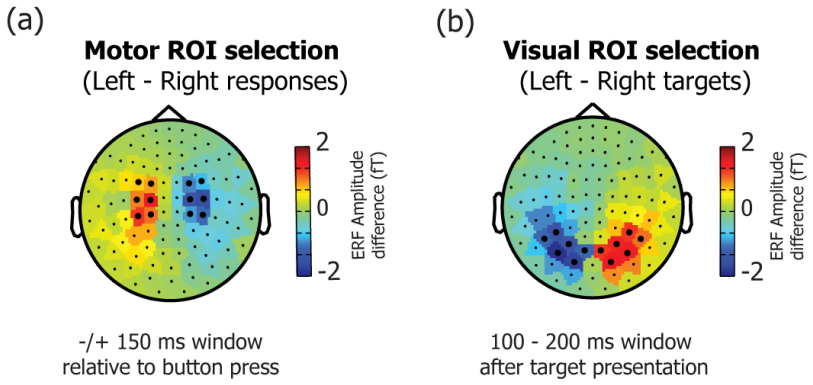


Figure 4.7 Region-of-interest selection. (a) Topographies for the amplitude difference in the ERF evoked by left vs. right responses in a 300-ms window centred on the button press (collapsed across RSIs). The six left and six right central-motor channels that were used as motor ROIs throughout the subsequent MEG analysis are marked in black. (b) Visual ROIs were based on the ERF amplitude difference evoked by left vs. right targets in the 100 – 200 ms window after target presentation. The six left and six right occipital-parietal channels that were used as visual ROIs throughout the subsequent MEG analysis are marked in black.

Left and right motor ROIs (Figure 4.7a) were selected based on the topography of ERFs evoked by left vs. right responses in a 300-ms window centred on the button press. These ROIs were used to extract anticipatory contra- and ipsilateral motor activity.

[19] I will therefore assume that at least spatial-temporal interactions in the current study were implicit.

Left and right visual ROIs (Figure 4.7b) were selected from the left vs. right target topography in a window 100 to 200 ms after target presentation, and were used to extract anticipatory contra- and ipsilateral visual activity.

Motor preparation

Figure 4.8b shows the time- and frequency-resolved normalised power differences between contralateral and ipsilateral ROI channels (contra vs. ipsi), as a function of block type (columns) and RSI (rows). Data are locked to the previous button press, such that the expected target and motor response (in repeated blocks) occur either early or late after this event. Contra- and ipsilateral ROIs are defined relative to the upcoming response (which was always opposite to the previous response; see 4.4.5 Time-frequency analysis for details). Topographies mark the same contra vs. ipsi difference (evaluated for each symmetrical channel pair), averaged over the indicated time-frequency windows depicted in Figure 4.8a Statistical testing was performed on the time-frequency matrices using cluster-based permutation statistics (Maris and Oostenveld, 2007). Significant clusters are outlined in white.

In both the repeated and the new blocks, for both the short and the long RSI, I observed a clear modulation of power that was largely restricted to the beta band. Beta power in the first 200 ms after the response (time point 0 in Figure 4.8b) was larger contralateral than ipsilateral (repeated short: two-sided cluster $p = .044$; repeated long: two-sided cluster $p = .014$; new short: two-sided cluster $p = .036$; new long: two-sided cluster $p = .014$), followed by a prolonged period with less power contralateral than ipsilateral (two-sided

cluster $p < .001$ for all four conditions). I must immediately point out that this is most likely a consequence of my analysis pipeline, in which I only included trials in which the previous response was made with the opposite hand compared to the upcoming response. Instead I was particularly interested in the differences in this modulation when the expected RSI was short or long (in repeated blocks) and between repeated and new trials (particularly for the short RSI, given our behavioural results). Critically, these contrasts of interest are not confounded by the previous response, because both the previous response side (always the opposite hand) and the previous RSI (always the intermediate RSI) were carefully equated in these four conditions.

I first considered the difference between short and long RSI trials within repeated sequences (Figure 4.8b, left column, bottom panel). Based on the behavioural results I hypothesised that participants would show a stronger engagement of their motor system (as reflected in lower contralateral, relative to ipsilateral, alpha and beta power) early after their response, when the next target/response was expected to follow after a short, compared to a long RSI. In accordance with this, I observed a significant cluster (two-sided cluster $p < .001$), revealing a stronger lateralisation (less power contralateral than ipsilateral) in short compared to long RSI trials. This effect was most prominent in the beta band and started well ahead of the anticipated target/response. The topography of this modulation was centred on the selected motor channels (indicating an origin in motor or premotor cortices) and this was the case for modulations in both the beta and the alpha band.

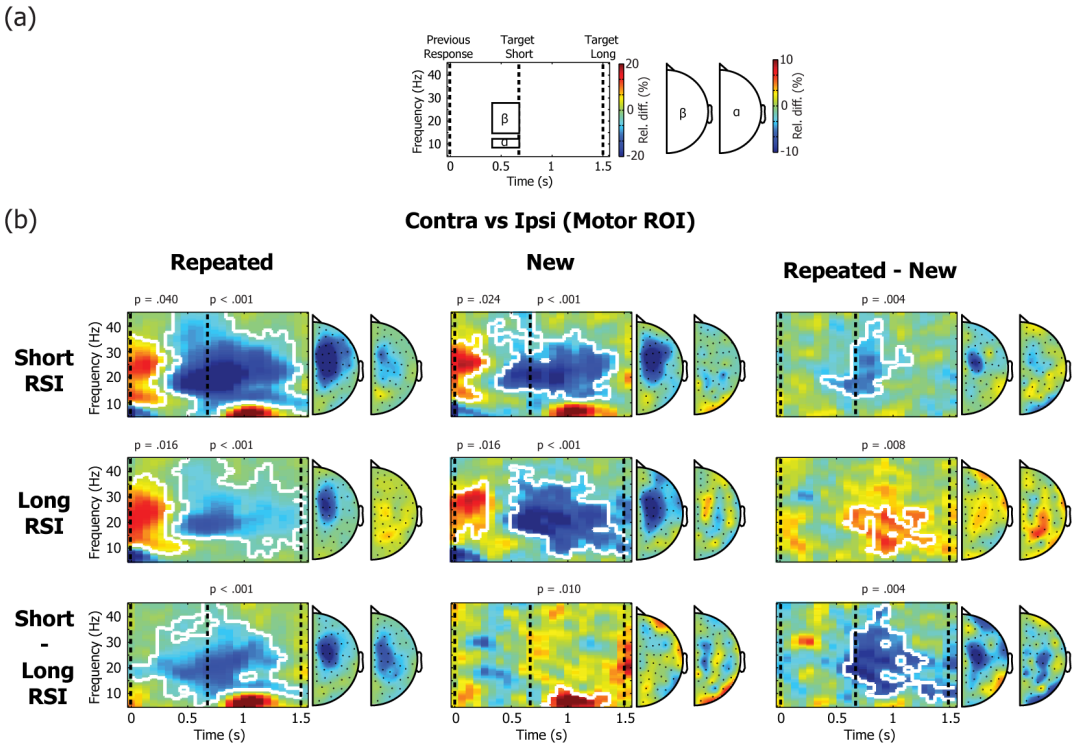


Figure 4.8 MEG results for the power difference between contralateral and ipsilateral motor channels. (a) Schematic of the data depicted in b. TFR plots reflect frequencies between 5 and 45 Hz, locked to the preceding button press, which always occurred with the opposite hand, compared to the (anticipated) current target. Results are shown for targets that occurred either after a short RSI (667 ms) or after a long RSI (1500 ms), and were always preceded by a medium RSI. Topographies show averages for the beta (15 - 28 Hz, shown on the left) and alpha (8 - 12 Hz, shown on the right) frequency bands, for a window between 400 - 667 ms after the button press (i.e. just before a "short target" would be presented). (b) Time-frequency representation (TFR) plots for contra vs. ipsi motor ROI channels (relative to the target location and therefore response side), shown separately for the repeated sequence condition (first column), the new sequence condition (second column) and for the repeated vs. new contrast (third column). Rows depict results for the short RSI (top row), the long RSI (second row), and the difference between the short and the long RSI (bottom row). Significant clusters are outlined in white. Topographies similarly reflect results for contralateral vs. ipsilateral activity in symmetrical channel pairs (for convenience, plotted in the right channel-element of each channel pair).

In contrast to these results, and according to my predictions, no significant short vs. long RSI difference was observed for the new blocks (Figure 4.8b, middle column, bottom panel). In new blocks, participants could not predict the upcoming RSI. Moreover, the contrast of the RSI effects between repeated and new blocks (third column, bottom panel) showed that the interaction between RSI and block type also survived statistical testing (two-sided cluster $p = .006$).

This pattern of results was replicated in the complementary contrast between repeated and new blocks, when considering the short RSI (Figure 4.8b, right column, upper panel; two-sided cluster $p < .001$). The topography of this contrast was again centred on the selected motor channels and seemed particularly pronounced in the beta band.

Visual anticipation

Because the spatial aspects of the task involved both a lateralised visual stimulus and a related lateralised motor response, one might expect that the utilisation of the learned spatial-temporal sequence structural might additionally modulate anticipatory perceptual dynamics in visual sites. Putative concurrent neural dynamics of visual anticipation would be expected to be most pronounced in the alpha band (Worden et al., 2000; Sauseng et al., 2005; Thut et al., 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Jensen and Mazaheri, 2010; Gould et al., 2011). Yet, the alpha-based topographies in Figure 4.8b revealed a largely motor origin of the anticipatory dynamics. To assess further the potential dynamics associated with visual

anticipation, I repeated the analysis performed over contralateral and ipsilateral motor channels with contralateral and ipsilateral visual ROIs.

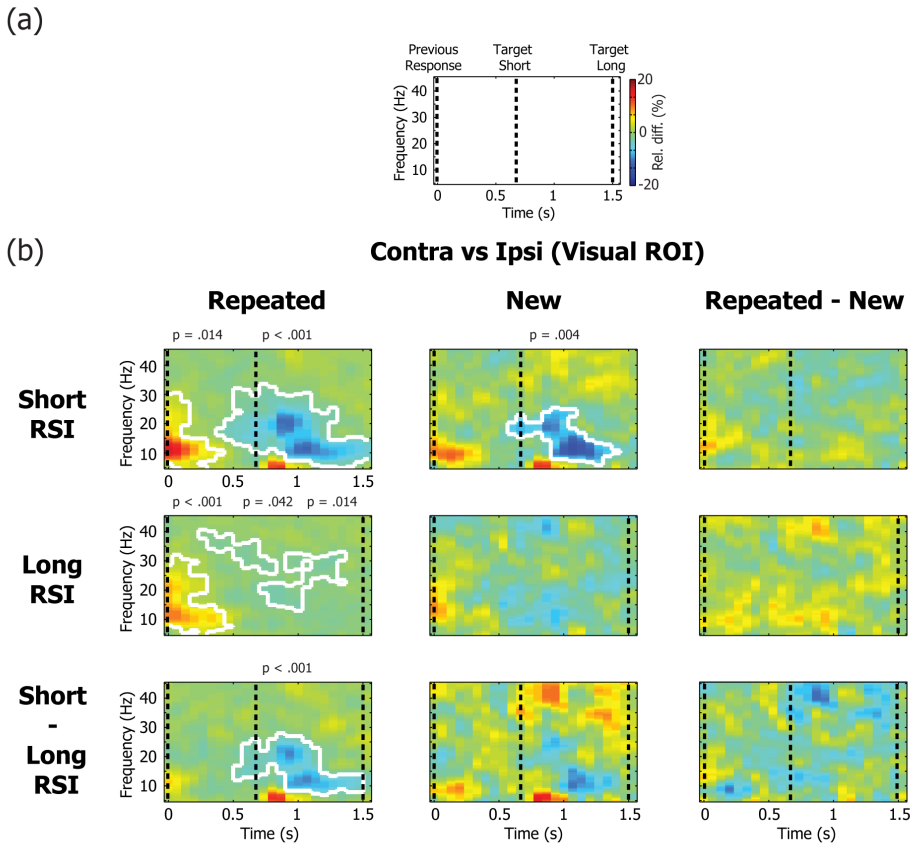


Figure 4.9 MEG results for the power difference between contralateral and ipsilateral visual channels. (a) Schematic of the data depicted in b. TFR plots reflect frequencies between 5 and 45 Hz, locked to the preceding button press, which always occurred with the opposite hand, compared to the (anticipated) current target. Results are shown for targets that occurred either after a short RSI (667 ms) or after a long RSI (1500 ms), and were always preceded by a medium RSI. (b) Time-frequency representation (TFR) plots for contra vs. ipsi visual ROI channels (relative to the target location and therefore response side), shown separately for the repeated sequence condition (first column), the new sequence condition (second column) and for the repeated vs. new contrast (third column). Rows depict results for the short RSI (top row), the long RSI (second row), and the difference between the short and the long RSI (bottom row). Significant clusters are outlined in white.

Time-frequency plots of the normalised power differences between contra and ipsi ROI channels (Figure 4.9b) are again shown as a function of block type (rows) and RSI (columns). Data are similarly locked to the previous button press, with the upcoming target/response occurring on the opposite side. Upcoming targets were again presented either after a short (667 ms) or long (1500 ms) RSI.

In contrast to the motor ROI results, in the visual ROIs differences in anticipatory activity between conditions were less convincing. Only the difference between the short and long RSI for repeated trials survived statistical comparison (two-sided cluster $p < 0.001$), but this difference could not convincingly be attributed to an anticipatory effect. Indeed, when inspecting the alpha topographies in Fig. 2c it is clear that (at least) the pre-target activity in this cluster may include a bleed through from more central (pre-) motor areas, where this anticipatory modulation by expected target/motor timing is most pronounced

Trial-wise correlations with reaction time

To investigate whether the contra vs. ipsi beta power difference was indeed associated with improved performance, I performed a post-hoc analysis of the correlation between power and RTs, focusing on short RSI trials in repeated blocks. If it is such that lower contra vs. ipsi beta power (putatively reflecting stronger expectation) confers an RT benefit (i.e., lower RT), then this should show as a positive correlation. For this purpose, I calculated the trial-by-trial Pearson correlation for each time-frequency point. Results are shown in

Figure 4.10, with significant clusters outlined in white. These results clearly show a significant correlation both pre- and post-target (two-sided cluster p = .050 pre-target and two-sided cluster p = .020 post target), indicating that participants responded more quickly when there was a larger contra vs. ipsi difference in beta power. In addition, RTs correlated negatively with post-target low-frequency power (putatively, the ERF; p = .038). The topography of this pre-target effect (the effect in which I was particularly interested) again confirmed a localisation to the (pre-)motor areas.

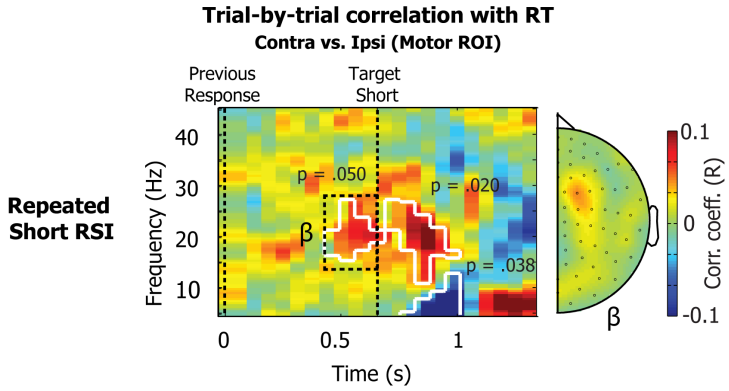


Figure 4.10 Trial-by-trial correlations between power and RT for the short RSI (667 ms) in the repeated condition. The data show the Pearson correlation coefficient for each time-frequency point between 5 and 45 Hz, for the contra vs. ipsi contrast, locked to the previous button press. Data are plotted for the motor ROI channels shown in Figure 4.7a. The topography shows the average for the beta (15-28 Hz) frequency band, for a window between 400 – 667 ms after the button press (i.e. just before the presentation of the short target). Significant clusters are outlined in white. The topography reflects results for contralateral vs. ipsilateral activity in symmetrical channel pairs.

Beta modulations in the medium interval

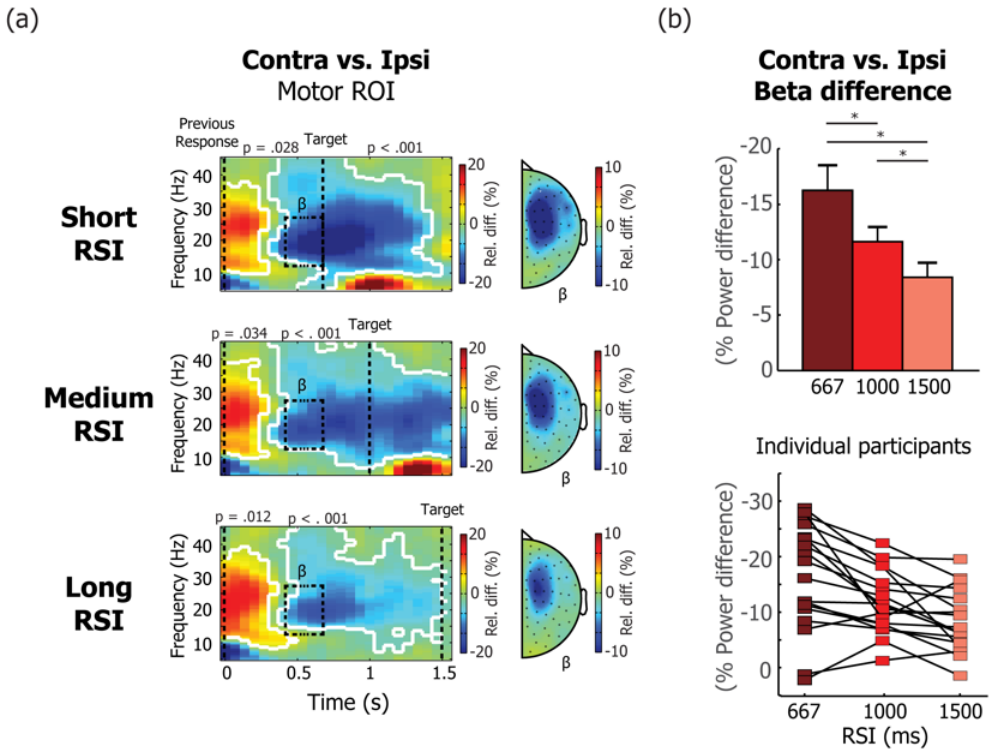


Figure 4.11 Beta power differences between contralateral and ipsilateral motor channels for all three RSIs. (a) TFR plots reflect frequencies between 5 and 45 Hz, locked to the preceding button press, which always occurred with the opposite hand, compared to the (anticipated) current target. Data are shown for the motor ROI channel selection shown in Figure 2a. Results are shown for targets that occurred either after a short RSI (667 ms; top plot), medium RSI (1000 ms; middle plot) or a long RSI (1500 ms; bottom plot). Significant clusters are outlined in white. Topographies show averages for the beta (15 – 28 Hz) band, for a window between 400 – 667 ms after the button press. (b) Beta power difference between contralateral and ipsilateral motor channels for the same time and frequency selection as used for the topographies in a. The bottom plot shows individual participant data. Asterisks indicate statistically significant effects.

To evaluate whether beta modulations varied parametrically according to the learned RSI, I re-ran the analysis for the repeated condition using all

three RSI lengths. Data are shown in Figure 4.11, for the same motor ROIs that were selected in Figure 4.7. Figure 4.11a follows the same convention as Figure 4.8, except that it also includes data from the medium RSI condition (note that for this analysis, I had to relax the constraint that the previous RSI should be the medium RSI). Figure 4.11 (top) shows the group average of the contra vs. ipsi beta power difference for the same time-frequency window as used for the topographies in Figure 4.11a, as well as Figure 4.8. Results for individual participants are shown at the bottom. A repeated-measures ANOVA showed a significant effect of RSI ($F(2,16) = 12.08$, $p < .0001$, partial $\eta^2 = 0.601$). Follow-up t-tests showed that the contra vs. ipsi beta power difference (here plotted as a positive effect) was significantly larger for the short, compared to the medium ($t(18) = 3.24$, $p = .005$, Cohen's $d = 0.98$) and long RSI ($t(18) = 5.02$, $p = .0001$, Cohen's $d = 1.44$) and also differed significantly between the medium and long RSI ($t(18) = 2.94$, $p = .009$, Cohen's $d = 0.69$). These results show that the strength of beta modulation differed depending on temporal expectation in a parametric fashion: the earlier a target is expected, the stronger the beta modulation early after the preceding sequence element.

4.6 Discussion

Behavioural data suggest that predictions in learned spatial-temporal sequences can be used proactively and dynamically to enhance performance. In this experiment, participants performed a SRT task involving complex

combined spatial-temporal visual-motor sequences. My aims for this multi-part experiment were as follows. First, I aimed to replicate and extend previous results (O'Reilly et al., 2008a), by establishing an SRT task that could be used flexibly in both behavioural, and neuroimaging settings. Second, I addressed the hypothesis that incidental sequential temporal orienting effects would be largest for targets following short (as opposed to longer intervals) between temporally structured sequence elements, thereby paralleling classical observations in tasks using explicit temporal cues (Coull and Nobre, 1998; Miniussi et al., 1999; Correa et al., 2006a; Nobre, 2010; Rohenkohl et al., 2014). Finally, and most importantly, in the MEG data I aimed to investigate anticipatory oscillatory dynamics related to the use of incidentally acquired, hidden, spatial-temporal sequences.

As hypothesised I found that performance benefits in the current SRT task were strongest for short (vs. medium and long) intervals. In line with these results, the MEG data revealed anticipatory power modulations in the beta band (lower contra vs. ipsilateral power) that adapted in a parametric fashion to the expected location and timing of elements within the visual-motor sequence. This difference was observed when comparing the short RSI for learned (repeated) vs. unlearned (new) sequences (i.e. "early" vs. "no" expectation), as well as when comparing short and long RSIs for the repeated sequence (i.e. "early" vs. "late" expectation). I further showed that responses to elements that were expected after a short preceding interval were faster in trials in which beta was more suppressed in contralateral (relative to

ipsilateral) motor cortical sites — suggesting a role for these anticipatory beta modulations in mediating the observed performance benefits.

These results advance the literature in three key ways. First, I show that the influence of learned spatial-temporal structure on behaviour resembles effects found in tasks using predictive temporal cues. Second, they complement the motor sequence-learning literature, by focusing on neural dynamics of sequence utilisation as opposed to sequence learning. Third, they reveal that typical behavioural and EEG/MEG patterns observed with explicit spatial and temporal cueing generalise to settings involving complex, incidentally acquired sequences. By doing so, they reveal that canonical neural dynamics of motor preparation flexibly adapt to learned spatial and temporal sequence structure, even when this structure remains largely implicit and even when inter-element intervals are variable (i.e., non-rhythmic). I will elaborate on all of these points below.

4.6.1 The influence of learned spatial-temporal structure on behaviour

One of the aims of this experiment was to replicate and extend previous results (O'Reilly et al., 2008a), by establishing an SRT task that could be used flexibly in both behavioural, and neuroimaging settings. In addition, in the behavioural analysis I set out to investigate how the influence of learned temporal structure develops over time. I addressed the hypothesis that the influence of learned temporal sequence would be largest for targets following short RSIs, similar to effects found for explicit forms of temporal cueing at short,

compared to long intervals (see the initial study by Coull & Nobre, 1998; but also e.g. Miniussi et al., 1999; Correa et al., 2006a; Correa and Nobre, 2008; Nobre, 2010; Rohenkohl et al., 2014; and Chapters 2 and 3 in the current thesis). These studies consistently show that temporal orienting of attention induced by temporal cues is most effective at short, compared to long intervals, due to evolving hazard rates. My results show that incidentally learned temporal structure (induced by the repeated temporal sequence) can have a similar influence on RTs, with temporal orienting induced by the learned spatial-temporal structure clearly being most beneficial for targets following short, as opposed to longer RSIs. One difference with results generally found in cued temporal orienting studies is that I also found a repeated versus new benefit for the longest interval, while such a benefit is usually not found with explicit cues, at least when the target is certain to appear (Correa et al., 2006a; Chauvin et al., 2016). However, it is feasible that this 'residual benefit' at the longest interval may be fully carried by the spatial sequence structure (rather than the temporal sequence structure), given that repeated and new sequences differed in both dimensions. In fact, I cannot exclude the possibility that all results are due to pure spatial expectations. However, I consider this unlikely because O'Reilly et al (2008a) showed substantial additional benefit of temporal structure when it was combined with spatial information. Furthermore, my results show characteristic behavioural effects of temporal expectations being strongest at short intervals. In future studies one could aim to decouple the spatial and temporal sequential predictions, to be able to distinguish purely temporal and purely spatial

predictions. It would also be interesting to investigate whether effects of cued temporal orienting and the effects of incidentally learned temporal order rely on similar neural mechanisms, or are different in mechanistic terms.

Two previous SRT studies also investigated the influence of learned temporal structure. Salidis and colleagues (2001) used a purely temporal SRT task (i.e. without the correlated spatial sequence) to investigate incidental temporal sequence learning in a between-subjects design using three different response-to-stimulus intervals. One single response button was used to respond to either each tone. Tones were presented in repeated sequences of temporal intervals for six beeps, or presented in a random order of intervals. This study showed a main effect of RSI, but contrary to my results, RTs decreased with increasing RSI length, even for the group in the repeated sequence condition. However, there are some important differences with the current study. The shortest RSI that Saladis and colleagues used was 180 ms, while the shortest RSI in my task was 667 ms, allowing for longer preparation, which might explain the discrepancy in results. Furthermore, in the Salidis (2001) task the upcoming spatial stimulus was always fully predictable, even when the timing was perturbed, while in my case four different targets (and thus responses) were used. Still, also in their study, the largest probe costs were found for the short RSI (compared to the long and medium RSIs) when perturbing the temporal sequence, and the RT difference between the sequenced and random group decreased with RSI length. Another study also testing for the effect of learned temporal structure (Shin and Ivry, 2003) did not find a systematic relationship between RSI and learning. Again, however,

there were some important differences with the current study. First of all, Shin and Ivry focused on the influence of RSI on spatial learning, i.e. they compared spatial-temporal blocks, to blocks in which the spatial sequence was changed, but the sequence of RSIs remained unchanged. Although the study showed no signs of a learned temporal sequence, in the absence of a correlated spatial sequence, it is possible that keeping the same temporal structure influenced the results. Furthermore, the length and range of RSIs used in this study was smaller (200, 500 and 800 ms) than used in the current study, making the task less sensitive to hazard rate effects (and therefore to the influence of temporal orienting). Finally, the participants included small groups of only 8-10 patients and elderly participants, who are generally more variable in their reaction times (Fozard et al., 1994).

Since my study contained three different sessions, taking place over the course of two weeks, I also aimed to look at whether and how the incidental temporal sequential learning effects change with time. Although I found that RTs continued to decrease over the course off the whole experiment (RTs for the third session were faster than for the second session), the pattern of RT results for the different RSIs developed over the course of the first session and then remained stable for the rest of the experiment. Therefore, once the temporal structure was incidentally acquired it could be applied consistently, and it continued to improve performance at a similar level (particularly at the short interval) throughout the rest of the experiment.

4.6.2 Neural dynamics of the utilisation of predictive spatial-temporal sequence structure

Most prior neuroimaging work investigating the neural basis of behavioural performance benefits associated with incidentally acquired sequence structure (typically in SRT tasks) focused on the learning of such sequence information. Moreover, most of these studies only investigated this for spatial structure. Complementing this work, I was particularly interested how, once such sequence structure has been acquired, this learned information (in my case both spatial- and temporal structure) is subsequently used to optimise behaviour.

Hemodynamic imaging techniques like fMRI have been useful for revealing areas and networks involved in learning in SRT tasks (e.g. Schendan et al., 2003; Gheysen et al., 2010; Hardwick et al., 2013) and for studying how spatial and temporal sequence features are represented (Kornysheva and Diedrichsen, 2014; Bednark et al., 2015). MRI is a useful tool for looking at brain areas involved in learning, which generally happens on a slow timescale, over the course of several blocks. However, it is not well suited for the investigation of fast temporal dynamics, which is essential when studying how these representations are used to guide behaviour, while sequences are unfolding. By turning to high-temporal resolution MEG measurements, I was able to study precisely this.

Although electrophysiological methods have been used to study learning in SRT tasks, these too have focussed primarily on the acquisition of spatial structure. An EEG study looking at lateralised readiness potentials within

learned visual-motor sequences also found that participants showed initial activation of incorrect (but expected) responses when they were presented with a deviant item (Eimer et al., 1996). Pollok and colleagues (2014) observed a stepwise decline of alpha desynchronization associated with motor learning. Furthermore, in their study the improvement of reaction times varied linearly with the amount of beta desynchronization, particularly during consolidation. Another recent study reported a reduction of alpha and theta power over posterior areas with learning for sequenced blocks (compared to random blocks), together with a reduction in alpha-to-low-gamma phase-amplitude coupling over right parietal and bilateral frontal areas (Tzvi et al., 2016). The authors suggest that the reduced phase-amplitude coupling reflects a shift away from visually guided motor-selection, towards implementation of the learned motor sequence. This study however, did not look at beta activity.

This experiment complements these studies in three key ways. First, it looked at power modulations reflecting the utilisation of the incidentally learned structure, rather than at the learning per se. Second, it looked at dynamic changes in neural activity at a much finer timescale, associated with spatial and temporal contingencies between successive sequences elements rather than changes in the state of brain activity over extended blocks of learning. Third, it considered both the temporal and spatial structure of sequences and showed that preparation is specific to precise target-interval combinations.

4.6.3 Anticipatory spatial-temporal beta modulations in hidden spatial-temporal sequences

The main finding in this experiment is that anticipatory power modulations in the beta band adapt to predictive sequential structure, with both spatial and temporal specificity. The effects point to proactive utilisation of spatial and temporal predictions embedded in sequences, in a way that resembles the use of explicit cues about the location and timing of upcoming targets or motor responses. It is well known that motor (and somatosensory) preparation is associated with attenuated alpha and beta power over corresponding motor and sensory regions, both when preparing voluntary movements and in anticipation of task-relevant targets (Jasper and Penfield, 1949; Pfurtscheller and Lopes da Silva, 1999; Jones et al., 2010; van Ede et al., 2010; Jenkinson and Brown, 2011; van Ede et al., 2011; Kilavik et al., 2013). Moreover, an increasing number of studies have shown that these modulations are not only sensitive to spatial expectations (showing larger attenuation in contralateral vs. ipsilateral sites; e.g. Nagamine et al., 1996; Taniguchi et al., 2000; Doyle et al., 2005; Alegre et al., 2006; Jurkiewicz et al., 2006; Zhang et al., 2008; van Ede et al., 2010), but also to temporal expectations (e.g. Schoffelen et al., 2005; Alegre et al., 2006; van Ede et al., 2011). If you know that a target requiring a response will appear shortly, beta power decreases earlier than when this target is expected only later, similar to the difference between short, medium and long RSIs for the repeated sequence in the current study. Interestingly, interval timing in perceptually guided motor tasks has been reported to be encoded by neurons in medial premotor cortex (e.g. Merchant et al., 2013b), which may

provide the possible source for instantiating the temporal alignment of the anticipatory beta modulation reported here.

Previous studies using regular, isochronous rhythmic sequence have also shown modulation of oscillatory power (e.g., Praamstra et al., 2006; Heideman et al., 2015). These studies also show that temporal regularities can modulate neural excitability in the absence of explicit temporal cues; showing that that beta power starts to decrease earlier in a faster, compared to a slower rhythmic stream. However, in these studies the spatial (motor) element was random, and therefore motor preparation was spatially (effector) unspecific.

This demonstration of spatially and temporally specific modulation of motor preparation in complex spatial-temporal sequences complements findings using rhythmic sequences in two important ways. My results show that proactive and flexible temporal modulation of brain activity by an implicit temporal structure does not require a simple, constant rhythm. Isochronous rhythms have been proposed to be able to align to endogenous, naturally occurring brain rhythms to regulate neural excitability in a rhythmic fashion (Schroeder and Lakatos, 2009; Schroeder et al., 2010). Although this may indeed be a potent mechanism for modulating excitability to enhance performance to naturally occurring rhythmic stimulation (e.g. Lakatos et al., 2008, 2009; Stefanics et al., 2010; Besle et al., 2011; Cravo et al., 2013), this would not be sufficient to support the effects observed in the context of our more complex spatial-temporal sequence. The temporal sequence in my study only repeated every twelve elements, and the specific intervals were not in a harmonic relation to one another.

The second intriguing and important aspect of my results is that temporal modulations following the hidden sequential structure of the task were spatially specific. This occurred despite the fact that the spatiotemporal contingencies were complex, with temporal-motor associations being specific to the different positions across the twelve items of orthogonal spatial and temporal sequences. Complementary studies looking specifically at interactions between spatial and temporal information have shown that such combined effects are especially powerful (i.e., 'super-additive'; Doherty et al., 2005; O'Reilly et al., 2008a; Rohenkohl et al., 2014), in comparison to either type of information in isolation. Following the strong synergy observed between spatial and temporal sequences in behavioural effects (O'Reilly et al., 2008a), I hypothesise that the temporal predictions in our task strongly potentiate the modulation of anticipatory motor preparation. It will be interesting to verify this in future studies by comparing markers of motor preparation in sequences with both spatial and temporal structure to sequences with either feature in isolation. Note that the current task does not allow me to make such a distinction, because both spatial and temporal sequences were always present, i.e. I can only establish an effect of spatial-temporal expectations. Another limitation of the current task is that due to the trial selection procedure, only a small number of trials (i.e. 20 per RSI) could be included for the new sequence conditions. At the same time, I note that I find an effect despite this limited number, and, moreover, that the main contrast of interest (repeated short vs. long) included 118 trials per RSI.

4.6.4 The nature of proactive anticipation in SRT tasks

Using whole-head MEG recordings, I was able to evaluate what type of anticipation (perceptual and/or motor) was particularly important for performance in the current SRT task. In the literature there are different proposals regarding exactly what information is acquired – whether more perceptual or motor-related in nature (Abrahamse et al., 2010; Schwarb and Schumacher, 2012). Not surprisingly, the debate has not fully been resolved and, most likely, the nature of the mechanisms will be strongly influenced by specific task parameters and demands. However, it is clear that the sequence of motor responses, or learned stimulus-response rules play an important role in sequence learning (Schwarb and Schumacher, 2012). While it seems that perceptual sequences, in some cases, can be learned independently of an accompanying motor sequence (e.g. Howard et al., 1992; Song et al., 2008), others failed to show independent perceptual learning (Willingham, 1999).

In the context of the current task there was surprisingly little evidence of visual anticipation, despite there being ample opportunity for visual spatial orienting given the layout of the stimuli and their correspondence to the finger movements. I found that the utilisation of the learned spatial-temporal structure proceeded primarily through motor preparation, as was evident in the strong beta modulations that were found over central sites. It may be, however, that the relative contribution of visual and motor areas changes over the course of learning. In the current task I was not able to assess this possibility since the learning primarily took place in the preceding behavioural session.

4.6.5 Conclusions and future directions

To conclude, in this experiment I have shown that despite the fact that spatial-temporal predictions remained largely implicit, learned task structure enhanced performance and dynamically modulated the time course of lateralised motor cortical beta oscillations, indexing motor preparation. Effects were largest for targets that were expected after short intervals, similar to effects found following explicit temporal cues. In future research it will also be interesting to establish how these proactive anticipatory spatial-temporal modulations emerge and evolve over the course of learning. It will also be important to use even better controlled tasks, to be able to disentangle the relative contributions of different contra- and ipsilateral motor areas. In addition, it will be interesting to use more realistic tasks, to see how these predictions hold in more naturalistic settings, where a less arbitrary sequence of behaviours is learned.

Chapter 5: General discussion

In this thesis I presented three studies on the behavioural and neural dynamics of temporal orienting of attention. In this final chapter I will discuss the insights that this research has provided on both temporal orienting for perception as well as action. I will also discuss what this research shows us about interactions between spatial and temporal orienting and changes that occur with ageing and neurodegeneration in Parkinson's disease. I will end this chapter by discussing interesting future directions that are inspired by my research.

5.1 Temporal orienting for perception

In this thesis I showed, in three different experiments, that temporal orienting of attention facilitates behavioural performance and influences neural modulation related to the anticipation of upcoming targets and responses. A recurring observation was the temporally specific anticipatory suppression of alpha and beta oscillations in task-relevant areas (in line with Schoffelen et al., 2005; Alegre et al., 2006; Praamstra et al., 2006; Ghose and Bearl, 2010; Rohenkohl and Nobre, 2011; van Ede et al., 2011; Zanto et al., 2011). It is generally believed that such brain states of suppressed alpha and beta oscillations are associated with enhanced cortical excitability (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011). My research consistently shows that such a mechanism may provide a powerful way to optimise our perception and actions not only for expected locations in space (as in Worden et al., 2000; Thut et al., 2006; Wyart and Tallon-Baudry, 2008; Kelly et al., 2009; Gould et al., 2011), but also for expected moments in time.

In Chapter 2 I showed that, in younger adults, temporal orienting of attention in the visual domain involves a decrease of alpha and beta band oscillations in posterior MEG channels. This anticipatory power decrease was temporally specific, because it was stronger earlier in the trial following short cues (i.e. when targets were expected early), compared to long cues (i.e. when targets were expected only later). Performance measured as perceptual sensitivity and reaction times was better for valid, compared to invalidly cued targets at the short interval, showing that temporal expectations indeed

positively influenced perception in this task. In Chapter 3, despite focusing more on the motor domain, temporally specific visual anticipation was also clearly present, at least in the healthy control group.

In addition to the hypothesised modulations in the alpha and beta bands, in Chapter 2 I also observed an increase in gamma with temporal anticipation. Effects in gamma are generally reported during stimulus processing, and therefore, show a dissociation from anticipatory modulations in the alpha and beta range (see also Bauer et al., 2014; van Ede et al., 2014). Instead, in Chapter 2, I found an anticipatory modulation, which may reflect anticipatory feed-forward communication (Fries, 2009; Bastos et al., 2015; Fries, 2015).

In contrast to the visual anticipation in Chapters 2 and 3, Chapter 4 suggested that anticipatory modulations in the visual domain play a less important role in the context of an already acquired spatial-temporal sequence. Even though there was a clear visual component in this task, anticipatory modulations with temporal orienting appeared a lot weaker than similar modulations in motor areas, even for the learned, repeated sequence.

I did find that certain aspects of orienting of visual attention differed between the different participant groups. In particular, in Chapter 2 I found a difference between younger and older adults in anticipatory alpha and beta modulations with temporal orienting, and in Chapter 3 I found a difference in such modulations between PD and control participants. I will further elaborate on these differences in section 5.4.

5.2 Temporal orienting for action

In Chapters 3 and 4 I investigated temporal orienting in the motor domain, in the context of a cued Go/NoGo task and an implicit serial reaction time (SRT) task with complex spatial-temporal sequences. In both cases, behavioural benefits of temporal information were strongest for the short interval, suggesting that anticipation of motor responses in spatial-temporal SRT tasks might be comparable to cued temporal orienting tasks in this respect. Similar to the (visual) modulations in Chapter 2, modulations in task relevant (in this case, motor) areas with temporal orienting involved a decrease of alpha and beta band oscillations that was strongest preceding moments that targets were expected.

Importantly, in both Chapter 3 and 4, this anticipatory beta decrease correlated with behaviour, establishing a robust link between these anticipatory modulations and the subsequent behavioural advantage of temporal expectations. In Chapter 4 I showed that behaviour correlated with beta power decreases on a trial-by-trial level, while in Chapter 3 this was shown at the group level, with healthy older adults with an overall larger power decrease across all trials showing the largest benefit of valid temporal cues. Although this correlation was not significant in the PD group (likely due to smaller overall modulations, both in behaviour and in the MEG data), the difference in correlation between both groups did not reach significance, suggesting that a similar, but reduced effect might be present in this group. These correlations suggest that these anticipatory power decreases are

consistent markers of the neural mechanisms that actually impact behaviour in a task-relevant manner.

I also noted some differences between the results concerning visual and motor anticipation. For example, whereas Chapter 2 demonstrated an anticipatory gamma amplification with temporal orienting, I did not observe a similar effect during temporally specific motor preparation. Moreover, the modulations in the visual modality seemed stronger in the alpha range, whereas modulations in the motor domain seemed stronger in the beta range.

5.3 Joint spatial and temporal orienting

Temporal orienting of attention is often studied in isolation of other forms of anticipatory biases, such as spatial expectations. However, in everyday life expectations of forthcoming events often involve multiple attributes, including expected timing as well as stimulus locations and response effectors. Moreover, a synergistic relationship between temporal and spatial orienting previously has been demonstrated in behaviour (O'Reilly et al., 2008a; Rohenkohl et al., 2014), ERPs (Doherty et al., 2005), and alpha and beta band modulations with tactile anticipation (van Ede et al., 2011).

In the current thesis, I therefore also investigated the behavioural and neural mechanisms of temporal expectations in the context of concurrent spatial expectations regarding stimulus location (left/right visual field; chapter 2) and response effector (left/right hand; chapters 3 and 4). Although I did not test for spatial-temporal synergies at the behavioural level in these

studies (since spatial and temporal expectations were always present concurrently and were never manipulated in isolation), such behavioural synergies have been shown in the past using very similar tasks (O'Reilly et al., 2008a; Rohenkohl et al., 2014). By recording MEG, I was, however, able to investigate the spatial and temporal specificity by which anticipatory neural dynamics would be modulated during joint spatial-temporal orienting of attention for upcoming perception and action.

In Chapter 2, the alpha and beta modulation with temporal orienting that was present in younger adults occurred largely bilaterally, despite the spatial anticipation inherent in the task (which was also clearly present in the strong alpha lateralisation, that was similar following short and long cues). Similarly, in Chapter 3, differences between short vs. long cues in the control group were again expressed in a largely bilateral power decrease. Although this modulation seemed visually slightly stronger in contralateral channels, the contra vs. ipsi difference did not reveal sufficiently reliable effects (and such plots were therefore not included in the results section of this chapter). I note that in the PD group, there did seem to be somewhat of a joint spatial-temporal orienting effect (since in the TFR plot, modulations were significant for the contralateral ROI only). However, in this group the modulations were overall much smaller in size, and were not significant when the whole time window of interest was considered. A more lateralised, compared to a more bilateral motor preparation has previously been noted in PD patients (Meziane et al., 2015).

Surprisingly, in Chapter 2, the only anticipatory modulation that seemed truly spatial-temporal was the modulation of gamma in older adults, which is an effect that has not very often been reported before (but see Lima et al., 2011; van Ede et al., 2014). This effect was spatially and temporally specific, because it was strongest in the hemisphere contralateral to the anticipated target and stronger following short compared to long cues.

Based on the results from Chapters 2 and 3, one might conclude that at least the effects in the alpha and beta band constitute a "pure" temporal orienting effect, that increases excitability at relevant time points, but does so not only in relevant (contralateral) brain areas, but also in less relevant (ipsilateral) brain areas. However, in Chapter 4 the complexity of the task required me to focus solely on modulations that were present in the difference between contra- and ipsilateral channels. Here, I was able to show that the influence of temporal orienting on anticipatory alpha and beta oscillations was indeed stronger in contra- relative to ipsilateral motor areas. There are several factors that are likely to explain this apparent discrepancy. First of all, it may still be the case that, also in the latter data, the temporal orienting modulations were largely, but just not exclusively, bilateral. (I was not able to resolve this, provided the complexity of analysing anticipatory modulations within a complex ongoing stream of stimuli and actions.) Second, motor demands in the SRT task were very different compared to the cued Go/NoGo task. In the SRT study there was more potential competition between different response effectors, as effectors changed rapidly within the sequence and therefore between both hands. In contrast, in the cued Go/NoGo task the respond hand

was fixed for a whole block. In the SRT task it would therefore have been beneficial to prepare one specific response while inhibiting other possible responses, while in the Go/NoGo task a more general preparation likely was sufficient[20].

Overall, it thus appears that the effects of temporal orienting in alpha and beta appear largely bilateral, with potentially more restricted effects when interactions with specific spatial preparation are especially beneficial, because other responses have to be inhibited. In future research it will be important to investigate if this speculation indeed holds, and also to investigate if a similar thing might be true for the visual domain, e.g. in tasks with a lot of spatial competition.

If it is indeed the case that interactions with spatial orienting only occur when there is a lot of competition, this might also provide an alternative explanation of why I didn't find an effect of temporal expectation in posterior (visual) channels in Chapter 4. There was no real spatial competition. Although the preparation of a competing response would largely interfere with the goals of the task (responding as fast as possible), in visual anticipation there was not a lot of competition, because no distractors were present in the period before target presentation (just four empty squares). Therefore, spatially specific temporal anticipation might not have been necessary. Furthermore, it was the

[20] Note that in the SRT study, even in new trials there could have been some form of more specific motor preparation or anticipation, since responses switched hands in 2/3 of cases (since targets were never repeated). However, this preparation would have been more general than for the repeated sequence, where a more specific expectation for both location and timing was present.

case that targets, although presented lateralized, were still presented relatively close to the fixation cross, to prevent eye moments.

Of course, we must question the respective roles of alpha and beta modulations in contra- and ipsilateral sensory and motor areas. Concurrent EEG-fMRI recordings have revealed that such bilateral alpha/beta modulations can co-exist with strongly lateralised BOLD modulations (Zich et al., 2015), suggesting that the contra- and ipsilateral modulations may be correlated with distinct physiological processes. Possibly then, the ipsilateral modulation merely reflects a "spill over" of a modulation that is instantiated and effective in contralateral sites only. How such contra- and ipsilateral modulations shape the firing rates in the underlying populations thus remains an important open question (see also e.g. Haegens et al. 2011; Spaak et al. 2012).

5.4 Changes with ageing and neurodegeneration

One main question of the current thesis is how temporal orienting for perception and action may be altered with healthy ageing and with neurodegeneration. In Chapter 2 I focused on temporal orienting for perception. A previous study (Zanto et al., 2011) had shown that older adults did not benefit from temporal expectations resulting from predictive cues and anticipatory alpha decreases were largely diminished in this group. Other studies had shown that also with spatial orienting, alpha and beta modulations were attenuated in older adults (Deiber et al., 2013; Hong et al., 2015). In

contrast to Zanto and colleagues (2011), in Chapter 2, I found that older adults were able to benefit from temporal cues to improve their behaviour in a stimulus discrimination task, which confirms other findings from the lab (Chauvin et al., 2016). However, the clear anticipatory alpha decrease with temporal orienting, that I found in younger adults, was absent in this group. Remarkably, I did find a strong lateralisation of alpha and beta band activity when contrasting channels contralateral and ipsilateral to the cue direction, showing that modulations with spatial orienting were intact in this group (see also Sander et al. 2012; Leenders et al., 2016; Mok et al., 2016). In fact, these effects were significantly larger in older adults. In addition, in the older adult group, I found the only clear spatial-temporal interaction effect that was present in this study, which was expressed as a gamma increase in channels contralateral to the cue direction, possibly reflecting enhanced feed-forward communication (Fries, 2009, 2015; Bastos et al., 2015). In younger adults only a hint of such an effect was present. More research is therefore necessary to determine the extent of anticipatory gamma-band increases with temporal orienting.

In Chapter 3 I found, similar to Chapter 2, that older adults were able to benefit from valid temporal cues. In addition, and perhaps surprisingly, considering the results of Chapter 2 and the results by Zanto et al. (2011; in this study no behavioural benefits were found for older adults and alpha decreases were significant, but largely reduced compared to younger adults), these effects were now accompanied by a strong anticipatory decrease in alpha and beta in both central (motor) and posterior (visual) areas. These

differences in results might be due to differences in task demands. In Chapter 2, symbolic colour cues indicated the expected time of target appearance, while in Chapter 3 and the study by Zanto et al. more intuitive cues were used. In addition, in both Chapter 3 and the Zanto et al. study targets were presented centrally, while in Chapter 2 targets were lateralised. Furthermore, two out of three tasks in the Zanto et al. (2011) study resembled the motor demands of Chapter 3 (detection and go/nogo), while Chapter 2 involved a difficult perceptual discrimination. In addition it should be noted that it is difficult to compare the size of alpha decrease between Zanto et al. (2011) and Chapter 3, because in Chapter 3 no young control group was present. It might therefore be that modulations in these two studies were not that different after all.

From Chapters 2 and 3 we can conclude that, in older adults, certain anticipatory modulations were at least as strong (if not stronger) than in younger adults, while others might be reduced, depending on the specific task context. In addition, in older adults, additional anticipatory processes may be found, which could either reflect enhancement of certain processes that are present in younger adults, but are harder to detect, or some form of compensatory activity. These results show that signatures of temporal orienting are not always diminished with ageing, but instead, that different neural dynamics appear differentially sensitive to ageing.

In addition to changes in healthy ageing, I also considered changes with neurodegeneration, focusing in particular on Parkinson's disease. It has been argued that PD patients show deficits in temporal processing and are impaired in the anticipation and preparation of future actions. In Chapter 3 we saw that

in PD participants, temporal expectations were clearly reduced compared to healthy control participants, not only in behaviour but also in neural modulations. Anticipatory power decreases with visual anticipation of the upcoming target appeared completely absent in this group, while anticipation of the timing of the upcoming motor response was only visible relatively late in the anticipatory window of interest and only in contralateral motor channels. Both behavioural effects, and neural signatures of visual and motor anticipation were therefore significantly smaller and less robust compared to control participants, suggesting a deficit in this group also during cued temporal orienting of visual-motor attention.

Importantly, the results of Chapter 3 also made it clear that in patient groups it is important to investigate potential changes in "baseline" physiology (e.g. spectral differences), in addition to differences in task-induced modulations. In future studies it will also be necessary to link these shifts to behaviour and neural modulations during task performance.

Further research is necessary to indicate the precise circumstances under which temporal orienting is spared vs. impaired in older adults and patient groups, and to start evaluating this in different types of neurodegenerative disorders. The current results also indicate that these processes might differ between the visual and the motor domain. Careful within-group comparisons are necessary to investigate these questions further. In such comparisons it will be essential to keep task difficulty and other task parameters as similar as possible between visual and motor tasks. Furthermore, it is important to control for possible strategic differences

between groups. In Chapter 3 it could be, for example, that PD patients used a different anticipatory strategy compared to control participants, because of more challenging task demands, and therefore displayed no visual anticipation. Alternatively, this seemingly absent visual anticipation might reflect a true impairment in this group.

5.5 Future directions in the field of temporal orienting

The work presented in this thesis makes it clear that changes with ageing and neurodegeneration are more complex than sometimes proposed. I would like to end this thesis with some speculations regarding broader future directions in the field of temporal orienting, not only in the context of the topics discussed in this thesis, but also relating to more complex forms and functions of temporal expectations.

First of all, in future studies it will be interesting to test neural modulations with more complex spatial-temporal SRT tasks (like the one used in Chapter 4) in both older adults and PD patients. Diminished behavioural performance in spatial SRT tasks has been shown for PD patients (Clark et al., 2014), and also for older adults, depending on task demands (Curran, 1997; Howard and Howard, 2013). Except for one study (Shin and Ivry, 2003), these groups have not previously been tested in spatial-temporal versions of this task. It will be important to see how both behavioural and neural modulations with implicitly acquired spatial-temporal structure differ in these groups,

since many behaviours in daily life (including the behaviours that become more difficult with ageing and neurodegeneration) follow (implicit) sequential structures.

In addition to studying the role of temporal orienting in anticipation and preparation, in future studies it will also be interesting and important to investigate its role in the cancellation of predictable, irrelevant or distracting input. Our senses are constantly bombarded with all kinds of information, of which only a small part is of key relevance for our goals and behaviour. Attention is the process that allows us to focus on the relevant information, and it does this by not only enhancing relevant information, but also putatively by suppressing irrelevant information. In this thesis I solely focused on anticipatory modulations that enhance perception and action, while the temporally specific suppression of irrelevant, or distracting information is perhaps just as interesting and equally relevant for our goals. This may be associated not with decreased alpha and beta oscillation, but with increased oscillations ahead of expected irrelevant target instead (see Worden et al., 2000; Kelly, 2006; Rihs et al., 2007). In addition, this may be interesting in the context of rhythmic, predictable input, like the ticking of a clock in the room, people talking in the background, or the sound of our own footsteps. Again, oscillatory brain activity might be used to cancel this out; in this case through temporally specific alignment of less excitable phases to expected irrelevant input. Lakatos and colleagues (2013) showed opposite phase entrainment in monkey auditory areas for neural ensembles that coded for task-relevant vs. irrelevant frequency content when monkeys had to select between competing

auditory streams. These opposite entrainment effects seemed to sharpen the contrast between the processing of targets vs. distractors. Horton and colleagues (2013) found opposite entrainment effects for speech suppression in a "cocktail party" situation where two competing auditory streams were present.

It will also be very relevant to study changes in these processes with ageing and neurodegeneration, since problems with interference by distracting information have been shown both in healthy ageing (see reviews by Zanto and Gazzaley, 2014, and Erel and Levy, 2016) and neurodegenerative disorders like Parkinson's disease (e.g. Cools et al., 2001; Wylie et al., 2009).

In general, in future studies it will be important to investigate further both enhancing and inhibitory functions of temporal orienting across the life span and across the whole range of neurodegenerative and psychiatric disorders. Impaired timing seems to be a characteristic of many disorders, like schizophrenia, autism, stuttering, and ADHD (see e.g. Toplak et al., 2006; Olander et al., 2010; Allman and Meck, 2012; Ward et al., 2012; Thoenes and Oberfeld, 2017). More insight in how these processes are altered in these diseases will not only provide us with more insight into the general nature of temporal expectations in the brain, but potentially also provide us with targets for future treatments and therapies. It will be important to investigate more complex and flexible patterns of predictions as well, so results will be better applicable to daily life.

Overall, the research in my thesis underscored the prevalence and importance of temporal expectations in guiding adaptive behaviour in

multiple task contexts. As with any body of work in a relatively new area of investigation, it has opened at least as many questions as it has addressed. Exploring the different consequences and mechanisms of the various forms of temporal expectations across the lifespan, and how these break down in disorders, should prove highly fruitful.

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Appendix 2.1 Clinical and neuropsychological evaluation of older adults

The older participant data in Chapter 2 were collected as part of a larger "Cognitive Health in Ageing" research project. Therefore, in addition to the MEG study, older adults, completed a set of demographic surveys and neuropsychological tasks to assess basic cognitive function. This session took approximately 90 minutes. Information was collected on medical history, handedness (Edinburgh Handedness Inventory; Oldfield 1971), years of education, highest educational qualification, work status/occupation, languages spoken, fluency in English; height, weight, alcohol consumption, smoking behaviour, recreational drug use, eyesight, hearing ability, (physical) activities, and musical abilities. No participants were excluded from the study based on these measures, because most of this information was collected with the aim to inform other ongoing studies on cognitive health and ageing within Oxford. From these measures, only relevant data on age and education are included in Table A2.1.2 below.

Information on older participants' psychological health and wellbeing was collected using a number of standardised clinical-assessment questionnaires. Data were collected on depression (Beck Depression Inventory, BDI-II; Beck et al. 1996), state and trait anxiety (State-Trait Anxiety Inventory, STAI; Spielberger et al. 1983), personality traits (Eysenck Personality Questionnaire, EPQ; Eysenck and Eysenck. 1975), optimism vs. pessimism (Life Orientation Test-Revised, LOT-R; Scheier et al. 1994), sleep problems (Jenkins Scale for the Estimation of Sleep problems; Jenkins et al.

1988), impulsivity (Barratt Impulsivity scale, BIS-II; Patton et al. 1995) and general health status across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression; EuroQol-5 Dimensions-5 Levels (EQ-5D-5L; EuroQol Group 1990; Brooks 1996). All clinical-assessment information was collected through a web-based platform for administering surveys (Qualtrics, Provo, UT). Table A2.1.1 represents a summary of the relevant questionnaire data.

To ensure that all older participants were cognitively healthy, their performance was evaluated across a battery of neuropsychological tests. We assessed general cognitive function (Montreal Cognitive Assessment version 7.1, MoCA; Nasreddine et al. 2005), attention/task switching (Trail making test, TMT; Reitan 1958; Reitan and Wolfson 1985; Tombaugh 2004), executive function (Rey-Osterrieth complex Figure test, RCF; Rey 1941; Osterrieth 1944; Fastenau et al. 1999), semantic memory (Category fluency - animal names only; Gladsjo et al. 1999), verbal language/verbal memory (Hopkins verbal learning test, HVLT; Brandt 1991; Vanderploeg et al. 2000), language/semantic memory (15 Boston Naming Test, BNT; Mack et al. 1992), verbal working memory (Digit span; Wechsler 2008), premorbid intelligence quotient (Test of Premorbid Functioning, TOPF; Wechsler 2009) and motor function (Purdue Pegboard; Desrosiers et al. 1995). Relevant test scores are summarised in Table A2.1.2. After the exclusion of two older adults who scored below 26 on the MoCA (see Nasreddine et al. 2005), all participants in the final analysis were within two standard deviations of normative values across all tests.

Table A2.1.1 *Clinical evaluation (older adults only; n=16).*

Clinical test	Mean ± SEM	Range of Participant scores	Normal Range	Definition
BDI-II	5.1 ± 1.1	0-14	0-63	> 13 = minimal depression
BIS-II	59.0 ± §.8	45-76	30-120	Higher score = more impulsive
EQ-5D-5L Health State	84.8 ± 2.7	52-99	0-100	Sliding scale of subjective health state
Jenkins	7 ± 1.2	1-16	0-20	Higher score = more sleep problems
LOT-R	21.4 ± 1.3	13-32	0-24	Higher score = more optimistic
STAI	34.5 ± 2.0	23-49	20-80	Lower score = lower anxiety

BDI: Beck Depression Inventory; BIS: Barratt Impulsivity Scale; EQ-5D-5L: EuroQol-5 Dimensions-5 Levels; Jenkins: Jenkins Scale for the Estimation of Sleep problems; LOT-R: Life-Orientation Test-Revised; STAI: State-Trait Anxiety Inventory.

Table A2.1.2 *Neuropsychological evaluation (older adults only; n=16).*

Neuropsychological Test	Mean ± SEM	Range of Participant scores	>2SD *
Age	67.3 ± 1.2	61 - 76	n.a.
Education	15.1 ± 0.7	11.5 - 21	n.a.
15-Item BNT	14.7 ± 0.2	13 - 15	-
Category Fluency	24.0 ± 1.0	17 - 31	
Digit Span (Scaled Score)	12.0 ± 0.3	10 - 14	-
HVLT-R			
TMT (s) Trial 1	5.7 ± 0.2	5 - 7	n.a.
TMT (s) Trial 2	9.3 ± 0.3	7 - 12	n.a.
TMT (s) Trial 3	10.8 ± 0.3.	7 - 12	n.a.
TMT (s) Learning	5.2 ± 0.4	2 - 7	-
TMT (s) Sum of 1-3	25.8 ± 0.6	22 - 30	-
TMT (s) Delayed Recall	10.3 ± 0.3	8 - 12	-
TMT (s) Percent Retained (%)	94.1 ± 2.2	75 - 110	-
TMT (s) True positives	11.5 ± 0.1	11 - 12	-
TMT (s) False positives	1 ± 0.1	0 - 5	1
TMT (s) Discrimination Index	10.5 ± 0.3	7 - 12	-
MoCA	28.0 ± 0.4	25 - 30	-
Purdue Pegboard			
TMT (s) Right	13.4 ± 0.4	10 - 15	-
TMT (s) Left	12.9 ± 0.4	10 - 16	-
TMT (s) Both	10.6 ± 0.2	9 - 12	-
TMT (s) Assembly	31.8 ± 1.9	22 - 49	-
ROCFT (score out of 36)			
TMT (s) Copy	32.8 ± 0.6	25.5 - 35	-
TMT (s) Immediate	19.5 ± 1.3	11 - 18.5	-
TMT (s) Delay	19.0 ± 1.2	10.5 - 26	-
TOPF-FSIQ	115.0 ± 1.9	96.7 - 124.4	-
TMT(s)			-
TMT (s) Part A (s)	25.7 ± 1.8	15.34 - 39.25	-
TMT (s) Part B (s)	55.6 ± 6.7	29.35 - 131.63	-

*This column contains the number of individuals who had a score that was two standard deviations away from the age-adjusted normative values. HVLT-R: Hopkins Verbal Learning Test; MOCA: Montreal Cognitive Assessment; ROCFT, Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test.

Appendix 3.1 Neuropsychological evaluation

At the start of the MEG session, both PD and control participants underwent a neuropsychological evaluation. The neuropsychological evaluation assessed general cognitive function (Montreal Cognitive Assessment version 7.1, MoCA; Nasreddine et al., 2005), attention/task switching (Trail making test, TMT; Reitan, 1958; Reitan and Wolfson, 1985; Tombaugh, 2004), executive function (Rey-Osterrieth complex Figure test, RCF; Rey, 1941; Osterrieth, 1944; Fastenau et al., 1999), semantic memory (Category fluency - animal names only; Gladsjo et al., 1999), verbal language/verbal memory (Hopkins verbal learning test, HVLT; Brandt, 1991; Vanderploeg et al., 2000), language/semantic memory (15 Boston Naming Test, BNT; Mack et al., 1992), verbal working memory (Digit span; Wechsler, 2008), premorbid intelligence quotient (Test of Premorbid Functioning, TOPF; Wechsler, 2009) and motor function (Purdue Pegboard; Desrosiers et al., 1995). In addition to these measures, participants were examined by a trained clinician using the UPDRS-III (Goetz et al., 2008), including the Hoehn and Yahr (1967) scale. Relevant test scores are summarised in Table A3.1.

Note: * These columns contain the number of individuals who had a score that was two standard deviations away from the age-adjusted normative values (n.a.: relevant normative values not available). MOCA: Montreal Cognitive Assessment; TMT: Trail Making Test; ROCFT: Rey-Osterrieth Complex Figure. Test; HVLT-R: Hopkins Verbal Learning Test-Revised; BNT: 15-Item Boston Naming Test; TOPF: Test of Premorbid Functioning, FSIQ: Full Scale Intelligence Quotient; UPDRS: Unified Parkinson's Disease Rating Scale; H & Y: Hoehn and Yahr scale. *p*: probability of difference between PD and healthy control participants, Mann–Whitney non-parametric test (n.s.: non-significant).

Table A3.1 *Neuropsychological evaluation of all participants in Chapter 3*

	PD participants (N = 18, 8F)			Control participants (N = 18, 9F)			
	Mean ± SEM	Range	> 2 SD*	Mean ± SEM	Range	> 2 SD*	*p*
Age	68.5 ± 1.5	54 - 79	n.a.	67.3 ± 1.1	60 - 76	n.a.	n.s.
Education	13.8 ± 0.8	10 - 23	n.a.	15.1 ± 0.9	10 - 20	n.a.	n.s.
15-Item BNT	14.4 ± 0.2	12 - 15	1	14.8 ± 0.1	14 - 15	-	n.s.
Category Fluency	21.1 ± 1.2	14 - 29	-	22.1 ± 1.0	14 - 31	-	n.s.
Digit Span (Scaled Score)	9.6 ± 0.6	4 - 13	1	11.3 ± 0.6	7 - 16	-	n.s.
HVLT-R							
TMT (s) Trial 1	4.6 ± 1.1	3 - 7	n.a.	5.6 ± 0.4	3 - 9	n.a.	.031
TMT (s) Trial 2	6.2 ± 0.4	3 - 9	n.a.	7.6 ± 0.5	3 - 11	n.a.	.034
TMT (s) Trail 3	7.2 ± 0.6	3 - 11	n.a.	8.9 ± 0.5	5 - 12	n.a.	.032
TMT (s) Learning	2.6 ± 0.6	-4 - 6	2	3.3 ± 0.6	-1 - 7	4	n.s.
TMT (s) Sum of 1-3	17.9 ± 1.0	9 - 26	1	22.1 ± 1.1	15 - 32	-	.009
TMT (s) Delayed Recall	5.4 ± 0.7	0 - 11	3	7.9 ± 0.7	0 - 12	1	.016
TMT (s) Percent Retained (%)	77.7 ± 11.3	0 - 233.3	-	87 ± 6.1	0 - 120	-	n.s.
TMT (s) True positives	10.8 ± 0.3	8 - 12	1	10.2 ± 0.5	6 - 13	1	n.s.
TMT (s) False positives	1.1 ± 0.2	0 - 3	-	1.7 ± 0.2	0 - 4	-	n.s.
TMT (s) Discrimination Index	8.5 ± 0.5	3 - 11	2	9.7 ± 0.4	7 - 12	-	n.s.
MoCA	26 ± 0.8	18 - 29	4	28.3 ± 0.3	26 - 30	-	.012
Purdue Pegboard							
TMT (s) Right	10.9 ± 0.7	4 - 15	6	13.1 ± 0.4	8 - 16	1	.016
TMT (s) Left	10.2 ± 0.5	8 - 15	5	12.8 ± 0.3	9 - 15	1	< .001
TMT (s) Both	8.8 ± 0.5	6 - 13	3	10.6 ± 0.3	8 - 14	-	.005
TMT (s) Assembly	20.4 ± 1.6	10 - 36	4	28.0 ± 1.3	20 - 37	2	.001
ROCFT (score out of 36)							
TMT (s) Copy	28.9 ± 1.7	5 - 36	2	31.5 ± 1.2	17.5 - 36	2	n.s.
TMT (s) Immediate	16.4 ± 1.7	1.5 - 28	1	18.5 ± 1.7	5.5 - 33	1	n.s.
TMT (s) Delay	15.1 ± 1.7	2.5 - 25.5	2	19.7 ± 1.9	4.5 - 31	-	n.s.
TOPF-FSIQ	110.4 ± 2.8	89.2 - 129	-	28 ± 1.3	20 - 37	-	n.s.
TMT(s)							
TMT (s) Part A	35.0 ± 2.8	14.8 - 56.6	-	28.5 ± 2.3	15.15 - 50.34	1	n.s.
TMT (s) Part B	77.8 ± 9.7	29 - 180	1	57.5 ± 8.8	23.22 - 188	1	n.s.
UPDRS-III	31.5 ± 3.1	11 - 51	n.a.	1.3 ± 0.4	0 - 4	n.a.	< .001
H & Y	1.75 ± 0.1	1 - 3	n.a.	0	0	n.a.	< .001

Appendix 3.2 Lateralisation of PD symptoms

Because PD patients often display symptoms asymmetrically (van der Hoorn et al., 2011; 2012; see also Chapter 3), I examined whether the use of the most affected vs. the least affected side influenced behavioural performance (see 3.2.2 Neuropsychological evaluation and UPDRS for clinical scores for each PD participant). Behavioural results for the PD group are plotted in Figure A3.2, with results for the least affected side shown in Figure A3.2a, and results for the most affect side shown in Figure A3.2b.

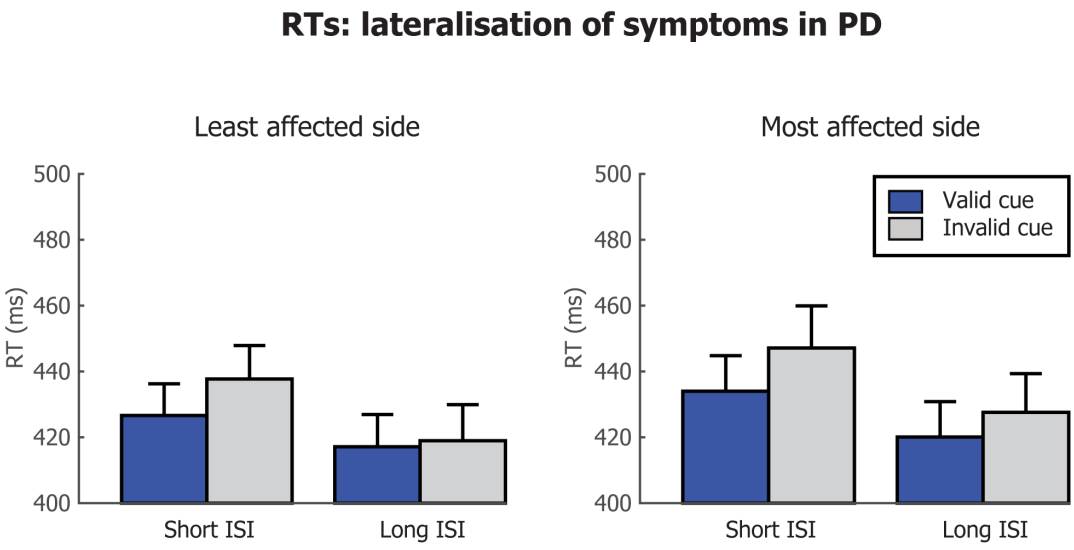

Figure A3.2 Behavioural results. (a) RT results for PD patients, for the least affected side, for each temporal cue type (valid vs. invalid) and each cue-target inter-stimulus-interval (ISI; short or long: 1 or 2 s). Error bars show standard error of measurement (SEM). (b) RT results for the most affected side.

To test for an effect of symptom lateralisation, I performed a repeated-measures ANOVA with the factors Lateralisation of Symptoms (least affected or most affected side), and Cue Validity for the short ISI (valid or invalid). This analysis showed a main effect of Cue Validity ($F(1,17) = 9.44$, $p = .007$, partial $\eta^2 = 0.36$), but no main effect of Lateralisation of Symptoms ($F(1,17) = 0.31$, $p = .585$, partial $\eta^2 = 0.02$). There was no interaction between Lateralisation and Cue Validity ($F(1,17) = 0.03$, $p = .859$, partial $\eta^2 = 0.002$). Because this analysis did not indicate any influence of lateralisation of symptoms on performance, I did not further investigate the possible influence of symptom lateralisation in the MEG data.

Appendix 3.3 Line plots of anticipatory alpha and beta band activity

Methods

To investigate further potential alpha and beta power differences between groups, I calculated alpha and beta time courses for each cue condition. Time courses were calculated by (for each participant) averaging the time-frequency data between 8 and 12 Hz and between 15 and 28 Hz, separately for each condition and each ROI. These data were baselined with a relative baseline across all trials, which was calculated as the average of the time period 500 - 250 ms before cue presentation. For both motor ROIs, time courses were subsequently averaged for left and right channels to obtain contra- and ipsilateral time courses. Cluster-based non-parametric permutation testing was performed using 1000 permutations with a cluster alpha of 0.05, to test for significant changes (clusters) against zero, and to test for significant differences between conditions and groups.

Results for the beta (14 - 28 Hz) band

To zoom in on the differences in anticipatory modulations between temporal cueing conditions and between groups, I calculated beta time courses for both short and long temporal cues, again for the short (0 - 1.2 s) cue-target interval. These time-courses showed a relative change from baseline (500 - 250 ms before cue presentation at time = 0). Beta (15-28 Hz) time courses for short

(yellow) and long (green) cues are shown in Figure A3.3.1a, separately for control and PD participants. Horizontal lines indicate significant clusters after non-parametric cluster-based permutation testing.

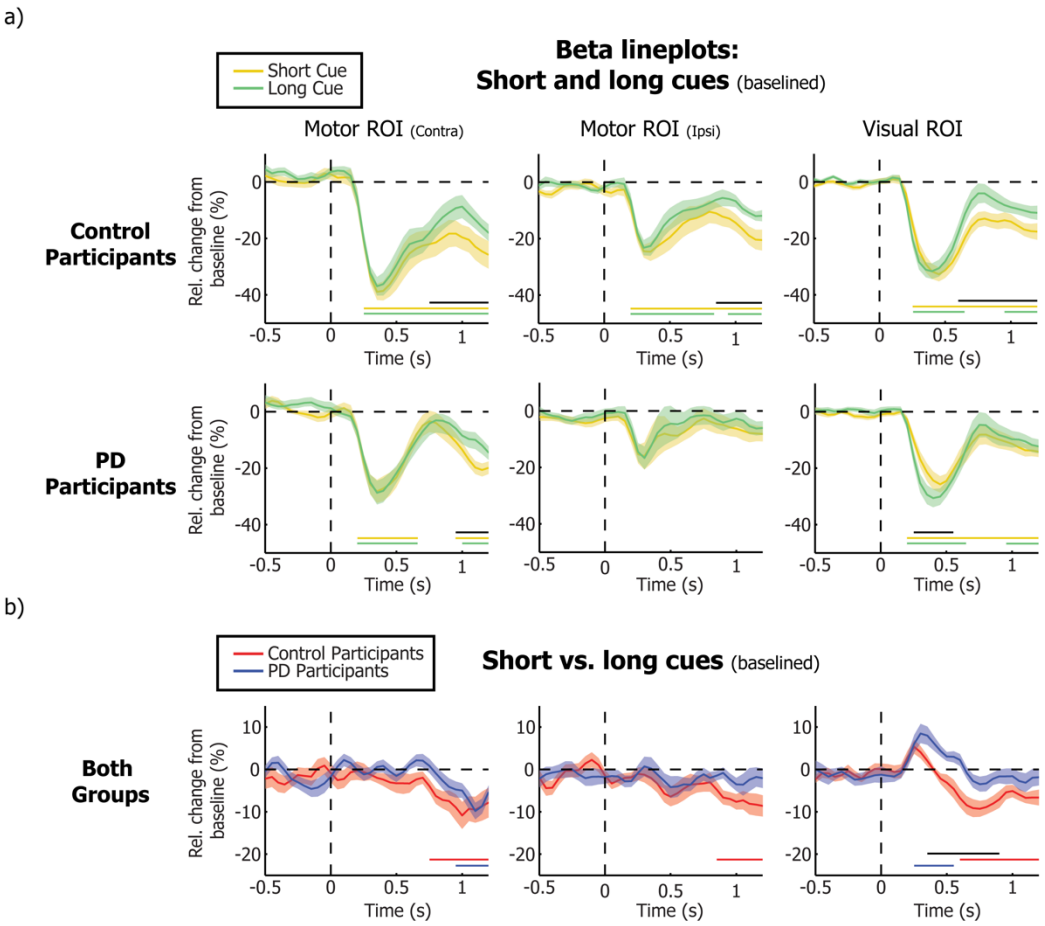

Figure A3.3.1 Beta time courses for the effect of temporal orienting of attention. (a) Beta (15 - 28 Hz) time courses shown separately for short (yellow) and long (green) cues, for control participants (first row) and PD participants (second row); for contralateral motor ROI channels (first column), ipsilateral motor ROI channels (second column), and visual channels (third column). Horizontal lines indicate significant clusters after non-parametric cluster-based permutation testing. Coloured lines indicate clusters significantly different from zero. Black lines indicate significant differences between both conditions. Shaded areas reflect the standard error of the means (SEM). (b) Beta time courses for the short-minus-long contrast for control participants (red) and PD participants (blue). The black horizontal line indicates a significant difference between both groups.

When inspecting the motor ROIs, it is clear that both control (short: two-sided cluster $p < .001$; long: two sided cluster $p < .001$) and PD participants (short early: two-sided cluster $p = .006$; short late: two-sided cluster $p = .006$; long early: two-sided cluster $p = .008$; long late: two-sided cluster $p = .046$) showed a strong initial desynchronization contralateral to the response hand, starting from around 200 ms after cue presentation, for both short and long cues, reaching a maximum around 400 ms after cue presentation. This desynchronization then relaxed for a while but then again started to increase in both groups at the end of the short interval. In both groups this anticipatory decrease was stronger (and seemed to start earlier) following short cues, compared to long cues (control participants: two-sided cluster $p = .004$; PD participants: two-sided cluster $p = .004$). For control participants the time courses for short and long cues in contralateral motor ROI channels clearly started to differentiate well before the short target was presented, while in PD participants this differentiation occurred slightly later, only after the beta desynchronization almost completely went back up to baseline levels (therefore resulting in two, rather than one cluster in this group), just before the target came up. Unfortunately, this optical difference in the short-minus-long cue time course between groups did not reach significance (see Figure A3.3.1b).

In ipsilateral ROI channels, in control participants a similar (although overall reduced, compared to contralateral channels) modulatory pattern was visible (short: two-sided cluster $p < .001$; long early: two-sided cluster $p = .006$; long late: two-sided cluster $p = .018$), with again a steeper or earlier decrease

following short, compared to long cues (difference: two-sided cluster p = .008), also visible in the fact that for the long condition two, instead of one significant cluster appeared. In PD participants such a decrease seemed to be largely absent, in line with the fact that no significant cluster was present for this group in Figure 3.5a. When inspecting the short vs. long cue difference time courses (Figure A3.3.1b) there was again no significant difference between groups, although the short vs. long difference only reached significance in the control participant group (as mentioned above; difference: two-sided cluster p = .008).

For the visual ROI, the modulations that were found in Figure 3.5 are again clearly visible. PD participants showed a difference in the large initial desynchronization between short and long cues (short: two-sided cluster p < .001; long early: two-sided cluster p = .001; long late: two-sided cluster p = .008; short-minus-long difference: two-sided cluster p = .008), but no clear further anticipatory modulation preceding the target (although the fact that for the long condition two, rather than one, clusters appeared may hint at a small effect). Control participants showed no difference in the cue-induced response, but instead showed a significant anticipatory cluster, with a stronger decrease preceding targets expected after a short (two-sided cluster p < .001), compared to a long (early: two-sided cluster p = .018, late: two-sided cluster p = 0.14) ISI (difference: two-sided cluster p < .001). The group difference again (as in Figure 3.5) presented itself as one broad cluster (two-sided cluster p < .001).

Results for the alpha (8 - 12 Hz) band

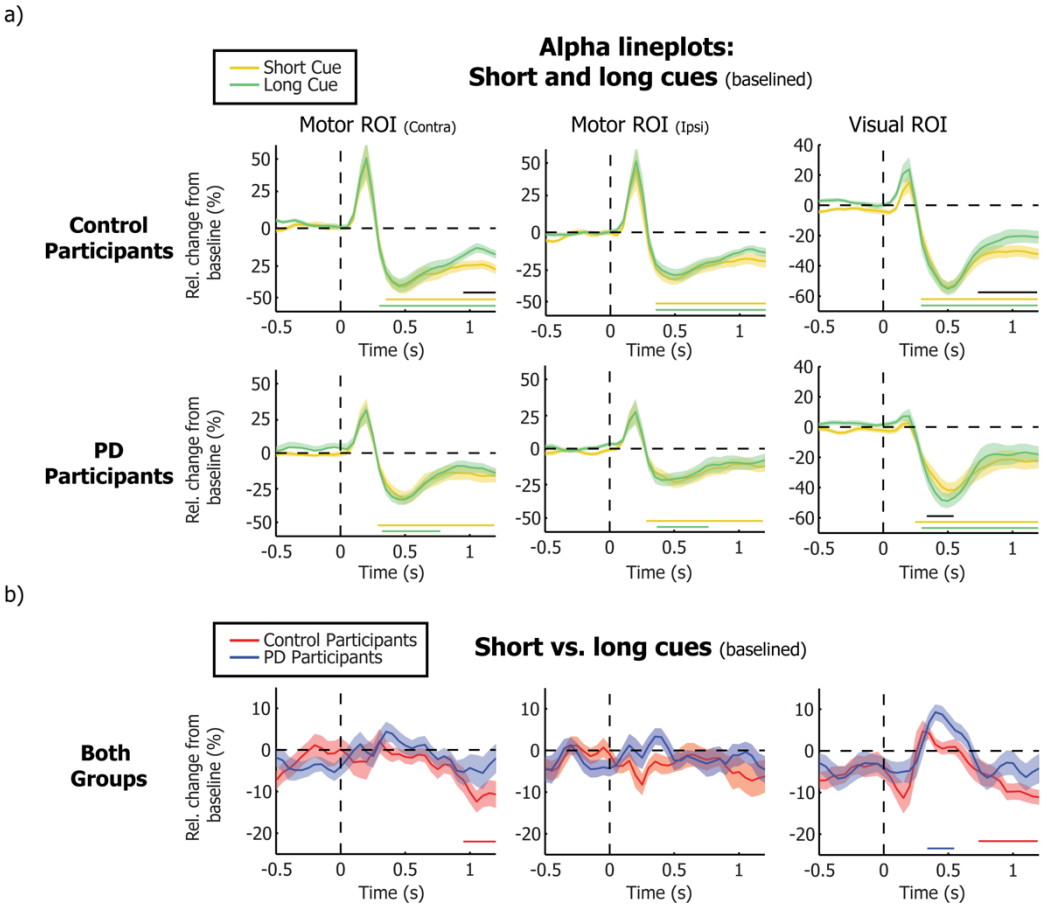

Figure A3.3.2 Alpha time courses for the effect of temporal orienting of attention. (a) Alpha (8 - 12 Hz) time courses shown separately for short (yellow) and long (green) cues, for control participants (first row) and PD participants (second row); for contralateral motor ROI channels (first column), ipsilateral motor ROI channels (second column), and visual channels (third column). Horizontal lines indicate significant clusters after non-parametric cluster-based permutation testing. Coloured lines indicate clusters significantly different from zero. Black lines indicate significant differences between both conditions. Shaded areas reflect the standard error of the means (SEM). (b) Beta time courses for the short-minus-long contrast for control participants (red) and PD participants (blue). The black horizontal line indicates a significant difference between both groups.

This analysis was repeated for the alpha (8 – 12 Hz) band. Alpha time courses are shown in Figure A3.3.2a. For the contralateral motor ROI, both control (short: two-sided cluster $p < .001$; long: two sided cluster $p < .001$) and PD participants (short: two-sided cluster $p < .001$; long: two-sided cluster $p = .008$) showed a strong desynchronization contralateral to the response hand, similar to what we saw in the beta band. In contrast to the results for the beta band, the short vs. long difference was only significant in control participants (two-sided cluster $p < .001$). The group difference did not reach significance.

In ipsilateral ROI channels, in both control and PD participants a similar modulatory pattern was now visible (control group short: two-sided cluster $p < .001$; control group long: two-sided cluster $p < .001$; PD group short: two-sided cluster $p < .001$; PD group long: two-sided cluster $p = .006$). No significant short vs. long difference was present in either group. There was again no significant difference between both groups.

For the visual ROI, the modulations that were found in Figure 3.5 are again clearly visible. PD participants showed a difference in the large initial desynchronization between short and long cues (short: two-sided cluster $p < .001$; long: two-sided cluster $p < .001$; short-minus-long difference: two-sided cluster $p = .030$), but no further anticipatory modulation preceding the target Control participants showed no difference in the cue-induced response, but instead showed a significant anticipatory cluster, with a stronger decrease preceding targets expected after a short (two-sided cluster $p < .001$), compared to a long (two-sided cluster $p < .001$) ISI (difference: two-sided cluster $p < .001$). The group difference was not significant.