Temporal Expectations in Healthy Ageing & Neurological Disorders

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ABSTRACT

Previous research has shown that orienting attention in time can help to improve behavioural outcomes. However, the extent to which temporal orienting can be preserved in ageing and in the context of neurological disorders remains unresolved. This thesis therefore explores temporal expectations in the healthy ageing and diseased brain by taking a neuropsychological approach. To begin, I provide an overview of the literature in **Chapter 1** most relevant for the following investigation. Four chapters of experiments then follow. To examine the effects of ageing on temporal expectation, the performance of healthy young adults and healthy older adults is presented and the results are discussed in **Chapter 2** and **3**. Though it had been previously shown that older adults seem to experience an expectation deficit on temporal expectation tasks, these chapters demonstrate the preservation of temporal expectation in ageing. On their own, these findings represent an important and novel contribution to the literature; however, this research is incapable of establishing the causal mechanisms involved in temporal expectation. To explore the causal role of relevant brain regions in temporal expectation, **Chapter 4** and **5** investigate the effects of temporal orienting in participants with damage to the basal ganglia — a brain region strongly implicated in temporal processing. In **Chapter 4**, the role of the basal ganglia in temporal expectations is examined using data collected from participants with Parkinson's disease and contrasts their performance with age-matched healthy controls. To complement this investigation, and to provide converging evidence for the basal ganglia's role in temporal expectations, **Chapter 5** investigates the behavioural performance of individuals with focal lesions to the basal ganglia. The findings in this thesis are discussed in their wider context in **Chapter 6**, and directions for future research are proposed.

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Dedicated to the memory of my MSc supervisor, Professor Glyn Humphreys.

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If the whole of Western Philosophy is merely a footnote to Plato, then surely this thesis is a footnote to the trailblazers who first surveyed the terrain of attention — most notably Herman von Helmholtz, Wilhem Wundt, and William James. The combined efforts of these scholars anticipate much of what is written and discovered herein. Representing only a modest contribution, this thesis attempts to push the bounds of what we know about attention ever-forward. Of course, these giants within the field of Psychology are not the only ones whose shoulders I have been fortunate to stand on in an attempt to see further. There are a great many people who have supported me throughout my time in Oxford, and it is to them I owe much and give my heartfelt thanks.

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Contents

List of Abbreviations

ANOVA	analysis of variance
BCoS	Birmingham Cognitive Screening test
BNT	Boston naming task
CNC	Cognitive Neuropsychology Centre
CSTCS	cortico-striato-thalamo-cortical system
CT	computerized tomography
d'	d-prime
DA	dopamine
DBS	deep brain stimulation
EEG	electroencephalogram
FLAIR	fluid rapid attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FSIQ	full-scale intelligence quotient
HVLT	Hopkins verbal learning test
IES	Inverse Efficiency Scores
IFG	Inferior Frontal Gyrus
IPS	intraparietal sulcus
MATLAB	Matrix Laboratory
MEG	magnetoencephalography
MoCA	Montreal Cognitive Assessment
MPRAGE	magnetization-prepared rapid gradient echo sequence

MRI	magnetic resonance imaging
OCMR	Oxford Centre for Clinical Magnetic Resonance Research
OHBA	Oxford Centre for Human Brain Activity
NT	not tested
PC	proportion of correct responses
PD	Parkinson’s disease
PFC	pre-frontal cortex
RCF	Rey-Osterrieth Complex Figure test
RSVP	rapid serial visual presentation
RT	response time
SOA	Stimulus onset asynchrony
SMA	sensori-motor area
SPM8	Statistical Parametric Mapping 8
SPSS	Statistical Package for the Social Sciences
STM	Subthalamic Nucleus
TOPF	Test of premorbid functioning
TMS	transcranial magnetic stimulation
TMT	trail making task
WM	working memory

1 Introduction

Chapter Abstract

This thesis is concerned with temporal expectations used to orient attention. It interrogates whether these decline with the natural, healthy ageing process; and additionally explores the contribution of the basal ganglia in supporting temporal expectations by studying individuals with degeneration or lesions to these nuclei. Before the chapters describing new empirical research, this introductory chapter reviews the relevant literature. To this end, I will summarize some of the history of attentional orienting, especially as it relates to goal-directed temporal orienting. This will be followed by an examination of the anatomical correlates that have been suggested to support interval timing and temporal orienting. After establishing the basal ganglia as one possible candidate to support temporal orienting, I propose a comparative approach that will examine temporal orienting in both healthy ageing and neurological populations.

1.1 Overview

> *"The boundary-line of the mental is certainly vague…minds inhabit environments which act on them and on which they react"* — William James

Our brains have been described by philosophers as 'projectors' (Dennett, 2013) — hurling on to the world an endless reel of footage in the form of expectations and biases. In a similar vein, brains have been characterized as 'prediction machines' (Clark, 2013). Through the act of predicting and anticipating, we are ceaselessly, albeit unknowingly, colouring the moments that fill our lives through the biases that shape, guide, and transform the stream of disconnected events that occupy our senses.

While ostensibly helpful, without further elaboration these metaphors fail to convey the complexity of the brain-body interactions with our surroundings. Perception is as much about projecting on to the world, and predicting, as it is about taking in bits of information and using that information iteratively to optimize our moment-to-moment behaviour proactively and adaptively. Through our interaction with the world, our brains integrate the information that we receive from the senses, stitching it together into a rich tapestry through consolidative processes, and projecting information back outwards to flexibly guide action. It is a dynamic and iterative process that relies on making use of internal representations of the external environment — including its temporal structure and temporal relations — to guide and select from the stream of events ever-unfolding before us.

The cognitive function associated with orienting, focusing, and selecting from the stream of rapidly unfolding events is what psychologists have come to know as *attention*. Put in neuroscientific terms, "attention refers to the set of mechanisms that tune psychological and neural processing in order to identify and select the relevant events against all the competing distractions" (Nobre & Mesulam, 2014, p. 105), or put more succinctly, attention is "the prioritization of processing information that is relevant for current task goals" (Nobre & Kastner, 2014, p. 1204). While attention is constrained by a variety of biases, such as spatial, featural, and object-based, this thesis examines temporal biases concerned with orienting attention in time.

Being able to time our behaviour effectively in a dynamic environment is fundamental to our successful interactions within it. By developing a more thoroughgoing understanding of how our expectations work to influence behaviour, and the conditions under which we can optimize performance, we will be better able to design cognitive interventions to aid people later in life — or to assist those with neurological damage — when there is a breakdown of cognitive capabilities.

As part of this grander vision, the work presented in this thesis is focused on how temporal expectations can be used to modulate motor responses and perceptual judgments in both non-clinical and clinical older populations. To this end, Section 1.2 of this introduction provides some background on temporal expectations and temporal orienting, and distinguishes this body of work from the larger body of research on orienting attention more generally. Section 1.3 provides an overview of the neuroanatomical correlates of timing and summarizes what we know about the role of the basal ganglia. Finally, section 1.4 provides the rationale for the comparative approach taken in this thesis and summarizes its scope and structure by motivating the importance of expanding the study of temporal orienting to these demographics — i.e. healthy older populations and those with neurological disorders, such as Parkinson's disease (PD) and stroke survivors with focal lesions in the basal ganglia.

1.2 Orienting Attention

No matter what our senses are occupied with at a given moment, whether we are moving around the world, listening to a symphony, reading a book, or socialising with others, our awakened brain is incessantly being bombarded with information. More often than not, the information being conveyed has a particular spatial and temporal structure to it, which our brain — having arisen in the world — is adept at being able to integrate and give shape to. To make sense of the incoming sensory patterns, the brain guides the perceptual process by prioritizing the extraction of the relevant signals that are predicted to occur. Prediction is pervasive, and has its origin within the regularities in the sensory stream itself, as well as in representations maintained in short-term memory or stored in our long-term memories (Nobre & Mesulam, 2014).

Consider catching a ball. As the ball comes closer to you, your brain is forming calculations and sending signals to your hands to make the necessary adjustments — about *where* and *when* your hand should move to grab it — and calibrating how your body should comport itself to receive the incoming projectile. The fact that most of us are able to do this so smoothly and unthinkingly is striking, especially given how difficult this ostensibly simple task has been to program in a machine (Bäuml, Wimböck, & Hirzinger, 2010) or to gain back after specific brain damage (Dawkins, 2016). Learning to catch a ball might take some time initially, but once we master this useful skill, the memory of the associated muscle commands is easily adapted to future (invariant) object-catching scenarios.

The example of the temporal sequence associated with catching a ball is helpful to keep in mind as we review some of the literature associated with orienting attention, particularly in the context of timing motor responses for appropriate actions or as an aid to enhance the perception of events and objects. Attention is best considered in an adaptive context — e.g. we attend *to* something, *for* something, often to optimize our behavioural responses. In this section I will review the research that has investigated how attention can be modulated (or directed) to serve and facilitate both motor and perceptual performance. To begin, I will provide an introduction to the study of orienting attention. This will include an examination of how spatial and temporal orienting cues have been used to modulate behavioural performance. I will then conclude with a summary of the different types of temporal expectations that exist to guide behaviour and introduce the reader to the types of predictive cues used in the experimental chapters to orient and manipulate attention in time.

1.2.1 Directing attention

In the late 19th century, William James — in the footsteps of his predecessors Herman von Hemholtz and Wilhelm Wundt — set the stage for the study of attention. In what is now a famous and oft-mentioned quote, James (1890) writes,

> "[e]very one knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others…" (p. 404).

Crucially, the most important role of attention as expressed here is to ensure that the vast multitude of (what James calls) 'items' made available to our senses is sifted through to provide a stable experience of the world, absent of 'chaotic indiscriminateness'. Building on Wundt's theories about 'apperception', or how attention and anticipatory processes can shape responses, James was well aware of how the concentration of attention can be used to accelerate and enhance both motor responses (as it prepares the 'motor centres') and perception, often by making a "sense-impression more intense" (p. 426). This ability of being able to focus and concentrate attention was understood, even in the early days of experimental psychology, as fundamental to behavioural optimization.

Today, attention is still one of the most studied domains in cognitive neuroscience and psychology, and research remains especially concerned with the functions associated with the prioritization — e.g. through selection and inhibition — of competing objects or trains of thoughts (for reviews, see Amso & Scerif, 2015; Nobre & Kastner, 2014). The study of the ability to use goals or predictions to focus mental resources on specific, task-relevant items has come a long way since it was first examined by Helmholtz (1867). We now know that there are many modes of selective attention (James, 1890; Enns & Trick, 2006) and a number of tasks have been used to measure their effects, including: visual search, dichotic listening or competing streams, to tracking targets, and covert orienting (see Nobre & Kastner, 2014).

Expanding on James' (1890) suggestion that there are two types of attentional processes — one passive and involuntary, and one active and voluntary — Posner (1980) referred to these processes as exogenous and endogenous spatial orienting, respectively. The former type of cueing, exogenous orienting, corresponds to a more bottom-up, involuntary, stimulus-driven, automatic process. Conversely, endogenous orienting involves the shifting of attention in a voluntary, goal-directed, intentional way (see Carrasco, 2014; Corbetta & Shulman, 2002). With this framing, researchers have since formalized the study of attentional orienting by developing paradigms to measure its effects.

Posner and colleagues (1980) thought of attention as a 'spotlight' that operates to enhance the "efficiency of the detection of events within its beam" (p. 172). In his original spatial cueing paradigm, the spotlight of attention was experimentally manipulated with the help of a symbolic cue (e.g. an arrow) that directed the observer's attention to a particular location (Posner, 1980)[1] The cue was manipulated to be predictive or non-predictive, depending on whether it accurately directed attention to the relevant location of the object in the scene. That is, in 80% of the trials the arrow pointed to where the target appeared, and in 20% of the trials, the cue directed the participant to an invalid location. Critically, in order to investigate endogenous attentional shifts, the location that the participants directed their attention to was made to vary from trial to trial, allowing for a comparison of performance when the target appeared at the attended (expected) or unattended (unexpected) location. The results indicated that by directing attention dynamically in space to predictable locations, processing of the stimuli could be facilitated, leading to more rapid and accurate responses than when targets were unpredictable. Effective spatial orienting of attention was found to be possible independently of overt eye movements (Posner, 1980).

The attentional cueing procedure Posner developed is now a common and accepted paradigm used to measure attentional orienting. His foundational study has led to numerous replications and has confirmed that spatial attention can be directed in an anticipatory way by using informative cues to enhance stimulus processing (for reviews, see Carrasco, 2014; Wright & Ward, 2008). These early experiments set the stage for examining attentional orienting, and have since enabled psychologists to develop a better understanding of goal-based attention and how we can optimize perception and action within a complex environment.

The behavioural mechanisms supporting spatial attentional orienting have been explored extensively (e.g. Carrasco, Eckstein, Verghese, Boynton, & Treue, 2009), and electrophysiological studies have revealed many of the neuronal mechanisms involved

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[1] The paradigm can be adapted to measure exogenous attention by providing a peripheral cue — e.g. a dot or a flash — next to the target location. In order to measure goal-based attention, endogenous, central instructive cues (e.g. arrows) are used.

(Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, Miller, Duncan, & Desimone, 1993; Reynolds & Chelazzi, 2004; Cohen & Maunsell, 2014). Further, imaging studies and findings from neuropsychological research have revealed the neural networks for spatial attention, which includes the posterior parietal cortex around the intraparietal sulcus (IPS), frontal eye fields in lateral and medial premotor cortex, anterior cingulate, and subcortical areas (see Corbetta, Miezin, Shulman, & Petersen, 1993; Corbetta & Schulman, 2002; Nobre et al., 1997; Corbetta & Shulman, 2002; Gillebert, et al., 2011; Gillebert, Mantini, Peeters, Dupont, & Vandenberghe, 2013; Shulman & Corbetta 2012).

In the preceding, we have seen how attention can be directed dynamically to boost behavioural performance. The introduction of predictive, endogenous cues into the experimental arena have facilitated the study of goal-based attention. While most studies using such directive, endogenous cues have focused on spatial orienting to particular locations (see Nobre, 2010; Theeuwes, 1994; 2010), researchers have also looked at how such goal-based attention can be used to orient to simple visual features (Martinez-Trujillo & Treue, 2004; Maunsell & Treue, 2006), objects (Abrams & Law, 2000; Duncan, 1984; Goldsmith & Yeari, 2003), and orienting motor actions (Rushworth, Ellison, & Walsh, 2001; Rushworth, Johansen-Berg, Gobel, & Devlin, 2003).

More recently, it has been established that it is also possible to orient attention to moments in time. It is to the study of temporal orienting — the central theme of this thesis — that we now turn.

1.2.2 Orienting attention in time

Just as we are able to anticipate objects appearing in certain locations, we are also able to anticipate events in time, and can do so at many different time scales. Perhaps of chief importance is our ability to anticipate external events in the time range for organizing online cognition (100's of milliseconds to seconds) — also known as the *interval timing* range — since it is timing at this scale that enables us to integrate action sequences, thoughts, and behaviour; to detect emerging trends and patterns; and to anticipate outcomes on a moment-to-moment basis. As such, these expectations form the bedrock for so much of our behaviour, from motor control, speech generation and recognition, to playing music and dancing. Think back to the example of catching a ball, or to reading, or reacting while driving. Timing at the interval range is fundamental to our day-to-day dealings, and is what enables us to navigate the world (for the most part) smoothly. While there are many unsolved mysteries at longer timescales, this thesis focuses on timing at this shorter timescale, and specifically as it pertains to our ability to form expectations in order to orient our attention in time to enhance motor and perceptual processing.

There is a long tradition in psychology of investigating temporal expectations at the interval time scale, and using expectations to direct attention to forthcoming events within it. The origins of the study of temporal orienting stretches back to Wundt (1874) and Woodrow's (1914) independent work on attentional preparation (for reviews, see Nobre & Rohenkohl, 2014; Nobre & Heideman, 2015). Firstly, Wundt (1874) found that observers responded more quickly to a target item when it followed a signal. This was demonstrated by using the sound of a steel ball hitting a plate as a signal (i.e. 'cue') to direct participants to release a key as quickly as they could. Carrying on this line of research, Woodrow's (1914) work expanded on Wundt's discovery by manipulating the duration of the interval between the target item and the warning signal, i.e. the *preparatory interval* or *foreperiod*, to show that attentional preparation can develop over time, and that reaction times can be improved (i.e. shortened) when actions follow a predictable foreperiod (— n.b. in the same experiment, Woodrow was also the first to show that reaction times became faster as the preparatory interval increased). Following these early experiments, researchers have continued to demonstrate the strength of the foreperiod effect, and responses to a stimulus occurring at an expected time have consistently been reported to speed up reaction times and improve accuracy when compared to those appearing at unexpected intervals (e.g. Earle & Lowe, 1971; Egan, Greenberg, & Schulman, 1961; Los, 2004; Los, Knol, & Boers, 2001; Los & Schut, 2008; Los & Van Den Heuvel, 2001; Niemi & Näätänen, 1981; Teichner, 1954; Vallesi, et al., 2007; Vallesi, Shallice, & Walsh, 2007).

It is now well understood that temporal expectations can be used to enhance both motor responses and perception. However, investigations into the study of how temporal expectations can be used to support the flexible and endogenous orienting of attention to instants in time has only recently been explored. In an extension of Posner's (1980) endogenous spatial orienting task, researchers introduced temporally predictive cues to investigate temporal orienting, with the aim of examining whether temporal anticipatory processes can be put under cognitive control (Coull & Nobre, 1998; Coull, Frith, Büchel, & Nobre, 2000; Miniussi, Wilding, Coull & Nobre, 1999).

In what is now considered a seminal study, Coull and Nobre (1998) hypothesized that participants could direct their attentional resources to moments in time by using an endogenous temporal orienting procedure. In their task, a symbolic cue manipulated the participants' expectations about where and/or *when* (the novel bit!) to direct their attention. The spatial/temporal cues directed the participants to the task-relevant target item, which appeared after a short or long foreperiod on the right or left of a centrally presented cue. Using a simple speeded target-detection task, participants were encouraged to make a response once they detected the peripheral target stimuli as quickly as possible while avoiding mistakes. In contrast to the foreperiod tasks previously mentioned, but similar to the spatial orienting paradigm that the researchers sought to emulate, Coull and Nobre's paradigm manipulated temporal orienting on a trial-by-trial basis in order to examine temporal orienting separately from the foreperiod effect. It was found that detection was faster when the target was preceded by a cue with temporally predictive information than when it was preceded by a neutral cue without temporally predictive information. The short cue produced the fastest reaction times at the short interval when the participant was correctly cued to the target item (i.e. 80% of the trials). As reviewed in Coull (2010), these effects were replicated in a series of follow-up investigations (see Coull, Nobre, & Frith, 2001; Griffin, Miniussi, & Nobre, 2001, 2002), and hold true even after the spatial component of the task is removed (Miniussi et al., 1999; Coull et al., 2000; Griffin, et al., 2001).

Moving on from Coull and Nobre's (1998) investigation — which was the first study to observe the benefits of the explicit, voluntary orienting of attention in time to task-relevant items — a number of studies using different cue-target intervals, physical stimuli, and response requirements have extended our understanding of temporal orienting, demonstrating benefits in accuracy in addition to response times when targets appeared at the expected time compared to when they were unexpected (Coull, et al., 2000; Los & Heslenfield, 2005; Miniussi, et al., 1999; Nobre, 2001). These studies have highlighted how temporal expectations can change dynamically, from trial-to-trial, and — as compared to the paradigms that measure the foreperiod effect, which involves much more automatic processing — show how temporal orienting tends to be voluntary and explicit (see Rohenkohl, Coull, & Nobre, 2011).

Correa (2010) summarizes the essential features of temporal orienting paradigms as they are now conceived and the processes they are designed to measure. Typically, temporal orienting tasks involve cueing participants to an early or late task-relevant item. Since the temporal cue typically directs the participants' attention to the target item with near fidelity (i.e. 75% to 80% validity), the cue is said to be predictive. When the target is validly cued, the target appears at the expected location; however, when it is invalidly cued, it appears at the unexpected location. Temporal cueing paradigms often measure behavioural gains by comparing valid and invalidly cued trials at the shorter time period only, and the results tend to show that the short interval produces the strongest cueing effects as measured by the differences in behavioural performance between valid and invalidly cued targets. This is because the effects associated with temporal orienting at the long interval may be diminished by foreperiod effects and because of the effects associated with the unidirectional flow of time itself. By comparison, the effects associated with temporal orienting tend to be most pronounced for targets appearing at the short interval, where the manipulation of the conditional probability for the appearance of the target is strongest (for reviews see Griffin, et al., 2001; Nobre, 2001; Nobre, Correa, & Coull, 2007). Put more concretely, if the observer is expecting a target to appear early, and the target item does not occur, the observer knows (unless there are catch trials) that the target item will appear at the later time. In other words, with mounting expectations over time, the conditional probability of target occurrence increases from a probability of $p = .05$ to $p = 1.0$ after the short interval passes (see Coull, 2009; Correa, Lupiáñez, Milliken, & Tudela, 2004). That is, since trials that present the target after the longer interval are guaranteed to appear at that location 100% of the time, benefits in response time are typically observed — this is also referred to as the '*hazard function*' (Luce, 1986; Nobre et al., 2007).

The question of whether the behavioural gains primarily reflect a benefit as oppose to cost has also been explored. By manipulating cue validity — for example, by cueing a participant to anticipate the target after a long delay, but having it appear unexpectedly early—these paradigms have also been found to lead to a slowing of RTs for invalidly cued targets, leading to what has been deemed an 'invalidity effect' (e.g. Griffin et al., 2001, 2002). Experiments that have compared valid and invalid trials to neutral trials separately have discovered that the effects of invalidity seem to be negligible in comparison to the validity effects (Coull, 2010). That is, many studies have deemed the behavioural advantages to be better conceptualised as 'validity effects' (i.e. cueing benefits) than costs associated with invalid cueing (Coull et al., 2001; Griffin et al., 2001).

While the earlier versions of temporal orienting tasks looked mainly at reaction-time gains, the paradigm has been adapted to examine the effects of temporal orienting on perceptual processing. For instance, Griffin and colleagues (2001) showed that by using a choice RT task (instead of a simple speeded RT task), temporal orienting can be used to enhance the speed of perceptual discrimination. Soon after, Correa, Lupiáñez and Tudela (2005) examined the effects on perceptual sensitivity more directly by measuring perceptual accuracy using d-prime — a common measure in psychophysics (see Green & Swets, 1966; Macmillan & Creelman, 1991) — as part of a perceptually demanding task. Their task used Rapid Serial Visual Presentation (RSVP) of stimuli, wherein a target letter "X" was hidden amongst a stream of rapidly presented distractor letters (i.e. 14 ms per item). Without time pressure, participants were asked to say whether or not the target letter had been presented in the stream. In advance of the presentation of the stream of letters, attention was directed to specific moments in time within the stream when the target letter was likely to appear. As with earlier studies that showed temporal orienting can speed up behaviour by enhancing the preparation of motor responses (see also Coull, et al., 2000; Miniussi et al., 1999), their results showed that perceptual sensitivity was enhanced for targets appearing after the correctly cued time interval. These results provided the first behavioural evidence that endogenous temporal orienting can enhance perceptual processing in a perceptually demanding context. These findings highlight that the effects of temporal orienting are not limited to the motor domain, even though the effects of temporal orienting tend to be greater for motor than perceptual tasks (see Coull, 2010).

In a study by Davranche and colleagues (2011) temporal orienting effects were again found using separate motor and perceptual tasks. Modelling the paradigm first used by Correa et al. (2005), the researchers compared the performance on trials with valid cues to trials with neutral cues on two temporal orienting tasks — a perceptual discrimination task (or RSVP task), wherein a target letter was presented in a stream of distractors, and a speeded motor response task, wherein the participants had to respond as quickly as they could upon detecting a single target item. In the RSVP task, perceptual performance and reaction times were improved for identifying targets (either following an early or late foreperiod) within the stream of rapidly presented letters. In the motor detection task, RTs were again shown to be significantly faster following a valid cue. It was concluded that temporal cues could be used to enhance target identification as well as improve the speed of target detection for validly cued items.

Even in the absence of explicit cues, it has been shown that temporal orienting can occur quite naturally (e.g. Cravo, Rohenkohl, Wyart & Nobre, 2011; Rohenkohl, Cravo, Wyart, & Nobre, 2012). Though exogenous cueing is not the subject of this thesis, it is worth mentioning that paradigms have been developed to measure the effects of automatic, stimulus-driven (i.e. exogenous) temporal expectations in ecologically relevant contexts. Some of these experiments manipulate temporal expectations through modifying the rhythmic movement (e.g. regular/irregular) of a visual stimulus, which is said to entrain expectations for when a target stimulus is anticipated to appear (e.g., see Jones, 2010). In contrast to endogenous cueing procedures, there is no pre-learned association between a cue and the delay (see review, Coull, 2010). Instead, experiments allow for temporal orienting to arise naturally over time. As an example, Doherty and colleagues (2005) used rhythmic stimulus presentation to manipulate temporal expectation. In their experiment, a virtual ball moves in a predictable or unpredictable pattern on a display monitor, from the left to right of the screen, moving in discrete steps. As the ball moves on the screen, it passes through an occluding band, and the participants are asked to discriminate a small shape embedded within the ball as it reappears (i.e. exits the other side of the occluder). In this experiment, both temporal and spatial expectations were manipulated, and findings confirmed that spatial and temporal expectations could contribute to speeded response times. These findings have been replicated in similar designs more recently (Correa & Nobre, 2008; Rohenkohl & Nobre, 2011).

The effects of temporal orienting — both endogenous and exogenous — have been consistently found across modalities and in many different tasks contexts (see Nobre & Rohenkohl, 2014). Taken together, the research suggests that voluntary temporal orienting is a robust process, which can yield many positive effects on performance. The effects are present in temporal orienting tasks in auditory and crossmodal tasks (Lange, Rösler, & Röder, 2003; Lange & Röder, 2006; Sanders & Astheimer, 2008), and can influence measures of perceptual processing (*d'*) in tasks with high perceptual demands and delayed responses

(Correa et al., 2005). Temporal orienting can also attenuate the attentional blink (Martens & Johnson, 2005). The benefits are clear and ubiquitous. Today, temporal orienting is recognized as a fundamental attentional mechanism that works to prioritize motor and perceptual processing by selecting task-relevant information with a high degree of flexibility (Correa, 2010; Davranche et al., 2011).

1.2.3 Different types of temporal expectations

Our brains are constantly generating low-level predictions about what we will see, touch, hear, taste or smell. Often, our expectations about the world are satisfied; however, they can also, on occasion, be violated. When our expectations break down, the implications on behaviour can be significant. In more extreme cases, prediction failures can have dangerous consequences (e.g. anticipating a green light and pressing down on the cars gas pedal before the light has changed at an intersection) — more commonly, however, they can be immensely annoying or inconvenient.

As researchers begin to learn more about temporal expectations, a complex picture is emerging. Temporal expectations have been revealed to be happening across modalities and at different levels of processing, often simultaneously and without our knowing. Rather than a singular type of temporal expectation, there appear to be a multitude of expectations and biases operating at the interval time scale — some considered more automatic than others. In what follows I will provide a brief overview of some of the different types of temporal expectations that have been shown to exist, and distinguish them from goal-directed temporal orienting, which is of interest herein.

So far, we have considered temporal expectations associated with foreperiod effects and temporal orienting (using both endogenous and exogenous predictive cues), however it is worth bearing in mind that there are many different types of temporal expectations relying on different sources of temporal information. For example, attentional preparation can be experimentally manipulated by temporal expectations related to predictive cues, or to temporal structure, such as through temporal regularity conferred by rhythms (e.g. Jones, 2010; Doherty et al., 2005; Cravo, Rohenkohl, Wyart & Nobre, 2011), probabilistic information associated with the passage of time (e.g. the source of the foreperiod effect), and the effects of preceding trial information (i.e. sequential effects) — which in the case of repetitions of foreperiod durations, can serve to bias subsequent responses. Importantly, these more automatic sources of temporal prediction occur in the richer context of other types of orienting (Nobre & Rohenkohl, 2014).

Coull and Nobre (2008) have suggested that one useful distinction along which to separate different types of temporal expectations is to divide them into endogenous (controlled) and exogenous (automatic) sources of temporal prediction (see also Los & Van Den Heuvel, 2001; Capizzi, Sanabria, & Correa, 2009). This type of classification system would see cue-based temporal orienting as relying on endogenous sources of information (i.e. controlled processing) and temporal expectations such as foreperiod effects, rhythmic expectations, and sequential effects as relying more on implicit sources of information. However, this distinction can get muddled, since some temporal orienting paradigms can rely on both implicit and explicit sources of temporal information, depending on whether the trial sequence is blocked or trial-by-trial (Nobre, 2010; Nobre & Rohenkohl, 2014). Despite the ostensible problems associated with the nomenclature, some studies have already shown that by making this distinction between endogenous and exogenous types of temporal expectations, temporal orienting and sequential effects yield separate consequences on behaviour (see Correa, Lupiáñez, & Tudela, 2005; Los & Van Den Heuvel, 2001; Los & Heslenfeld, 2005), and may be dissociable at the neural level (e.g. Coull & Nobre, 2008; Vallesi et al., 2007).

Multiple sources of temporal expectations may influence perception and action simultaneously. Effects can be dissociable, and in some cases may also interact (see Nobre & Rohenkohl, 2014).[2] For example, interactions have been found between temporal orienting and foreperiod effects (Correa, Lupiáñez & Tudela, 2006) and between rhythmic expectations and foreperiod effects (Correa & Nobre, 2008). In addition to these interactions, exogenous and endogenous cueing seem to lead to independent behavioural effects, seemingly supported by separate mechanisms (e.g. Rohenkohl, Coull & Nobre, 2011). As potential support for this claim, Triviño and colleagues (2010) offered neuropsychological evidence that temporal orienting and sequential effects rely on independent structures. Yet more recent findings by Coull and colleagues (2016) show that there can be dissociated neural effects of foreperiod and temporal orienting.

The different types of temporal expectation may furthermore influence perception and action via multiple mechanisms. Depending on the type of temporal expectations and the task parameters and demands, the levels of modulation may differ significantly. To date, different tasks have revealed modulation at different levels. For example, while early studies focused mainly on post-perceptual effects (e.g., Miniussi et al., 1999; Griffin et al., 2002), perceptual effects have also been noted (Correa et al., 2005; Correa et al., 2006). The level of processing affected by temporal expectations may partly reflect whether the task has high perceptual demands to discriminate stimuli or instead emphasize speeded action. Davranche

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[2] For a detailed summary of the different types of cues and their effects, see Nobre and Heideman (2015).

and colleagues (2011) compared behavioural performance and patterns of brain activation in temporal orienting tasks with high perceptual vs. motor demands. Temporal orienting for motor and perception both led to the left IPS being activated. However, in addition, task-specific networks were also activated. That is, while the left IPS was involved in both motor and perceptual discrimination tasks, in the case of the motor detection task, the level of activity in the left IPS correlated with bilateral pre-motor/motor cortex, but for the perceptual discrimination task the left IPS activity correlated more with activity in the bilateral occipital cortex. In other words, functional activity differed based on whether temporal orienting was used for motor responses or perceptual performance.

1.3 Sources of temporal orienting

To motivate the experimental investigation that will follow, I will explore (in brief) what we now know about the neural systems involved in supporting interval timing (section 1.3.1). Following this, I will go on to highlight some of the neuroanatomical units found to play a central role in temporal orienting (1.3.2). Taken together, these findings leave the contribution of the basal ganglia to temporal orienting unclear. In the final section (1.3.3), I provide an overview of the anatomy of the basal ganglia, and consider it as a candidate for supporting temporal orienting.

1.3.1 Neural systems for interval timing

If we are looking to better understand how temporal orienting is supported in the brain, an examination of the neural systems underlying the coding of temporal intervals may serve as a useful starting point. How temporal information is coded in the brain has been the subject of much debate, but theories can be organized into two main camps: the first camp proposes that there are dedicated and specialized (i.e. modular) timing systems, while the second proposes that the computations associated with time are distributed across neural systems.

In line with the first view, it has been argued that the neural representation of timing information at the interval timescale is dependent upon at least one central mechanism, which has been described as an internal clock (Ivry, 1996; Ivry & Schlerf, 2008; Meck, 1996; Treisman, 1963; see Cope, Grube, Singh, Burn & Griffiths, 2014 for review). Candidates for such a mechanism have included the basal ganglia (Gibbon, Malapani, Dale, & Gallistel, 1997; Grahn & Brett, 2007; Grahn & McAuley, 2009; Meck & Benson, 2002; Meck, 2005), the cerebellum (Ivry, 1993; Ivry & Keele, 1989; Spencer & Ivry, 2013), the supplementary motor area (Grahn & Brett, 2007; Halsband, Ito, Tanji, & Freund, 1993; Macar, Anton, Bonnet, & Vidal, 2004; Schwartze, Rothermich, & Kotz, 2012), the right parietal cortex (Harrington et al., 1998), and the pre-frontal cortex (Belin et al., 2002; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Lewis & Miall, 2003, 2006; Oshio, 2011; Oshio, Chiba, & Inase, 2008). Importantly, these regions seem to be anatomically linked (Akkal, Dum, & Strick, 2007; Bostan, Dum, & Strick, 2010; Bostan & Strick, 2010; Hoshi, Tremblay, Feger, Carras, & Strick, 2005; Jürgens, 1984) and functionally interconnected during timing tasks (Chen, Zatorre, & Penhune, 2006; Grahn & Rowe, 2009). Of these candidates, the basal ganglia and cerebellum seem to be two of the more consistently observed in interval timing tasks. In support of this claim, Gibbon and colleagues (1997) summarized some of the results from psychophysics, highlighting evidence that suggests that temporal processing deficits are common in patients with basal ganglia and cerebellar damage.

In the case of the thalamo-cortical-striatal circuits — which subsumes some of the regions proposed as the centralized timing system — it has been suggested that the basal ganglia (specifically the dorsal striatum) is responsible for monitoring oscillatory activity associated with a given duration, and functions as a "coincidence detector" (see Coull, Vidal, Nazarian, & Macar, 2004; Matell & Meck, 2004; Matell, Meck, & Nicolelis, 2003; Meck, Penney, & Pouthas, 2008; Miall, 1989; Oprisan & Buhusi, 2011; Turgeon, Lustig & Meck, 2016). In support of this theory, auditory studies on temporal perception, which have included functional imaging studies, have shown that the basal ganglia are strongly implicated as a basis for processing relative time (Geiser, Notter, & Gabrieli, 2012; Grahn & Brett, 2007; Grahn & McAuley, 2009; Teki, Grube, & Griffiths, 2011).

The other strong candidate for the source of such a dedicated timing system is the cerebellum, since it has been shown to be involved in estimating the timing of events at sub-second duration (Ivry, 1996; Ivry & Schlerf, 2008; Spencer & Ivry, 2013). Early research by Ivry, Keele and Diener (1988) showed that lateral cerebellar lesions lead to timing errors, such as deficits in interval discrimination. The cerebellum seems also to be responsible for some motor timing tasks, with damage to the region leading to related motor deficits (Holmes, 1939; Ivry & Keele, 1989). Additional (but disputed) findings have shown that damage to the cerebellum contributes to deficits in timing actions to events (Ivry & Keele, 1989; Ivry et al., 2002) and in perceptual judgments of brief intervals with trans-cranial magnetic stimulation (Koch et al., 2007; Lee et al., 2007). In addition, brain-imaging studies have shown the involvement of the cerebellum in learning temporal sequences (Sakai, Ramnani, & Passingham, 2002) and during perceptual tasks where temporal judgments are required (O'Reilly, Mesulam & Nobre, 2008).

While the basal ganglia and cerebellum do seem to be important for interval timing, the number of regions that have been implicated in temporal processing at the interval time scale strongly suggests that a singular region is unlikely to be completely responsible for its support. Ultimately, these regions are unlikely to operate in isolation. Instead, the basal ganglia and cerebellum may work together as part of a dedicated timing system (see O'Reilly, Mesulam, & Nobre, 2008). As Gibbon et al. (1997) suggested early on, cerebellar dysfunction might induce deregulation of tonic thalamic tuning, which disrupts gating of the temporal information generated in the basal ganglia through striato-thalamic-cortical loops. While there may not be a clear dissociation between cerebellar and basal ganglia contributions to temporal processing tasks — since similar deficits have been observed in patients with lesions in both areas (see Harrington, Haaland, & Hermanowicz, 1998) — there may be dissociable timing circuits that work in parallel involving the cerebellum and other subcortical structures like the basal ganglia (Buhusi & Meck, 2005; Buhusi, Perera, & Meck, 2005). Indeed, research examining temporal aspects of prediction in audition has suggested that the temporal structure of acoustic events might rely on a division of labour between the cerebellum and the basal ganglia (e.g. Schwartze, Tavano, Schröger, & Kotz 2012). One conceivable explanation is that the basal ganglia play a functional role in sequence integration (e.g. bringing spatial and temporal sequence information together), whereas the cerebellum might play a more general role in forming associations within a sequence (Shin & Ivry, 2003).

Moving away from a central clock mechanism, researchers embracing the second broad category of theories have also considered a more distributed timing system, arguing that internal clocks may not be altogether necessary for the coding of temporal patterns. After all, as we have seen, there seems to be an overwhelming amount of evidence that timing is processed across many brain areas, including motor and perceptual areas. According to a distributed timing scheme, the processing of durations could be a ubiquitous and intrinsic property of neural circuits (Buhusi, et al., 2005; Buonomano, 2007; Durstewitz, 2003; Mauk & Buonomano, 2004), or could be encoded in the firing rate of neurons like other stimulus features (Durstewitz, 2003).

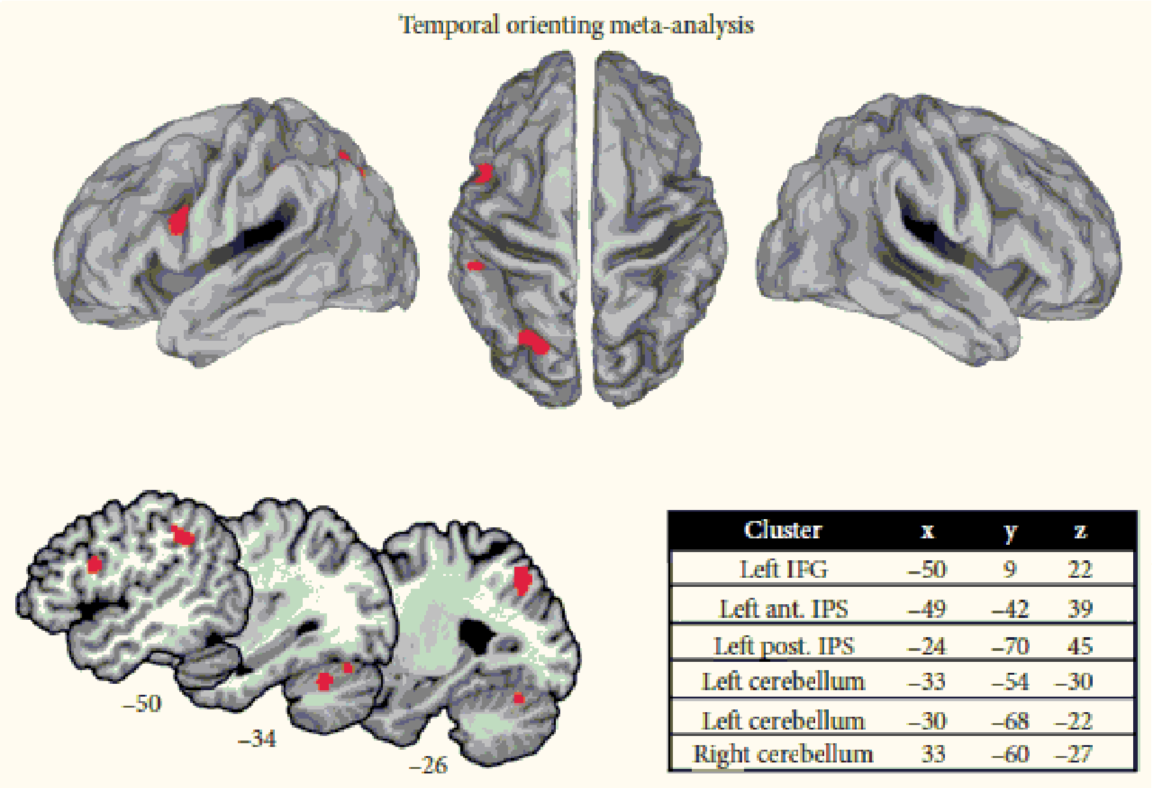
Given these separate theoretical explanations, and the lack of agreement on how interval timing is processed, it remains unclear how systems responsible for interval timing might work to support temporal orienting — or if they are even required. While the scientific understanding moves to a more distributed conceptualization of temporal processing, it is important to recognize that the regions mentioned above — such as the basal ganglia and cerebellum — may still play a key role within dedicated or distributed systems. For instance, these sites may act by influencing the downstream effects related to orienting attention in time to optimize motor responses and perceptual performance.

1.3.2 Neuroanatomical correlates of temporal orienting

The debate concerning how temporal information is processed in the brain is still very much an active one, and as the above research demonstrates, it is not clear how goal-directed temporal orienting might be supported by such neural systems. Brain imaging studies have, indeed, highlighted many differences in the patterns of brain activity observed during explicit timing and temporal orienting tasks (Coull & Nobre, 2008). Understanding what brain areas are causally involved in supporting temporal orienting, and identifying any important points of contact with the network(s) supporting explicit timing, remain of fundamental interest and importance.

In the earliest investigation of its kind, Coull and Nobre (1998) used Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) to explore the correlates of temporal orienting. As part of a factorial design, their study made use of four types of cues in an orienting task (Spatial, Temporal, Spatiotemporal, and Neutral) to compare and contrast the neuroanatomical substrates specific to temporal and spatial orienting. As described in section 1.2.2, their task used endogenous central cues to orient participants to temporal intervals or spatial locations. They discovered a pattern of activation that included the dorsal frontoparietal circuit, left posterior parietal cortex, and left inferior premotor cortex. When they contrasted spatial and temporal orienting conditions against a visual fixation task, their findings revealed considerable overlap in the fronto-parietal networks — n.b. areas that have been implicated in the control of spatial attention (see Kastner & Ungerleider, 2000; Nobre, 2001). Contrasting spatial and temporal conditions directly, they showed that temporal orienting preferentially activated the left IPS and left inferior premotor cortex. In subsequent fMRI investigations using a similar paradigm, Coull and colleagues (2000; 2001) investigated these effects without manipulating spatial attention. Replicating their earlier findings, they found that temporal orienting activated the inferior parietal cortex, the inferior premotor cortex and the prefrontal areas in the left hemisphere (for review, see Coull, 2010; Coull, 2014). Coull's group have since replicated the pattern of left parietal and frontal activations in a number of studies manipulating temporal orienting of attention in various types of tasks (Coull & Nobre, 2008; Cotti, Rohenkohl, Stroke, Nobre, & Coull, 2011; Davranche et al., 2011; Coull, Davranche, Nazarian, & Vidal, 2013; Bolger, Coull, & Schön, 2014; Marchant & Driver, 2013).

In a recent meta-analysis of the experiments that have looked at the neuroanatomical correlates of temporal orienting (see Figure 1.1), Rohenkohl and Nobre (2014) summarized the findings of the studies that measured temporal orienting across motor and perceptual tasks. The neuroanatomical correlates of temporal orienting include a range of brain regions, such as the left posterior parietal cortex along the IPS, left inferior premotor cortex, left inferior prefrontal cortex, and left and right cerebellum (Cotti, et al., 2011; Coull & Nobre, 1998; Coull et al., 2000; Coull et al., 2013; Coull, et al., 2016; Davranche, et al., 2011). These regions seem to tap into fronto-parietal networks associated to the control of action and motor preparation more generally, but engage a qualitatively distinct sensorimotor circuit from oculomotor control (Coull, 2014; Nobre & Rohenkohl, 2014). The left hemispheric dominance, engagement with the sensorimotor circuit, and systematic activation of prefrontal structures for motor control, suggest that temporal orienting is part of a strategic process that involves planning for and control of action.



Cluster	x	y	z
Left IFG	–50	9	22
Left ant. IPS	–49	–42	39
Left post. IPS	–24	–70	45
Left cerebellum	–33	–54	–30
Left cerebellum	–30	–68	–22
Right cerebellum	33	–60	–27

Figure 1.1 Meta-analysis of temporal orienting studies as presented in Nobre and Rohenkohl (2014). Results based on activation likelihood estimation (ALE — GingerALE 2.0 software) maps for eight temporal orienting studies. Values are significant at FDR $q < 0.05$, minimum cluster size > 200 mm^3. (Figure used with the permission of the authors.)

The findings that have shown the involvement of the left posterior parietal and left premotor cortex suggest an important connection between temporal orienting and motor preparation. Noted by Coull et al. (2000), the pattern of activation for the temporal orienting effects is similar to the activations observed in motor preparation and motor attention tasks (e.g. Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Rushworth et al., 2001; Rushworth, et al., 2003). And more recently, it has been suggested that predictive timing mechanisms may even be instantiated by the motor system (Morillon, Schroeder, Wyart, & Arnal, 2016). The involvement of the sensorimotor circuits has been explained as being analogous to how the oculomotor system participates in the spatial allocation of attention (Nobre, 2001, 2004, 2010). However, it remains unclear whether these are part of a general control network or a set of regions whose activity is modulated by temporal expectations in the tasks (see Nobre, 2010). Intriguingly, researchers have noted that the overlap of the neural circuitry involved in timing and motor functioning suggests that timing processes may be grounded in action (see Coull, 2014). These findings leave open whether there exists a network for the control of temporal orienting that can be dissociated from any intrinsic task-related sensorimotor networks or from other confounding cognitive processes.[3]

1.3.3 Involvement of the basal ganglia

The network linked to interval timing (reviewed in section 1.3.1) looks different than the one proposed for temporal orienting (1.3.2) (Coull & Nobre, 2008). However, it is noteworthy that both seem to include elements of the thalamo-cortical-striatal motor circuits. These findings therefore provoke an interesting question about whether the basal ganglia are necessary for temporal orienting. As I review in this section, the structure of the basal ganglia — and the relationship to many of the neuroanatomical correlates of temporal orienting — is suggestive of an important role in supporting temporal orienting.

The basal ganglia represent a multi-level, heterogeneous structure composed of subcortical nuclei with functionally distinct regions and parallel circuits that bear anatomical and neurochemical similarities across all vertebrate species, and are likely responsible for performing similar computations (Stephenson-Jones, Ericsson, Robertson & Grillner, 2012). Anatomically, the basal ganglia are comprised of a group of several subcortical nuclei, including the striatum (caudate, putamen and ventral striatum), the pallidum (internal and

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[3] However, as Coull (2014) notes citing her previous work, sensorimotor networks seem still to be activated even when motor preparation processes are controlled for (Coull, Nazarian, & Vidal, 2008). Moreover, in a study using TMS by Levit-Binnun and colleagues (2007), a dissociation between neural systems for timing and motor functions was found in a finger-tapping task.

external segments of the globus pallidus, external pallidum and internal pallidum, and two brainstem nuclei, the subthalamic nucleus (STN) and the substantia nigra (pars reticulate and pars compacta, SNR and SNc) (Barker, Cicchetti & Neal 2012; Braunlich & Seger 2012; Herrero, Barcia, & Navarro, 2002; see Figure 1.2).

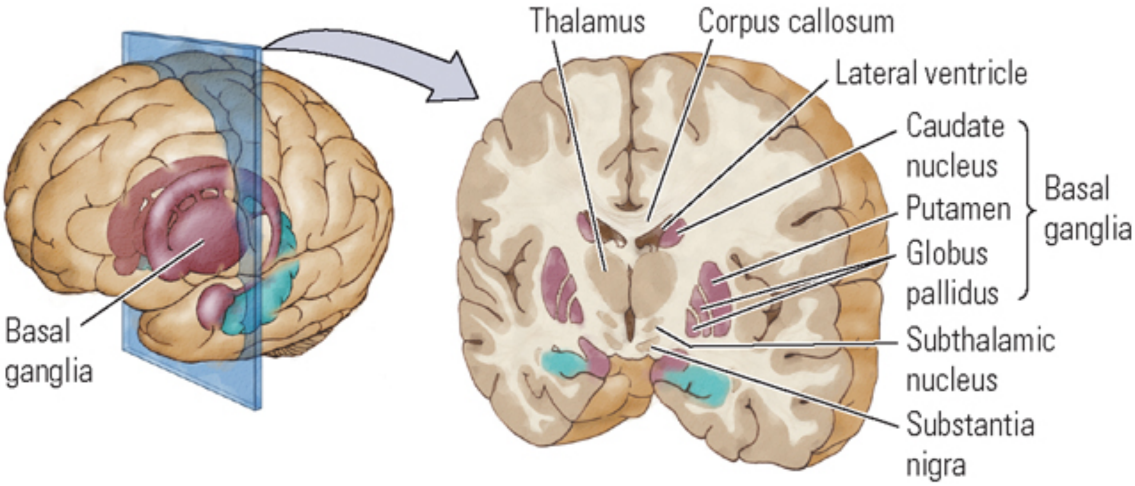

Figure 1.2 Anatomy of the basal ganglia (from Kolb and Whishaw, 2015, p. 73).

Given the basal ganglia's complexity and multiple cortical connections, it is perhaps of no surprise that it is implicated in a variety of behaviours. Though the basal ganglia has traditionally been considered largely a motor structure, it is also responsible for non-motor behaviour; receiving projections from all lobes of the cerebral cortex (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000; Haber, 2003) and playing a significant role in the control of information processing associated with sensorimotor, limbic, cognitive, and motivational aspects of behaviour (Middleton & Strick, 2002). For example, studies of non-human animals and people with neurological disorders demonstrate that the basal ganglia are involved in diverse domains including movement (especially the gating and thresholding of motor actions), higher-level cognition, reward and emotional processing (Alexander et al., 1986; DeLong & Georgopoulos, 2011; DeLong, Georgopoulos, & Crutcher, 1983; MacLean, 1972). In reward processing, because the basal ganglia receive cortical projections from all lobes of the cerebral cortex, it is taken to be responsible for facilitating and inhibiting patterns of cortical activity in response to reward-associated feedback signals from mesencephalic dopaminergic inputs (Braunlich & Seger, 2013; Mink, 1996).

The basal ganglia form circuits with the cortex and with subcortical areas — notably the thalamus and cerebellum. These regulate cortical and subcortical excitability through multiple pathways with different numbers and degrees of relays (Braunlich & Seger, 2013; Nambu et al., 2000). There are three primary pathways through which the basal ganglia interacts with the cerebral cortex: direct, indirect, and hyperdirect (Calabresi, et al., 2014; Jahanshahi, Obeso, & Rothwell, 2015). In addition to these pathways, there also exists a network of cortico-striatal loops. These circuits are differentiated based on what cortical areas and thalamic nuclei are interconnected. A set of cortico-striatal loops link areas related to motor control, visual and sensory processing, executive functions, and motivational regulation (Braunlich & Seger, 2013).

Investigations on non-human primates have demonstrated that the basal ganglia are functionally linked to the cerebellum via disynaptic projections from cerebellum to the striatum, enabling the cerebellar output to influence basal ganglia function (Hoshi, et al., 2005), as well as a comparable pathway from the basal ganglia, which influences cerebellar function (Bostan, et al., 2010). Thus, there exists a two-way communication between the basal ganglia and cerebellum, as well as the existence of an integrated functional network

(Bostan et al., 2010; Hoshi et al., 2005).[4] Though the subthalamic nucleus (STN) may still represent the driving force of the basal ganglia (see Kitai & Kita, 1987), Bostan and colleagues (2010) suggest that this "driving force" extends to the cerebellum as well, enabling signals from the STN to influence cerebellar processing. The authors go on to suggest that this reciprocal connection between the basal ganglia and cerebellum forms an integrated functional network, wherein the basal ganglia implement reinforcement learning algorithms and the cerebellum implements supervised learning algorithms (see Doya, 2000).

At first glance — and most relevant for the purposes of this thesis — the basal ganglia seem to have the right pattern of inputs and outputs to integrate temporal patterns and influence cortical networks appropriately. It is a highly interconnected region, with connections to the parietal and frontal areas implicated in temporal orienting. It would therefore appear to provide a good source of temporal information to influence perceptual and motor processing during temporal orienting. However, as we reviewed in section 1.3.2, the basal ganglia are not really conspicuous in brain imaging studies of temporal orienting with cues. This absence might be partly explained by the difficultly in imaging subcortical areas reliably. It may also be the case that the imaging methodology may not be the most appropriate or sensitive way to reveal participation of a brain area in providing temporal inputs to attention-orienting circuits. For example, it could be the case that temporal orienting utilizes signals from the basal ganglia without necessarily modulating its level of activation (see Nobre & O'Reilly, 2004).

Knowing something about the functional organization of the basal ganglia, and most importantly their connections to neuroanatomical regions critical to supposed timing systems, we can now better consider their putative role in supporting temporal orienting.

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[4] The interactions between these regions, and the above-examined role in internal timing, offer further evidence for a distributed timing system.

1.4 Scope and structure of this thesis

As captured in the preceding sections, the brain is continuously generating predictions about expected events that are relevant to behaviour, including about their timing, in order to enhance perception and prepare our actions. Existing research has started to identify the network of brain regions that participate in the control of temporal orienting, suggesting a different frontal-parietal system to that involved in spatial orienting may be involved. One intriguing question concerns the putative role of subcortical areas, such as the basal ganglia. The basal ganglia are intimately linked with frontal-parietal systems linked to spatial cognition and action control, such as those activated in spatial and temporal orienting tasks respectively. They have also been proposed to play an important role in processing temporal information in explicit timing tasks. Despite these suggestive links to temporal orienting, however, the basal ganglia has not been commonly observed in imaging studies of temporal orienting. One of the main aims of this thesis is to use an alternative, neuropsychological approach to explore whether the basal ganglia are essential for temporal orienting. A comparative approach is adopted, which involves examining temporal orienting in a non-clinical healthy ageing population, and comparing performance to that of younger cohorts in order to gain a better understanding of baseline levels of temporal orienting in older individuals (Chapters 2 and 3). Two neuropsychological investigations follow, assessing performance in separate clinical populations with known basal ganglia dysfunction (Chapter 4 and 5). The motivation and rationale for studying these groups are briefly summarized in this section, as part of providing an overview of this thesis.

1.4.1 Temporal orienting in healthy ageing: Chapters 2 and 3

In order to establish any consequence of brain damage to performance in temporal orienting tasks in clinical populations, it is imperative to begin with an understanding of baseline performance and variability in healthy groups with similar demographics. The first two experimental chapters in this thesis therefore determine the extent to which temporal orienting is preserved in healthy ageing populations. This forms the basis of comparison to patient populations in later chapters.

To date, several studies have investigated the effects of cueing spatial attention in ageing populations indicating that cue-based facilitation of an attentional shift to a location is relatively preserved in ageing (Nissen & Corkin, 1985; Hartley, 1993; Gottlob & Madden, 1998). In experiments that have used spatial orienting cues (regardless of whether the cueing is endogenous or exogenous), older adults have been shown to exhibit similar spatial cueing effects compared to young adults (e.g. Folk & Hoyer, 1992; Gottlob & Madden, 1998; Hanh & Kramer, 1995; Lincourt, Folk & Hoyer, 1997; Tales et al., 2002). Nonetheless, older adults typically experience a general slowing of information processing (Salthouse, 1996, 2000; Glisky, 2007), and some difficulties associated with shifting attention have been noted (Madden, Connelly & Pierce, 1994). These may reflect inhibitory failures (Kramer & Kray, 2006), or declines in early sensory (bottom-up) processes (Yamaguchi, Tsuchiya, & Kobayashi, 1995; Curran, Hills, Patterson & Strauss, 2001; Lorenzo-López et al., 2002), or a reliance on the recruitment of frontal (top-down) resources to compensate for declines (Talsma, Kok, & Ridderinkhof, 2006). However, on the whole, research in spatial selective attention suggests that this ability is largely preserved in ageing (except for possible attentional decline in the left visual field) after accounting for age-based general slowing and declines in bottom-up processing (see Zanto & Gazzaley, 2014).

In contrast to the preservation of spatial orienting in ageing, the only previous study to directly examine endogenous temporal orienting in healthy ageing population found this ability to be significantly compromised (Zanto et al., 2011). This more recent finding comes on the back of much research that has found timing-related impairments in healthy normal ageing. Such age-related differences in timing include: greater variability when judging a timed interval (Block, Zakay, & Hancock, 1998; Wild-Wall, Willemssen, & Falkenstein, 2009); reduced accuracy in producing intervals (Bherer, Desjardins, & Fortin, 2007; Gooch, Stern, & Rakitin, 2009); deficits in the temporal ordering of sequential stimuli (Ulbrich, Churan, Fink, & Wittmann, 2009); declines in interval timing-related abilities (Lustig, 2003; Balci, Meck, Moore, & Brunner, 2009); slower tapping rates when producing syncopated movements (Stegemöller, Simuni, & MacKinnon, 2009); and decreased accuracy in time estimation (see Craik & Hay, 1999; Ferrandez & Pouthas, 2001; Lustig & Meck, 2001; McCormack, Brown, Maylor, Richardson, & Darby, 2002; for reviews, see Block, Zakay, & Hancock, 1998; Lustig, 2003).

In addition, Zanto et al.'s (2011) study has been interpreted as representing a specific instance of a more general ageing deficit in using predictive and anticipatory attention-related functions to aid in the encoding of relevant objects or object features to guide performance (Bollinger, Rubens, Masangkay, Kalkstein, & Gazzaley, 2011; Bollinger, Rubens, Zanto, & Gazzaley, 2010; Zanto & Gazzaley, 2014). Such an array of deficits are likely to have strong consequences for adapting cognition, leading (or contributing) to the aforementioned deficits noted in temporal orienting.

Given the paucity of data on temporal orienting in ageing, it remains largely unknown whether (and in what circumstances) this ability can still be preserved as we age. While it seems as if deficits in temporal expectations can arise in healthy ageing, the source of this impairment is unclear, since older adults can also be more affected by fatigue, boredom, increases in task difficulty, and loss of attention (or divided attention) (Lustig & Meck, 2001; Lustig, 2003). In addition, attentional deficits may also contribute to the impairment of performance on timing tasks (see McDowd & Shaw, 2000).[5] Moreover, in many timing related studies, results can differ significantly based on the methodology or task design used (Block et al., 1998).

Though ageing seems to bring general cognitive decline (Zanto & Gazzaley, 2014), it has been established that cognition, brain function, and structures do not decline uniformly as we age (see Kramer & Kray, 2006). Rather, deficits may arise in perceptual, cognitive, and motor processes independently and across separate domains. In the following, special attention will be given to designing a task appropriate for measuring temporal orienting in ageing.

To investigate the breakdown of specific functions as we age — such as being able to isolate deficits associated with temporal orienting — and to transfer the task to measure effects in clinical groups, it is imperative for the experimental tasks to be made as straightforward as possible. For instance, we now know that in as we age our ability to rapidly process perceptual information (Salthouse, 1985; 1996), and inhibit task irrelevant information (Hasher & Zacks, 1988) becomes increasingly difficult. In the experiments of Chapter 2 and 3, I explore the results of experiments conducted on older adults across a range of temporal orienting tasks. These tasks vary in complexity and demands. By

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[5] The reasons for such differences might be accounted for by changes in brain structure and function in ageing (Raz, 2000; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010.), and it is often considered (most likely not unrelated to ageing) that dopamine neurotransmission and functions related to frontal-striatal circuits affect timing (Ivry & Spencer, 2004; Malapani et al., 1998; Meck & Benson, 2002). It may also be the case that age-related declines in anticipation may result from PFC failing to prime sensory regions specific to the expected stimulus category (Bollinger, et a., 2011).

manipulating task variables, I have explored the conditions under which temporal orienting can be preserved.

1.4.2 A neuropsychological approach: Chapters 4 and 5

Having developed temporal orienting tasks that are able to elicit temporal orienting effects in a healthy older population, these tasks can be used in clinical groups that are known to suffer from degeneration of the basal ganglia. While brain imaging technologies have become a popular method for measuring brain activation across an array of timing tasks, these techniques — taken on their own — are unable to provide information about causality. Rather, imagining studies on their own only provide correlational data from which researchers are able to infer possible functionality (Rorden & Karnath, 2004; Rorden, Karnath, & Bonhila, 2007; Chatterjee, 2005; Müller & Knight, 2006). For this reason, disruption techniques need to be used to provide a stronger test of necessity. Given that the focus of this thesis is on distant subcortical locations (i.e. the basal ganglia), techniques such as transcranial magnetic stimulation (TMS), which can only provide temporary neural disruption on surface structures (Bolognini & Ro, 2010), are less than ideal. For this reason, one of the best available options is to look at neuropsychological deficits linked to neurodegeneration of the basal ganglia, such as that which occurs in Parkinson's Disease (Chapter 4) or the result of stroke (Chapter 5).

1.4.2.1 Temporal orienting in Parkinson's disease

One way of assessing basal ganglia involvement in temporal orienting is to investigate individuals with PD. This is because PD is largely considered to be a basal ganglia disorder characterized by a generalized (and progressive) degeneration of a set of dopaminergic input neurons in the pars compacta of the SNc (Bostan, Dum & Strick, 2010; Davie, 2008), and to some extent, in the ventral tegmental area (Alberico, Cassell, & Narayanan, 2015). These dopaminergic projections from the SNc to the striatum have been found to be critical to the proper functioning of the basal ganglia, and when they are degraded — as is the case with PD — it can cause a breakdown in motor and perceptual timing abilities, leading to timing-related deficits (Jones & Jahanshahi, 2014). In addition to the destruction of dopaminergic neurons, PD's pathological signature includes the presence and accumulation of cytoplasmic protein aggregates known as Lewy bodies (see Manohar, Bonnelle, & Husain, 2013). Given that these systems have been implicated in various aspects of timing, Chapter 4 of this thesis goes on to explore the effects of PD on temporal orienting in order to provide insight into whether dysfunction in the basal ganglia may lead to deficits in temporal orienting.

Despite the lack of evidence implicating the basal ganglia in temporal orienting directly, the basal ganglia have been shown to be involved in explicit timing tasks (Coull et al., 2004), but seem to be less critical for implicit timing. In a study conducted by Coull and colleagues (2013), fMRI was used to measure the neural correlates of temporal reproduction and temporal orienting within the same experimental paradigm. They observed right-hemispheric activation for overtly timing a currently elapsing duration and a left-hemispheric specificity for predicting future stimulus onset. More specifically, they found that a right-lateralised frontal-striatal network was engaged when timing was measured explicitly; however, when timing was measured implicitly, the left inferior parietal cortex, left premotor cortex, and cerebellum were more likely to be activated. Further evidence from a study on participants with PD conducted by de Hemptinne and colleagues (2013) support a possible dissociation between explicit and implicit timing in the recruitment of the basal ganglia. The researchers investigated the role of the basal ganglia in implicit timing by examining the latency of anticipatory eye movements in PD patients and age-matched controls. Although PD patients made fewer anticipatory eye movements, the timing of the anticipation of target motion reversal was akin to the performance of control participants. In other words, the implicit timing of salient events seems to be largely unaffected by PD. Although the researchers did not examine explicit timing, these findings provide some evidence in support of the hypothesis that implicit and explicit timing may be differently affected by basal ganglia dysfunction.

Using PD as a model of basal ganglia dysfunction is not uncommon. As Cope and colleagues (2014) review, to date the majority of neuropsychological investigations into the basal ganglia's role in time perception have used participants with PD (for reviews, see Allman & Meck, 2012; Jones & Jahanshahi, 2014). While there is no evidence that damage to the basal ganglia leads to a deficit in temporal orienting *per se*, patients with PD have shown deficits in temporal tasks, possibly as a result of dopamine disregulation (Rammsayer & Classen, 1997). Moreover, research shows that there are timing deficits following damage to the striatum in humans (Malapani et al., 1998) and animal models have implicated the striatum and dopamine in timing (Meck, 1996; 2005). Coull (2010) has argued that a distributed frontal-striatal network is involved in the perception of time intervals.

1.4.2.2 Temporal orienting in stroke survivors

While examining temporal orienting in PD sufferers is a useful starting point to gain critical insight into the basal ganglia’s involvement in temporal orienting, a comparison between participants with PD and healthy controls cannot provide conclusive evidence for its support of temporal orienting. The principal limitation is that the basal ganglia are not the only site in the brain affected by the disease. Although there is generalised neuronal degeneration in the basal ganglia common in PD, the dysfunction is not only a degeneration of the striatum, but rather an uneven loss of its dopaminergic input (Kish, Shannak, & Hornykiewicz, 1988). Moreover, the excessive inhibitory outflow from the basal ganglia in PD means that cortical structures to which they project are not adequately activated (Jones & Jahanshahi, 2014). Interpretation of the findings in Chapter 4 are therefore limited *ab initio*, since poor performance on timing tasks could be underpinned by dysfunction across connecting cortical sites, or other areas in the degenerated network, just as it could be limited by dysfunction within the basal ganglia. Furthermore, there could be residual functions masking deficits. Investigating temporal orienting on participants with focal lesions to the basal ganglia in Chapter 5 therefore offers convergent findings.

While we do not yet have a clear idea about how temporal orienting is substantiated via neural systems and mechanisms in the brain, further experiments with individuals who have known damage to the basal ganglia may be able to provide additional insight into how temporal orienting is supported. While it is hoped that this Chapter offers findings to compliment Chapter 4, it too is not without its limitations. For instance, problems associated with diaschisis and reorganization with chronic lesions present one potential complication (Carrera & Tonini, 2014; Gillebert & Mantini, 2013). However, similar effects observed in both clinical populations would provide strong support for the basal ganglia's involvement in temporal orienting both for motor and perceptual performance.

1.5 Summary of thesis statement

Broadly speaking, this thesis has two closely related aims: firstly, I am interested in understanding more fully the effects of ageing on temporal orienting. This involves looking at how attention can be directed within time, to specific moments, in order to optimize behavioural performance. Traditionally researchers have been interested in spatial and temporal orienting of attention in younger populations, but, as we've seen — and will review further in Chapter 2 and 3 — researchers have also started to investigate how temporal orienting can change as we age, from studies in children (Johnson, Burrowes, & Coull, 2015) to studies in older populations (Zanto et al., 2011) Though a number of temporal expectation studies have found deficits in ageing, few have focused on what gets preserved in normal ageing. Here, I am interested in learning more about the boundary conditions for temporal expectations. To that end, this thesis seeks to discover the conditions under which temporal expectations can be preserved. If it is the case that there are age-related differences, one might also speculate on the sources of the decline in performance. Deficits in performance ability might be the result of attentional changes or the result of other changes, such as those related to alterations in sensory or perceptual abilities, memory, or processing speed (see Zanto & Gazzaley, 2014).

Relatedly, in addition to studying a healthy ageing population, and with a desire to understand more about the brain-structures, networks and mechanisms implicated in temporal orienting, Chapters 4 and 5 complement this investigation with a neuropsychological investigation of participants with Parkinson's disease and stroke survivors with focal lesions that involve the basal ganglia. Specifically, by looking for converging results in these two clinical populations with dysfunction in the basal ganglia, the aim is to understand whether this region plays a crucial role in supporting temporal expectation by helping to tune motor responses and optimize perception. The principle aim of the latter part of this thesis is therefore to investigate the extent to which basal ganglia related circuits are critically involved in temporal orienting.

2 Spatio-temporal expectation in elderly adults

Chapter Abstract

By helping observers to anticipate where and *when* something will happen, spatially and temporally predictive cues have been shown to optimize both motor and perceptual performance. While older adults tend to be slower on spatial orientation tasks, they are still able to use information about the location of an object to improve their behavioural performance. In contrast to studies on spatial orienting, only one study has demonstrated a deficit in the ability of older adults to benefit from temporal orienting cues (Zanto et al., 2011). Given that there has been considerably less exploration of the effect of temporal orienting on performance in older adults, the extent of this impairment is not yet known. To investigate whether the effects of temporal orienting could be preserved in older age, the experiment in this chapter combined temporally predictive cues (80% validity) with fully informative spatial cues (100% validity). Eighteen older participants completed a challenging perceptual orientation discrimination task on backward-masked peripheral grating stimuli occurring in the left or right visual field, wherein temporal cues predicted the stimulus appearance after a short (800 ms) or long (2000 ms) interval. Participants responded with either their left or right hand to indicate the orientation of the target item (i.e. a horizontal or vertical Gabor grating). Based on previous investigations on younger adults that have reported attentional gains when spatial and temporal of cues are used in combination (Doherty, et al., 2005; Rohenkohl & Nobre, 2011; Rohenkohl, et al., 2014), it was hypothesized that temporal information could be used to improve behavioural performance in older adults when expectations were combined. The results of the experiment show for the first time that older adults are able to use temporal information to optimize behavioural performance in a perceptually demanding task. These findings provide the first evidence for temporal expectation being preserved in ageing; however, further experimentation will be needed to determine the reliability and extent of these findings.

2.1 Introduction

In Cicero's essay *On Old Age* (106 B.C. – 43 B.C.), Cato the Elder explains to two younger men that successful ageing depends upon using one's cognitive resources adaptively, not in struggling to regain the strength of youth:

> Nor, again, do I now miss the bodily strength of a young man...any more than as a young man I missed the strength of a bull or an elephant. You should use what you have, and whatever you may chance to be doing, do it with all your might (Section, 9).

Though Cato was speaking principally of the waning physical strength associated with ageing — which thankfully, he says, can be improved by exercise and temperance — he goes on to discuss the changes that happen to our cognitive faculties as well: unlike the body, which he says may become 'gross' with excessive exercise, our intellect may become 'nimbler' with time, armed against some of the pitfalls associated with ageing. On one interpretation, Cicero seems to be suggesting — with the proviso that one must put some effort in — that the preservation of certain cognitive abilities in old age is possible. Further, as various cognitive faculties decline naturally, other faculties can take over to compensate for their loss. What cognitive capacities are preserved as we age, what changes take place in the brain, and what (if any) compensatory mechanisms are involved are among the more pressing (and largely unsolved) mysteries in the cognitive and neuropsychological literature on ageing. Fortunately, however, the effect of ageing on cognition and the role compensatory mechanisms play in preserving specific cognitive processes in old age — such as the many aspects of cognition that are associated with attention — are beginning to be investigated in earnest.

Among the many aspects of attention in ageing that are being explored is the ability to orient our attention to specific points in time. The investigation into this ability is largely inspired by the recognition that the preservation of our ability to successfully orient ourselves within our environment is fundamental to behaviour. By coming to understand the scope of attentional decline associated with healthy ageing, and learning more about what can be preserved, we will be better positioned to (for instance) design ageing-friendly environments and/or cognitive training tools to stave off the negative effects of ageing — or as Cicero might have it, assist the intellect in becoming 'nimbler'. In the following, I will briefly bring together some of the relevant ageing literature on the orienting of attention and motivate the experimental design with which I chose to investigate temporal orienting in older adults.

Selective attention — the aspect of attention associated with goal-directed behaviour towards relevant information — is essential for supporting cognition; however, as we age, selective attention (broadly speaking) has largely been found to decline (see Deiber, Ibañez, Missonnier, Rodriguez, & Giannakopoulos, 2013). In a review by Zanto and Gazzaley (2014), it was found that across studies on selective attention in healthy older adults, deficits exist in a variety of domains, including feature selection, object-based attention, and imagery abilities. However, the authors concluded that spatial selective attention, i.e. the ability to orient attention in space and ignore distracting information, seems to be largely preserved. In line with earlier research on younger adults (see Chapter 1, section 1.2.1) — which has consistently shown that by manipulating spatial attention to validly cued locations, behavioural performance (such as response times and perceptual performance) can be enhanced relative to invalid, neutral or uncued locations (Posner, 1980; Posner, Walker, Friedrich, & Rafal, 1984; Yantis & Jonides, 1990) — studies on older adults have reported preservation of cue-based attentional shifting (see Nissen & Corkin, 1985; Hartley, Kieley, & Slabach, 1990; Gottlob & Madden, 1998). Further, these findings have been found to be independent of whether the cue is presented peripherally (exogenous) or centrally (endogenous) (Tales, et al., 2002).[6]

In contrast to spatial orienting, studies on older adults so far demonstrate an impaired use of temporal information to guide attention flexibly and optimize behavioural performance (Zanto & Gazzaley, 2014). As introduced in Chapter 1, temporal cueing is a simple and robust way to manipulate temporal expectation to achieve reliable performance benefits in young adults (see Nobre & Heideman, 2015; Rohenkohl & Nobre, 2014). However, in the only study that was specifically designed to manipulate temporal expectation using centrally presented symbolic cues, Zanto and colleagues (2011) found that older adults experienced an expectation deficit across three temporal tasks that varied in complexity (e.g. simple detection, go/no-go, and discrimination tasks). This was consistent with earlier findings by Zanto and colleagues (2010) wherein temporal cues were used to guide performance in a delayed working memory task and it was found that older adults did not use temporal information to enhance performance. Taken together these results seem to suggest an age-related decline in temporal orienting processes amongst older adults, and have led Zanto and Gazzaley (2014) to argue that temporal expectation deficits in ageing are part of more general expectation deficit.

While studying temporal expectation in isolation without manipulating spatial location can provide insights into temporal-based (anticipatory) attentional processes, it is important to note that in our everyday interaction with the environment around us, temporal expectations regularly combine both the information about *where* and *when* an event will

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[6] The experimental paradigms that are often used to manipulate spatial selective attention tend to employ either a central (endogenous) or peripheral (exogenous) informative cue, which directs the observer's attention to a task-relevant location on a computer screen. While peripheral cues are thought to evoke more reflexive responses, central cues evoke both reflexive and volitional orienting (Ristic & Kingstone, 2006; Olk, Cameron & Kingstone, 2008).

occur. In addition to studies that have sought to examine the effects of temporal and spatial orienting independently, research has also been conducted to examine the combined, or 'synergistic' effect of spatial and temporal orienting (Doherty et al., 2005; Nobre, 2010; Rohenkohl et al., 2014; Nobre & Rohenkohl, 2014). The synergistic effect was first shown in an investigation by Doherty and colleagues (2005), who found that spatial and temporal expectations, when coupled, can act to modulate neural activity and further boost visual perceptual functions. The researchers manipulated the spatial trajectory of a ball jumping across the screen alongside either a regular (i.e. linear) or random rhythm. The ball vanished behind an occluding band, and when it emerged, participants had to make a discrimination judgment about whether the ball contained a small black dot at its center. Effects of temporal and spatial expectations derived from the movement of the ball on response times were additive — with faster responses occurring when participants combined spatial and temporal expectations, compared to when spatial and temporal expectations were cued independently. The electroencephalogram (EEG) recordings furthermore revealed a strong synergistic interaction between temporal and spatial expectations on sensory processing. While temporal expectation alone did not influence the earliest visual P1 potential, it strongly and significantly enhanced the gain modulation of this potential by spatial expectation.

Since Doherty et al.'s (2005) task was sub-optimal for revealing behavioural evidence of a synergistic enhancement in accuracy scores, Rohenkohl et al. (2014) extended these findings by creating a more perceptually demanding discrimination task in which to probe sensory consequences of manipulating temporal and spatial cues. Relying on symbolic temporal cues instead of having participants derive temporal expectations from the inherent dynamics of an object in motion, they found that temporal and spatial expectations could work together to enhance perceptual sensitivity on trials in which both cues were valid. In isolation, temporal cues did not confer benefits to perceptual sensitivity when the location of the target was uncertain.

In an attempt to revisit the question of whether older individuals are able to benefit from temporal expectations, and to test how general the deficits may be in ageing, this chapter examines temporal orienting ability using a similar task to the one used by Rohenkohl and colleagues (2014). Temporal cues were combined with spatial cues in a perceptually demanding visual discrimination task. In contrast to Zanto et al.'s (2011) study, where very high accuracy was achieved for older adults (~97%) — thus prohibiting an investigation into the perceptual gains associated with temporal expectation — perceptual demands were increased to examine whether perceptual benefits could be observed in older adults. It is possible that increased perceptual demands are needed in order to expose the effects of temporal expectation on sensory processes in ageing. Indeed, perceptual benefits as a function of temporal expectation have been found to depend on the parameters and demands of the task, and different types of tasks enable an examination into different effects (Correa et al., 2005).

In the current study, foveal cues were used to manipulate temporal expectation in a group of healthy older adults. The cues were in the shape of an arrow, and were used to indicate the upcoming location of a peripheral visual grating (i.e. a Gabor patch) requiring orientation discrimination. The contrast level of the visual targets was adjusted individually to ensure participants were challenged but could perform above chance level (~75%). The colour of the cue indicated whether the target would likely appear after a short (800 ms) or long (2000 ms) foreperiod. At the time it was conducted, this study was the first investigation of temporal orienting in ageing using a perceptually demanding task.

2.2 Methods

2.2.1 Participants

All experimental methods received ethical approval from the Central University Research Ethics Committee of the University of Oxford and the Medical Sciences Inter-divisional Research Ethics Committee (IDREC) (Reference number: MSD-IDREC-C1-2013-062). Twenty-one individuals (M_{age} = 66.9, 11 F) were invited to take part in the study following a telephone screening procedure, and all participants provided informed consent. The screening procedure was aimed at excluding: volunteers with metal implants; volunteers taking psychotropic, hypertensive or vasoactive medication; and volunteers with a self-reported neurological or psychiatric history. All participants self-reported to be right-handed, with the exception of one participant, who was left-handed; and all had normal or corrected-to normal vision.

Volunteers were excluded from the analyses if they had structural brain abnormalities identified through structural magnetic-resonance imaging (MRI) or a low score (< 26) on the Montreal Cognitive Assessment (MOCA), indicative of a mild cognitive impairment (Nasreddine et al., 2005) (see below for more details). As a result, data from 18 healthy older adults (M_{age} = 66.9, 11 females; 17 right handed) were included in the final analyses. All participants were compensated at a rate of £10 an hour for their participation, and their travel expenses were also reimbursed.

2.2.2 Structural Brain Scans

As part of a joint investigation with the Cognitive Health and Ageing group, a structural MRI scan was acquired for each participant using a Siemens 3-Tesla scanner

(University of Oxford Centre for Clinical Magnetic Resonance Research (OCMR), John Radcliffe Hospital). These scans were visually inspected to determine whether there were any structural abnormalities in our sample. As a result of these scans, one participant was excluded because of structural abnormalities in the MRI.

2.2.3 Clinical & Neuropsychological Evaluation

Online questionnaires were used to gain demographic information and insight into the participants' medical history prior to their participation in the study. Demographic information was collected on the following: major illnesses, current medication, history of neurological/psychiatric/vascular disorder, 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, as well as data on eyesight and hearing ability. Since much of this information was collected to inform other studies on cognitive health and ageing within our lab, no participant was prevented from participating in our study based on their responses given to the above information.

Clinical-assessment questionnaires were used to collect information on the participants' psychological health and physical wellbeing. The clinical information was collected using a battery of standardised clinical assessment tools to examine the severity of depression (Beck Depression Inventory (BDI-II); Beck, Steer, & Brown, 1996), trait and state anxiety (State-Trait Anxiety Inventory (STAI); Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), personality traits (Eysenck Personality Questionnaire (EPQ); Eysenck & Eysenck, 1975), individual differences in generalized optimism versus pessimism (Life Orientation Test-Revised (LOT-R); Scheier, Carver, & Bridges, 1994), problems with sleeping (Jenkins Scale for the Estimation of Sleep Problems; Jenkins, Stanton, Niemcryk & Rose, 1988), impulsiveness (Barratt Impulsivity Scale (BIS-11); Patton & Stanford, 1995), and generalized health status across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (EuroQol-5 Dimensions-5 Levels (EQ-5D-5L); Brooks, & Group, 1996) (Table 2.1). All clinical-assessment information was collected through a web-based platform for administering surveys (Qualtrics, Provo, UT).

To ensure the cognitive health of all participants, their performance was evaluated across a battery of neuropsychological tests. The neuropsychological evaluation consisted of tests designed to assess general cognitive function (Montreal cognitive assessment (MoCA, version 7.1; Nasreddine et al., 2005)), attention/task switching (Trail making test (TMT); Reitan, 1958; Reitan & Wolfson, 1985; Tombaugh, 2004), executive function (Rey-Osterrieth complex Figure test (RCF); Fastenau, Denburg, & Hufford, 1999; Osterrieth, 1944; Rey, 1941), semantic memory (Category fluency — names of animals 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, Freed, Williams, & Henderson, 1992), verbal working memory (Digit span; Wechsler, 2008), premorbid intelligence quotient (Test of premorbid functioning (TOPF); Wechsler, 2009), and motor function (Purdue Pegboard; Desrosiers, Hebert, Bravo, & Dutil, 1995). The test scores are summarized in Table 2.2. After verifying the homogeneity of variance within the sample by ensuring that all participant scores were within 2 SDs of the average score across participants, all participants in the final analyses were confirmed to be within two SDs of normative values.

Table 2.1

Clinical assessment data (n = 18).

Variables	Mean	SEM	Range	Normal Range	Definition
BDI	4.5	1.1	0-14	0-63	>13 = minimal depression
STAI	34.2	1.8	23-49	20-80	lower score = lower anxiety
Jenkins	6.4	1.1	0-16	0-20	higher score = more sleep problems
EQ-5D Health State	85.6	2.5	52-99	0-100	Sliding scale of subjective health state
LOT-R	20.9	1.2	13-32	0-24	higher score = more optimistic
BIS-II	58.8	1.7	45-76	30-120	higher score = more impulsive
GMSI - general factor	55.2	4.9	23-99	18-126	higher score = more musical
GMSI - formal musical training	18.3	2.5	7-38	7-49	higher score = more musical

Note: All participant clinical assessment values were found to be within 2 SD's of the normal range values across all tests.

Table 2.2

Mean scores from the neuropsychological evaluation in participants (n = 18).

	Mean	Range	SE	> 2SD*
Age	66.9	61-76	1.1	
Education	15.3	11.5-21	0.7	
MOCA	28.2	26-30	0.4	
TMT: A (s)	25	15-39	1.7	
TMT: B (s)	53.6	29-132	6.1	
ROCFT				
Copy (out of a possible 36)	32.8	25.5-35	0.6	
Immediate (out of a possible 36)	18.3	7.5-28.5	1.5	
Delay (out of a possible 36)	17.9	6-26	1.3	
Category Fluency	23.5	17-31	0.9	
HVLT-R				
Trial 1	5.9	5-9	0.3	
Trial 2	9.3	7-12	0.3	
Trial 3	10.8	7-12	0.3	
Learning	4.9	2-7	0.4	
Sum of 1-3	26.1	22-31	0.6	
Delayed Recall	10.3	8-12	0.3	
Percent Retained (%)	94.2	75-110	2.0	
True Positives	1.0	11-12	0.3	
False Positives	10.6	0-5	0.3	1.0
Discrimination Index	94.2	7-12	0.3	
BNT	14.4	13-15	0.2	
Digit Span (Scaled Score)	12.3	10-15	0.3	
Purdue Pegboard Right	13.6	10-15	0.3	
Purdue Pegboard Left	12.9	10-16	0.4	
Purdue Pegboard Both	10.5	9-12	0.2	
Purdue Pegboard Sum	37	30-41	0.7	
Purdue Pegboard Assembly	31.9	22-49	1.7	
TOPF - FSIQ	116.1	96.7-128.6	1.9	

Note. *This column contains 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 Fig. Test; HVLT-R, Hopkins Verbal Learning Test-

2.2.4 Apparatus

Stimuli were created on MATLAB v. 7.10 (MathWorks) and presented using the Psychotoolbox v. 3.0 package for MATLAB (Kleiner, Brainard, & Pelli, 2007). The behavioural data were collected while magnetoencephaloghy (MEG) signals were being recorded in a sound-attenuated and electrically and magnetically shielded room at the Oxford Centre for Human Brain Activity (n.b. analysis of the MEG data is beyond the scope of the current thesis, and part of a parallel investigation.) Stimulus images were back-projected (Panasonic PT D7700E) onto a screen at a viewing distance of 120 cm with spatial resolution of 1280 by 1024 pixels and a vertical refresh rate of 60 Hz. Responses were collected using a response box (DirectIN High Speed Button; Empirisoft Corp., New York, NY). Binocular eye positions were recorded with a video-based eye-tracking device with 500-Hz resolution (EyeLink 1000, SR Research, Ontario, Canada).

2.2.5 Stimuli and experimental design

In order to investigate temporal expectation, we adapted the spatiotemporal orienting task used by Rohenkohl et al. (2014). A schematic of the display sequence is shown in Figure 2.1. Participants were asked to discriminate the orientation of peripheral target stimuli, which were preceded by foveally presented cues indicating where and when a target item would appear. Trials commenced following the presentation of a fixation dot (diameter: .08° of visual angle), which was presented alongside two luminance pedestals that remained on the screen for the duration of each trial, and indicated possible target positions. The luminance pedestals were both presented at 10% contrast, and set 3.2° below and 4.6° to the left and right of the central fixation dot. They were kept on the screen throughout the experiment in order to reduce spatial uncertainty (Gould, Wolfgang, & Smith, 2007; Smith, 2000; Smith, Ratcliff, & Wolfgang, 2004; Smith & Wolfgang, 2004; Smith, Wolfgang, & Sinclair, 2004).

Following the presentation of the fixation dot, a cue was presented foveally (2° visual angle) at a random interval between 750 and 1200 ms. Cues were presented for 200 ms and consisted of equally luminant pink or blue coloured arrows (line width: 0.1° visual angle). The direction of the arrow cues indicated whether the target stimuli would appear on the right or left of the cue. Temporal information was provided by the colour of the cue (Stimulus onset asynchrony [SOA]: 800 ms if short foreperiod, and 2000 ms if long foreperiod), with the association of cue colour and foreperiod counterbalanced across participants. There were an equal number of left and right cues, and short and long foreperiod cues, presented during each experiment. The spatial information carried by the cues was 100% valid, whereas the temporal information was 80% valid. High validity of the temporal cues was chosen to encourage participants to make use of the predictive information provided by the cue. Cues were randomized on a trial-by-trial basis.

After the delay period, targets appeared overlaid over the luminance pedestals for 50 ms (1.91° visual angle). Targets consisted of either a horizontally or vertically oriented Gabor patch with a spatial frequency of two cycles, or degrees, of visual angle. The target item was immediately followed by a backwards-mask that was presented for 283 ms (117 ms target to mask SOA). The backward-mask was created by applying a Gaussian-vignette to the convolution of 100% contrast square-wave gratings at the two possible target orientations. The backward masking procedure ensured that behavioral performance in the task was limited by the participants' attentional state at the time the target appeared, and also served to limit the possibility of interference that may have occurred as a result of re-orienting to invalid stimuli (Rohenkohl et al., 2014). The diameter of the target and mask stimuli was 1.91° of visual angle.

All stimuli were presented against a uniform mid-gray background (RGB values). Participants responded to each target with their left or right index finger to indicate the target orientation. Cue-colour assignment to each cue-target and response mapping were counterbalanced across participants. Prior to undergoing the experimental test, target contrast was adjusted for each participant using a staircase procedure (see section 2.2.6).

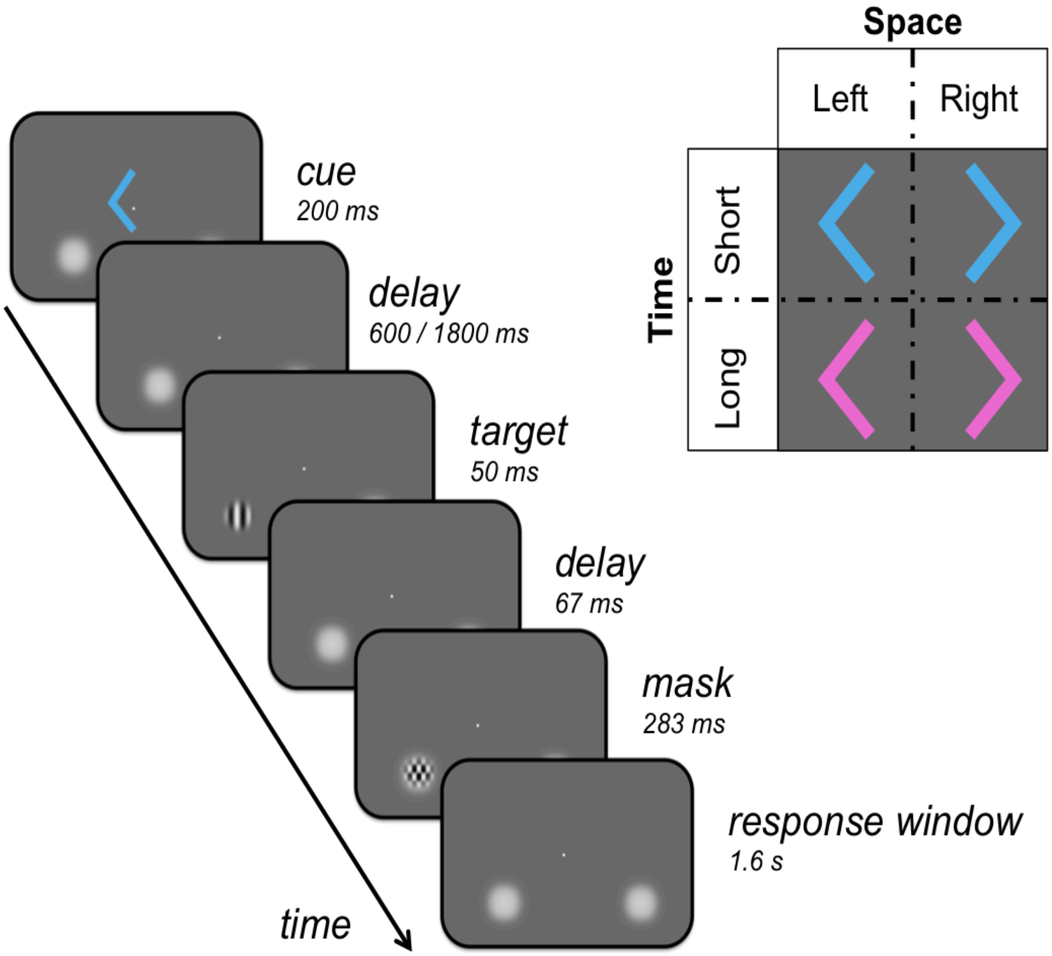

Figure 2.1 Experimental task structure. Both the location of the target and the foreperiod were manipulated using a trial-by trial cueing procedure. Foveally presented cues indicated where and when targets were likely to occur. Cue validity for spatial expectation was 100% and temporal expectation was fixed at 80%. The circular target stimulus was comprised of either vertical or horizontal black and white Gabor gratings followed by a checkerboard figure as the backward mask. Location of targets and foreperiods were randomized over trials. Participants responded with either their left or right index finger to indicate the orientation of the stripes. The colour of the cues was counterbalanced across participants.

2.2.6 Procedure

The study was run in four separate sessions that took place across separate days: a training visit, an experimental testing session, a session to collect MRI data, and a session to conduct the neuropsychological evaluation. The second experimental testing session took place in a MEG scanner as part of a larger investigation. Eye movement data were not analysed in this experiment.

2.2.6.1 Session one: training visit

The behavioural tasks were conducted in a quiet, dimly lit room at the Oxford Centre for Human Brain Activity (OHBA). The training visit first involved participant's undergoing an introduction to the experimental task. Participants were informed that the experiment would be a peripheral vision task, and they were encouraged to keep their eyes fixated on the centre of the screen. They were notified that the eye-tracker would be used to monitor their gaze. Participants were reminded throughout of the importance of maintaining visual fixation on the centre of the screen, and were encouraged to use the cues to anticipate when and where the targets would appear.

As in Rohenkohl et al. (2014), each participant underwent a calibration session that involved using an adaptive psychophysical staircase procedure to estimate the threshold contrast (~75% accuracy) for perceiving the Gabor gratings (Kaernbach, 1991). The calibration was conducted by using valid spatial and valid temporal cues only on 120 trials. As participants took part in the task, the threshold contrast of the Gabor patch was increased or decreased in line with their performance (i.e. the target contrast would increase if they made an accurate response to the stimuli across two trials, and decreased if they made two errors in a row). After the calibration was concluded, results were visually inspected to determine the contrast level yielding 75% accuracy during the session. For each participant, the Gabor contrast for the experimental

2.2.6.2 Session two: main experiment

After completing the initial training session, all participants were invited back to participate in a longer version of the experimental task during the first session at OHBA. At the same time as taking part in a behavioural experiment, MEG scans were recorded. Analysis of the MEG data is outside the scope of this thesis. The overall session, including setting up the participant (15 to 30 minutes), a practice with the task (15 minutes), and the experimental task (1 hour), lasted no longer than 2 hours for each participant. The experiment took place within a week of the first visit.

Before participating in the experimental task, participants completed a brief practice session to reacquaint them with the experimental task. The practice session contained 50 trials. The cues were the same as in the main experimental task with 100% valid spatial information and 80% valid temporal information. Participants were again reminded to maintain fixation and encouraged to use the information in the cues to anticipate the target stimulus.

Following the practice session, participants completed a total of 600 trials of the spatio-temporal orienting task. In total, targets appeared at the validly predicted interval on 480 trials (240 Short Valid, 240 Long Valid targets) and at the invalid interval on 120 trials (60 Short Invalid targets, 60 Long Invalid targets). The main experiment was subdivided into three blocks. These large blocks were further subdivided into ten smaller sub-blocks made up of 20 trials to avoid fatigue. Participants initiated each sub-block when they felt ready. In each short block, trials with targets at the different locations (always valid) and intervals were intermixed at random.

2.2.6.3 Session three: MRI Scan

Following the behavioural task, participants were invited back a third time to take part in a one-hour session at the Oxford Centre for Magnetic Resonance Imaging at the John Radcliffe

Hospital at Oxford. During this session, a high-resolution 3D whole-brain T1-weighted MRI scan was acquired on a 3 Tesla Trio scanner (repetition time 2400 ms, echo time 4.7 ms, flip angle 8 degrees, 1 mm isotropic resolution). This structural scan was used to detect brain lesions or significant levels of brain atrophy.

2.2.6.4 Session four: Cognitive and Neuropsychological Assessment

This final session took place at the OHBA, and lasted on average 1 hour and 30 minutes. Participants were asked to complete a number of paper and pencil neuropsychological tests detailed in section 2.2.2.

2.2.7 Data analysis

Data analysis was performed using Matlab and SPSS.

All behavioural responses were collected from the offset of the backwards-mask stimulus. Behavioural performance was analyzed using perceptual sensitivity values (*d'*), proportion of correct responses (PC), Response Times (RTs) (ms), and Inverse Efficiency Scores (IES) (ms) for each condition. All trials in which the RT was above 2000 ms or 3 SDs above or below the mean reaction time were dropped from the analyses, as they likely represented a lapse in attention. After removing all trials where the responses were above 2000 ms (*M* = 11.78, *SEM* = 4.78), the largest number of trials removed for any participant was 15 out of the remaining trials, and the average number of trials removed across participants was negligible (*M* = 6.11, *SEM* = 0.84). Participants' average performance was also checked for outliers. No participant scored more than three standard deviations (SD) beyond the mean for any condition on any of the dependent variables.

Sensitivity to stimulus orientation was calculated according the formula:

$$d' = z[PC_H] + z[PC_V]$$

where PC_H and PC_V corresponds to the proportions of correct responses to horizontal and vertical stimuli respectively, and z corresponds to the inverse normal (z-score) transformation (Rohenkohl, et al., 2014). In cases where PC_H or PC_V was equal to 0, the value was replaced with $0.5/N$, and if the value was equal to 1, it was replaced with $(N – 0.5)/N$, where N reflects the number of trials with a horizontal or vertical stimulus for that condition, thereby penalizing for conditions with fewer trials (i.e. conditions with invalid temporal cues).

Response times on each trial were adjusted according to the participant's accuracy in order to account for possible speed-accuracy trade-offs. As with previous investigations, this adjustment was conducted using a measure called inverse efficiency (Chambers, Stokes, & Mattingley, 2004; Romei, Driver, Schyns, & Thut, 2011; Townsend & Ashby, 1983). The IES is calculated by dividing the mean reaction time by the proportion of correct responses. Importantly, only correct trials were included in the reaction-time analyses.

Effects of temporal expectations were explored using two-way repeated-measures analysis-of-variance (ANOVA) with foreperiod (short, long) and temporal cue validity (valid, invalid) as within-subjects factors for each separate measure of behavioural performance. As mentioned in Chapter 1, temporal expectations arise as the result of interactions between the cue validity and the interval of the foreperiod. It is important to note that, as with many temporal orienting experiments that cue participants to only two moments in time, the manipulation of temporal prediction is asymmetrical. That is, while the early targets are presented at the expected interval 80% of the time and unexpectedly on 20% of trials, targets at the later interval are always fully predictable. This is because temporal expectations related to foreperiods are linked to the passage of time itself; as time elapses, the probability of the target occurring once the short interval has passed increases independently of cue validity. In other words, without catch trials, in the event that the target did not appear early, targets presented following the later foreperiod are always to be expected. In the temporal orienting literature, this effect has become known as that it has not yet occurred (Luce, 1986). The targets appearing after the earlier foreperiod are therefore more informative in assessing the effects of temporal orienting.

The trial-by-trial nature of the design also allowed for an investigation into the influence of the cue-target interval length of the previous trial. The effects of the previous trial on the performance of a given trial are sometimes referred to as sequential effects (Los, 2010). When it comes to sequential effects, previous studies have found that RTs are lengthened when the previous foreperiod is longer than the current foreperiod (e.g. Baumeister & Joubert, 1969; Capizzi, Correa, & Sanabria, 2013; Drazin, 1961; Los & Van Den Heuvel, 2001; Karlin, 1959; Schupp & Schlier, 1972; Steinborn, Rolke, Bratze & Ulrich, 2008; Vallesi, Shallice, & Walsh, 2007; Van der Lubbe, Los, Jaśkowski, & Verleger, 2004; Woodrow, 1914; Zahn & Rosenthal, 1966). As with the effects of temporal expectation per trial outlined above, sequential effects should occur primarily at short-interval trials (Steinborn, et al., 2008). To explore whether or not such asymmetrical effects existed in the data presented herein, the sequence of foreperiod durations and the associated behavioural performance was examined. Sequential foreperiod effects were only evaluated for sequences of valid trials in order to avoid complex interactions with validity and to circumvent problems evaluating effects given the small number of invalid trials. Performance on valid trials preceded by valid trials was analyzed using a two-way repeated measures ANOVA with current foreperiod (short, long) and previous foreperiod (short, long) as the within subjects factors.

2.3 Results

2.3.1 Effects of temporal orienting

Data were submitted to a 2 x 2 repeated-measures ANOVA with interval (short, long) and validity (valid, invalid) as within subjects factors. Analyses of the proportion of correct (PC) trials demonstrated a trend towards a main effect of foreperiod ($F(1, 17) = 3.707$, $p = .07$, $\eta^2 = .18$), with PC being higher for short foreperiods compared to long foreperiods. However, there was neither a main effect of validity or an interaction between the two factors (all other ps > .14). Figure 2.2a shows PC values for targets across the four conditions. An equivalent pattern of statistical inferences was obtained for the analysis of perceptual sensitivity values (d') for discriminating targets (Figure 2.2b). Again, there was a trend towards a main effect of foreperiod at the $p < .05$ level ($F(1, 17) = 12.31$, $p = .06$, $\eta^2 = .20$), with d' being higher for short foreperiods compared to long foreperiods, but no main effect of cue validity ($F(1, 17) = 1.16$, $p = .30$, $\eta^2 = .06$) and no interaction ($F(1, 17) = 2.20$, $p = .16$, $\eta^2 = .12$).

Analysis of RTs (Figure 2.2c) revealed a main effect of foreperiod ($F(1,17) = 6.41$, $p < .001$, $\eta^2 = .49$) with RTs being faster for short foreperiods compared to long foreperiods, and a main effect of cue validity ($F(1,17) = 11.07$, $p < .01$, $\eta^2 = .39$), with RTs being shorter on validly cued trials compared to invalidly cued trials. There was no significant interaction effect between foreperiod and cue validity ($F(1,17) = .026$, $p = .86$). An investigation of the inverse efficiency scores (IES) yielded similar results (Figure 2.2d), revealing a trend towards a main effect of foreperiod ($F(1, 17) = 4.12$, $p = .06$, $\eta^2 = .20$), with RTs being faster for short foreperiods compared to long foreperiods, and a significant main effect of cue validity ($F(1, 17) = 5.30$, $p = .03$, $\eta^2 = .24$), with RTs being short when participants were validly cued. However, there was no interaction between foreperiod and cue validity ($F(1,17) =1.46$, $p = .24$).

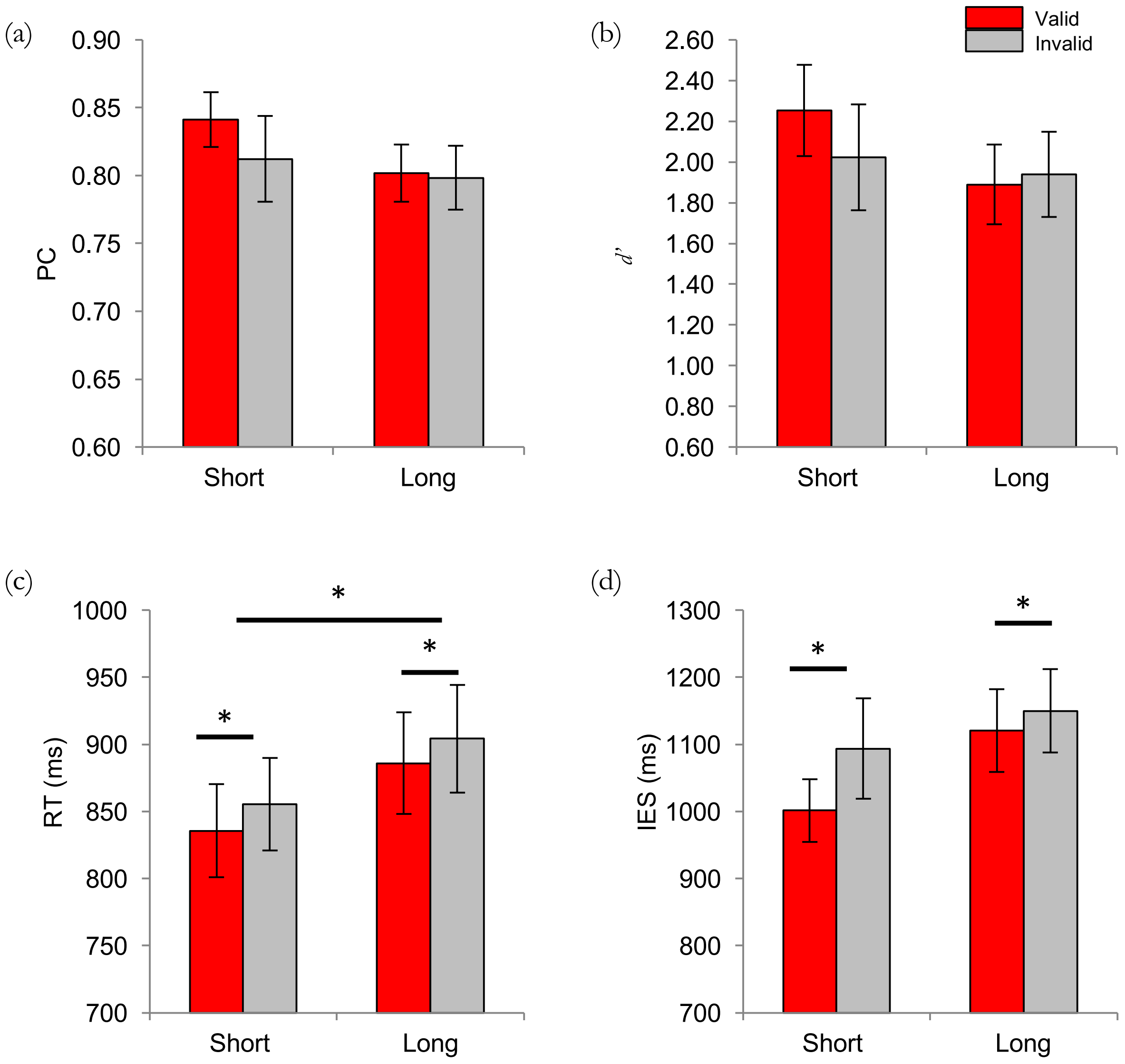

Figure 2.2 Effects of temporal orienting on (a) proportion correct, (b) d-prime, (c) reaction time (ms) and (d) inverse efficiency scores (ms). Results are averaged across left and right cues. A significant main effect of cue validity is observed in (c-d). Error bars represent standard errors of the means (SEM). Significant effects ($p < .05$) are indicated by a star.

2.3.2 Sequential effects

Sequential effects were analyzed in order to examine whether there was an effect of the previous target interval on participant responses. Analysis was limited to valid trials preceded by valid trials. Data were submitted to a repeated-measures ANOVA with previous target foreperiod (short, long) and current target foreperiod (short, long) as within subjects factors. Analyses of the proportion correct responses (Figure 2.3a) indicated that there was a main effect of previous target interval ($F(1, 17) = 10.47, p < .01, \eta^2 = .38$) as well as a main effect of the current target interval ($F(1, 17) = 21.50, p < .001, \eta^2 = .56$), indicating that participants were more accurate when the previous trial was a short relative to long duration, and when the current trial was of a short versus long duration. There was, however, no interaction between current and previous foreperiod ($F(1,17) = 1.19, p = .29$). An equivalent pattern of statistical inferences was obtained for the analysis of perceptual sensitivity values (*d'*) for discriminating targets (Figure 2.3b). There was a main effect of the length of the previous target interval ($F(1, 17) = 7.71, p < .05, \eta^2 = .31$) and a main effect for current target interval ($F(1, 17) = 31.21, p < .001, \eta^2 = .65$); again, there was, no interaction between these two effects ($F(1,17) = .43, p = .52$). Overall, participants were both more precise when the previous trial was a short duration and when the current trial was of a short duration.

Analysis of RTs (Figure 2.3c) revealed a main effect of previous target interval ($F(1, 17) = 9.84, p < .01, \eta^2 = .37$), a main effect of the current target interval ($F(1, 17) = 21.60, p < .001, \eta^2 = .56$), and an interaction between current and previous foreperiod ($F(1, 17) = 8.30, p < .01, \eta^2 = .33$). Post-hoc paired sample *t*-tests were conducted to inform the interaction between the length of the current target interval and the length of the previous target interval interaction. When the current interval was short and it was preceded by a trial with a short target interval, participants were significantly faster to respond ($M \pm SD = 823 \pm 34$) than in trials where the current target appeared early but the previous trial had a long interval ($M \pm SD = 848 \pm 35$), ($t(17)$

= -4.40, $p < .001$). In trials with a long foreperiod, responses were not modulated by the foreperiod of the previous trial ($t(17) = -.78$, $p = .45$).

To explore this pattern of results further, an analysis of IES was conducted. This yielded a slightly different pattern of results (Figure 2.3d). Though there remained a main effect of the length of the previous target interval ($F(1, 17) = 12.81$, $p < .01$, $\eta^2 = .43$) and a main effect for current target interval ($F(1, 17) = 21.85$, $p < .001$, $\eta^2 = .56$), there was no interaction ($F(1,17) = .02$, $p = .89$). The difference between the RT and IES effects demonstrate that there are speed-accuracy trade-offs at play.

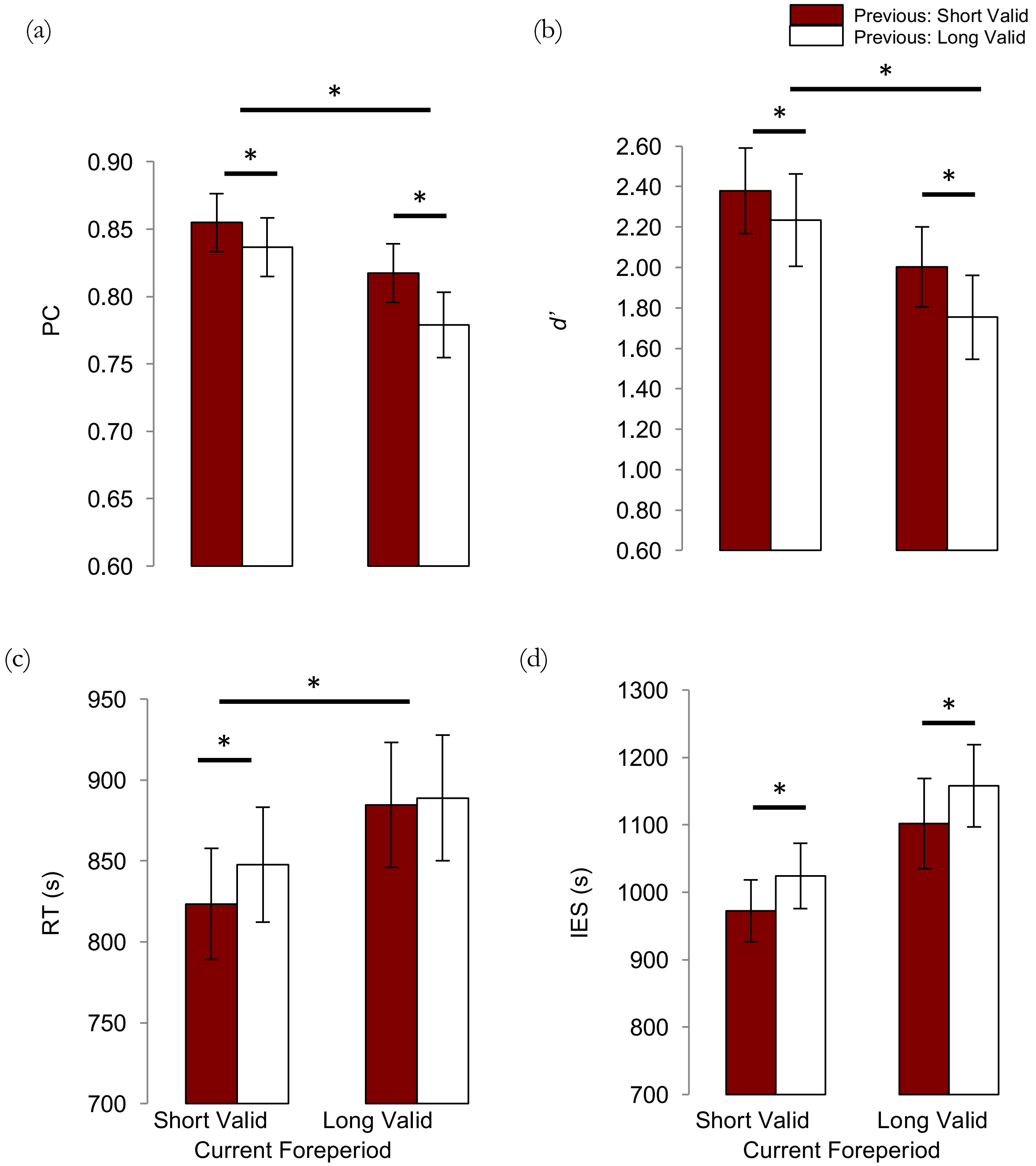

Figure 2.3 Sequential effects of temporal expectations on (a) proportion correct, (b) d-prime, (c) reaction times (ms) and (d) inverse efficiency scores (ms). Only valid trials preceded by valid trials were included. Results are averaged across left and right cues. Error bars represent standard errors of the means (SEM). Significant effects ($p < .05$) are indicated by a star.

2.4 Discussion

In the preceding investigation, temporal expectation was investigated using spatial and temporal predictive cues, which were designed to manipulate temporal certainty in the context of fully predictive spatial cues. The results provide evidence that older participants benefit from temporal cues in a perceptually demanding task. This suggests that if there is a temporal expectation deficit in ageing, it is not absolute, since older participants showed temporal orienting benefits in their response speed. Furthermore, by analyzing the sequential effects, it was discovered that the order of the cue-target intervals also influenced behavioural performance. In contrast to Zanto et al. (2011), who convincingly suggested that older adults experience a temporal expectation deficit, these results confirm that under certain task conditions, temporal expectations may still be preserved in ageing. However, it is important to note that the results differ qualitatively from the effects reported in younger participants across similar tasks, where much stronger perceptual sensitivity benefits were found (Rohenkohl, et al., 2014).

One of the main aims of this study was to examine whether temporal expectations could be preserved in older adults in a demanding perceptual context. By analyzing the effects of temporal orienting, a significant cueing benefit in the reaction time data (both RT and IES) was observed. The paradigm can therefore be judged to have been successful in eliciting temporal orienting effects in older adults. While previous studies show that temporal cues work best in the context of spatial certainty (at least in the case of peripheral targets), since spatial orienting was not manipulated, it is difficult to know whether the availability of spatial cues may have mitigated deficits by boosting spatial attention effects. Further, it is noteworthy that the typical effect of faster response times for the long foreperiod condition (i.e. the "variable foreperiod effect") was not observed (Woodrow, 1914; Karlin, 1959; Niemi & Näätänen, 1981); however, a similar pattern of RT results was noted in Rohenkohl et al. (2014).

In contrast to the response-time gains for valid trials, the hypothesized enhancement of perceptual sensitivity for temporal orienting was not significant. Moreover, there was no interaction between cue validity and temporal expectation for the short and long foreperiod. In other words, there was no evidence to suggest that the cueing benefit was asymmetrical. This is in contrast to a similar study run on younger participants by Rohenkohl and colleagues (2014) who found an asymmetrical effect on a spatial and temporal orienting task.

In addition to the effects of temporal orienting, the trial-by-trial nature of the experimental design allowed for an exploration of the sequential foreperiod effects. In line with previous evidence, it was found that participants were overall faster and more accurate when the target item was presented at a short duration, and on targets that were preceded by trials with targets presented at a shorter duration (e.g. Capizzi, et al., 2013; Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn, et al., 2008; Vallesi & Shallice, 2007; Woodrow, 1914). The finding of sequential effects suggests the preservation of more automatic temporal processing abilities in ageing (see Vallesi, McIntosh, & Stuss, 2009). Arguably, the pattern of modulation according to effects of foreperiod sequence was more robust than the effects of temporal orienting cues. This suggests that non-coextensive mechanisms may exist for the modulation of behavioural effects according to different types of temporal structure between events (see Nobre & Rohenkohl, 2014).

Despite the ostensible departure from Zanto et al.'s (2011) study, the results of the temporal orienting effects are, admittedly, not as strong as observed in studies that have examined younger cohorts. In hindsight, when evaluating the adequacy of the task to explore temporal expectation in older participants, several shortcomings can be noted: (1) cue interpretation may have placed excessive demands on participants, requiring multiple endogenous shifts to spatial and temporal information concomitantly; (2) similarly, shifting between cue information on a trial-by-trial basis may have added executive demands; and (3) cue

With increasing task complexity, temporal orienting effects may have been diminished. Therefore, it remains unclear how much of the performance on the temporal orienting tasks was affected by the task demands. Because of these reasons, the experimental design may have been incapable of yielding stronger temporal orienting effects.

If a lot of effort is required to form an internal representation of the cue, it may be difficult for visual timing cues to aid perceptual performance. This may have been particularly problematic given that task complexity has previously been shown to interfere with significant effects of timing amongst older adults (Block et al., 1998). The importance of having an intuitive cue that facilitates the development of an internal representation is non-trivial. While the participants had to orient their attention both in space and in time, the spatial cue might be considered to have been more intuitive (e.g. relying more on previously learned associations to arrows as typically indicating directionality), whereas the temporal cue was based on a learned association on the day of the task between the colour of the cue and the foreperiod. In addition to this being potentially confusing to participants, participants may have focused on the spatial cue (as it was more salient) rather than on the temporal aspect of the cue.

It is also possible that performance may have been adversely affected by a decline in the ability to integrate successfully multiple types of expectation, or competing streams of information (e.g. spatial and temporal). Though temporal expectation may operate synergistically with other top down expectations (e.g. those related to spatial orientation) to enhance effects in young people, this may well degrade with age. In other words, it is still possible that temporal and spatial orienting abilities could be independently preserved, but the synergistic benefit observed in young people may be impaired. Unfortunately, given that spatial validity was not manipulated, this hypothesis cannot be explored further in the current set of results.

Overall, the pattern of behavioural results suggests that older individuals can maintain some benefits of temporal expectation (validity effects) and temporal structuring of events (sequential experimental task used to probe effects of temporal expectation, such as the use of more intuitive cues and cutting back on executive demands associated with the task.

2.5 Conclusion

The aim of the current experiment was to establish whether combined spatio-temporal cues would be adequate for revealing temporal expectation benefits in older adults. For this reason, no cohort of younger adults was included. While comparing old and young cohorts is problematic for various reasons (e.g. differences in education and upbringing), it would have been beneficial to have a younger group of participants to understand the degree to which older participants were impaired. Results are therefore unresolved with regard to lack of proactive control in older adults extending into the temporal domain. In order to be confident in this finding, it will be worth replicating and contrasting the results with a younger cohort.

The above investigation is the first of its kind to suggest that temporal expectations might be preserved in ageing. As such, it provokes a number of important questions yet to be examined. For instance, can temporal orienting work independently of spatial orienting cues in older populations? Can performance be further enhanced if task demands are lowered? We now know that temporal expectations can benefit performance in different ways depending on the parameters and demands of a task. Using simple speeded detection tasks, it is possible to measure gains in RTs, but there is little information provided about possible effects on earlier, perceptual stages of stimulus analysis. Using challenging unspeeded perceptual discrimination tasks provides more limited information about response variables, but enables investigation of possible perceptual gains (see Correa et al., 2005). In a study devised by Davranche and colleagues (2011), temporal orienting tasks were created to measure performance at both the motor and perceptual levels. In the next chapter I will investigate the aforementioned questions using similar tasks with intuitive temporal cues and determine whether effects of temporal orienting can be obtained in older adults in the absence of spatial orienting

3 Temporal orienting of attention can be preserved in normal ageing*

Chapter Abstract

Being able to orient our attention to moments in time is crucial for optimizing behavioural performance. In young adults, flexible cue-based temporal expectations have been shown to modulate perceptual functions and enhance behavioural performance. Recent studies with older individuals have reported significant deficits in cued temporal orienting. To investigate the extent of these deficits, and to expand on the findings in older adults in Chapter 2, we conducted three studies in healthy old and young adults. For each study, participants completed two tasks: a reaction-time task that emphasized speeded responding and a non-speeded rapid-serial-visual-presentation task that emphasized visual discrimination. Auditory cues indicated the likelihood of a target item occurring after a short or long temporal interval (foreperiod) (75% validity). In the speeded-RT task, participants were asked to respond as quickly as they could to a green circle that appeared at the centre of the screen. Reaction times were measured in order to examine whether benefits were conferred by temporal expectation. In the non-speeded perceptual discrimination task, participants were asked to make a judgment about whether they saw an 'X' or an 'O' in a stream of rapidly presented letters. Using *d*-prime as a measure of perceptual sensitivity, discrimination performance for the target letter was assessed. In the first study, cues indicating a short or a long foreperiod were manipulated across blocks. The second study was designed to replicate and extend the first study by manipulating the predictive temporal cues on a trial-by-trial basis. The third study extended the findings by including 'neutral' cues so that it was possible to separate cueing validity benefits and invalidity costs. In all three studies, cued temporal expectation conferred significant performance advantages for target stimuli occurring after the short foreperiod for both old and young participants. Contrary to previous findings, our results suggest that the ability to allocate attention to moments in time can be preserved in healthy aging. Further research is needed to ascertain whether similar neural networks are used to orient attention in time as we age, and/or whether compensatory mechanisms are at work in older individuals.

*This chapter has been published in the Journal of *Psychology and Aging*
(Chauvin, Gillebert, Rohenkohl, Humphreys & Nobre, 2016).

3.1 Introduction

Our brains continuously generate expectations about what we are about to see, touch, taste, or hear. These predictions operate to guide and enhance our behavioural performance, which in turn enables us to interact effectively with our complex and ever-changing environment. At the core of our predictive capabilities is our ability to orient our attention proactively to key moments in time — enabling us to ready ourselves to perceive and respond to relevant events. Our abilities to orient ourselves in time and form expectations about the world can lead to improved behavioural outcomes, such as faster response times, greater accuracy, and increased perceptual sensitivity in perceptually demanding conditions (for a review, see Nobre & Rohenkohl, 2014).

Predictive temporal cues provide an effective means of manipulating temporal expectations that are under top-down control (Nobre & Coull, 2010; Rohenkohl, et al., 2011). Just as spatial cues can be used to direct a participant's attention to specific locations (Posner, 1980), temporally predictive cues have been used to manipulate participants' expectations and guide their attention to key moments in time when a task-relevant target is likely occur (Correa, Sanabria, Spence, Tudela, & Lupiáñez, 2006; Coull & Nobre, 1998; Miniussi, et al., 1999; Todorovic, Schoffelen, van Ede, Maris, & de Lange, 2015; Triviño, Correa, et al., 2010). The use of temporal cues to direct an observer to a moment in time has been referred to as *temporal orienting* (see Nobre, 2001, for review). Temporal orienting appears to be a flexible ability that is not only capable of speeding motor preparation and response times (Correa, et al., 2004; Griffin, Miniussi, and Nobre, 2001), but can also improve the perceptual sensitivity to detect or discriminate stimuli (Correa, et al., 2005; Correa et al., 2006; Davranche, et al., 2011; Rohenkohl, et al., 2012).

Whereas in younger adults cued temporal orienting has consistently been shown to optimize behavioural performance in speeded motor tasks as well as in unspeeded, perceptually demanding tasks (Correa et al., 2004; Coull & Nobre, 1998; Davranche et al., 2011; Miniussi et al., 1999), the extent to which temporal orienting is preserved in healthy aging is a matter of debate (Zanto & Gazzaley, 2014), and significant deficits have indeed been reported for older adults in cued temporal orienting tasks (Dempster, 1992; Zanto et al., 2011). Zanto and colleagues (2011) directly manipulated temporal expectation in young and old adults across a range of tasks. While younger adults were able to use temporal cues to enhance reaction times in a detection task, a forced-choice discrimination task and a go/no-go discrimination task, older adults did not gain any benefit from temporal cueing in any of the task conditions. The researchers suggested that older adults have a deficit in temporal expectation, as evidenced by their inability to use temporal cues to successfully allocate attentional processes in time. Based on such results it has been argued that deficits in temporal orienting exist as part of a wider set of problems related to reduced, proactive top-down control of attention (Zanto & Gazzaley, 2014). In the following set of experiments, we investigated the generality of these deficits, by asking again whether, in some cases, temporal orientation can be preserved in healthy aging.

To gain a clearer picture of the boundaries of temporal expectation abilities and deficits, younger and older adults participated in two types of tasks, emphasizing speeded responding and perceptual discrimination. The task designs we used were adapted from those used by Davranche et al. (2011) (see also Correa et al., 2005). A speeded RT task emphasised the effects of orienting on response preparation. This task demanded a speeded response, and did not require participants to discriminate between detailed features of a target item. Separately, a rapid serial visual presentation (RSVP) task emphasizing perceptual discrimination was used to examine the temporal expectation effects associated with perceptual processing. Participants made a non-speeded response to indicate whether an 'X' or 'O' target appeared in the preceding stream of letters. Temporal expectations were manipulated by auditory cues that predicted the onset time of target stimuli with 75% validity. Participants were instructed to make use of the

Based on the sparse previous literature (for review see Zanto & Gazzaley, 2014), we hypothesized that older adults would show significant deficits in using temporal orienting cues. Our study was designed to extend the previous literature by examining whether temporal orienting effects could be unmasked in older adults by reducing executive demands in the task. Complex or demanding tasks could, in theory, compromise performance in the elderly for reasons unrelated to deficits in deriving or using temporal expectations. In addition, by including the two types of experimental paradigms, we were able to examine whether modulation of motor or perceptual functions by cued temporal expectations could be differentially preserved in healthy aging.

Three experiments were conducted using variations of these two tasks. In the first experiment, we presented blocks of trials where the audio cues predicted either a short (540 ms) or a long (1600 ms) interval until the target appeared. We chose to block the cues in order to isolate putative effects of temporal orienting, since blocking of cues reduces the demands on other executive processes that are not specifically linked to temporal orienting, such as interpretation and updating of the cue information. In this task, the group of older participants showed significant benefits of temporal orienting cues for both the speeded RT and RSVP tasks. In a second experiment, we increased task demands by intermixing cues predicting short and long intervals. This allowed us to examine whether older adults could still benefit from temporal orienting cues when they had to rely on executive functions related to encoding and updating the meanings of cues on a flexible basis. Temporal orienting deficits in this case would suggest that these additional executive demands might have contributed to the temporal expectation deficits observed in previous studies. However, the older participants in this study still showed significant benefits of temporal orienting cues for both the speeded RT and RSVP tasks. In the third and final experiment, we included blocks of non-informative temporal cues in addition to blocks of temporally predictive cues in order to separate validity benefits from invalidity costs.

As in the two previous studies, the older group showed significant effects of cued temporal orienting, which consisted of both validity benefits and invalidity costs.

3.2 Methods

3.2.1 Participants

Each experiment consisted of 18-20 participants in both younger and older groups. Each participant took part in only one experiment, with the exception of 13 older participants who took part in Experiment 1 and Experiment 2. All experiments were conducted more than six months apart. All participants self-reported to be right-handed, with the exception of four older (one in Experiment 1, three in Experiment 3) and two younger (in Experiment 3) participants, who were left handed. The participants all reported normal or corrected-to-normal vision, were free of psychotropic or vasoactive medication, and had no neurological or psychiatric history. Volunteers gave informed consent and were reimbursed for their participation (£10 an hour plus travel expenses). The studies were reviewed and approved by the Central University Research Ethics Committee of the University of Oxford.

3.2.2 Neuropsychological Evaluation

To ensure that our older participants were cognitively healthy, we evaluated their performance using a neuropsychological test battery. In Experiment 3, we performed the neuropsychological test battery for both older and younger participants. The neuropsychological evaluation consisted of tests designed to assess general cognitive function [Montreal Cognitive Assessment (MoCA, version 7.1; Nasreddine et al., 2005)], attention/task switching [Trail Making Test (TMT); Reitan, 1958; Reitan & Wolfson, 1985; Tombaugh, 2004], executive

Meyers, 1995; Osterrieth, 1944; Rey, 1941), semantic memory (Category fluency—names of animals 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; Yuedall, et al., 1986). The test scores are summarized in Tables 3.1 and 3.2.

Table 3.1

Neuropsychological evaluation conducted in older adults from Experiments 1 and 2 (n = 26, 11F).

	Mean	Range	SE	N > 2SD*
Age	66.4	61 - 82	1.0	-
Education	18.0	11 - 29	0.8	-
MOCA	28.0	26 - 30	0.2	-
TMT: A (s)	32.1	16 - 68	1.9	-
TMT: B (s)	66.8	41 - 160	4.8	-
ROCFT				-
Copy (out of a possible 36)	34.1	30 - 36	0.4	-
Immediate (out of a possible 36)	20.5	3.5 - 34	1.2	1.0
Delay (out of a possible 36)	18.9	2.5 - 34	1.3	-
Category Fluency	21.9	15 - 34	1.0	-
HVLT-R				
Trial 1	5.5	3 - 9	0.3	-
Trial 2	8.1	3 - 12	0.4	-
Trial 3	9.6	6 - 12	0.3	-
Learning	4.2	1 - 7	0.3	-
Sum of 1-3	23.2	13 - 32	0.8	-
Delayed Recall	8.3	0 - 12	0.5	1
Percent Retained (%)	83.6	0 - 110	4.5	1
True Positives	11.0	7 - 13	0.3	1
False Positives	0.7	0 - 3	0.2	-
Discrimination Index	10.4	7 - 13	0.3	-
BNT	14.5	12 - 15	0.2	-
Digit Span (Scaled Score)	10.4	6 - 14	0.5	n.a.
Purdue Pegboard Right	12.5	9 - 17	0.4	-
Purdue Pegboard Left	12.4	9 - 17	0.4	1
Purdue Pegboard Both	10.3	8 - 13	0.3	-
Purdue Pegboard Sum	35.2	28 - 44	0.9	3
Purdue Pegboard Assembly	26.0	15 - 33	0.9	1
TOPF - FSIQ	120.3	102 - 138.9	2.1	-

Note. *This column contains 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 Fig. Test; HVLT-R, Hopkins Verbal Learning Test-Revised; BNT, 15-Item Boston Naming Test; TOPF, Test of Premorbid Functioning.

Table 3.2

Mean scores from the neuropsychological evaluation conducted for the old and young adults who participated in Experiment 3.

	Old (n = 19, 11F)				Young (n = 18, 12F)				
	Mean	Range	SE	> 2 SD*	Mean	Range	SE	> 2 SD*	*p*
Age	67.1	51 - 83	2.0	0	22.7	19 - 28	0.6	0	< .001
Education	15.6	10 - 24	0.8	0	17.8	13 - 23	0.6	0	< .05
MOCA	28.1	26 - 30	0.3	0	27.6	26 - 30	0.3	0	n.s.
TMT: A (s)	32.9	18 - 87	3.9	1	23.6	12 - 49	2.4	1	< .05
TMT: B (s)	78.8	32 - 178	9.4	2	50.8	22 - 183	8.5	1	< .01
ROCFT									
Copy (out of a possible 36)	31.5	19 - 36	0.9	1	33.5	28 - 36	0.5	n.a.	n.s.
Immediate (out of a possible 36)	16.2	6 - 27	1.5	0	20.6	12.5 - 28	1.3	n.a.	n.s.
Delay (out of a possible 36)	14.7	3 - 27	1.7	1	20.6	10 - 28.5	1.5	n.a.	< .05
Category Fluency	22.9	6 - 24	0.8	0	23.1	9 - 34	1.5	1	n.s.
HVLT-R									
Trial 1	5.7	2 - 9	0.4	0	5.8	3 - 8	0.3	n.a.	n.s.
Trial 2	8.1	4 - 11	0.4	0	8.7	6 - 12	0.4	n.a.	n.s.
Trial 3	9.3	6 - 11	0.4	0	10.3	7 - 12	0.4	n.a.	< .05
Learning	3.6	0 - 7	0.5	0	4.6	2 - 7	0.3	n.a.	n.s.
Sum of 1-3	23.1	13 - 29	0.9	0	24.8	16 - 32	24.8	n.a.	n.s.
Delayed Recall	8.7	4 - 12	0.6	0	9.2	6 - 12	0.5	n.a.	n.s.
Percent Retained (%)	94.6	44 - 133	5.2	0	89.2	50 - 109	3.4	n.a.	n.s.

True Positives	11.3	9 - 12	0.2	1.0	11.7	10 - 12	0.1	n.a.	n.s.
False Positives	1.2	0 - 13	0.3	0	0.4	0 - 2	0.1	n.a.	< .05
Discrimination Index	10.2	7 - 12	0.4	0	11.3	9 - 12	0.2	n.a.	n.s.
BNT	14.2	12 - 15	0.2	0	11.8	7 - 14	0.4	n.a.	< .001
Digit Span (Scaled Score)	10.7	7 - 16	0.6	n.a.	9.3	5 - 17	0.6	n.a.	n.s.
Purdue Pegboard Right	12.4	7 - 19	0.6	1	14.3	12 - 18	0.4	1	< .01
Purdue Pegboard Left	11.6	9 - 15	0.4	1	13.0	10 - 17	0.5	5	n.s.
Purdue Pegboard Both	9.5	5 - 12	0.5	3	11.4	9 - 15	0.4	4	< .01
Purdue Pegboard Assembly	24.6	14 - 37	1.5	3	32.1	20 - 48	1.8	6	< .01
TOPF - FSIQ	114.3	96.9 - 132.5	2.4	0	110.6	101.1 - 120.1	1.3	0	n.s.

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 Fig. Test; HVLT-R, Hopkins Verbal Learning Test-Revised; BNT, 15-Item Boston Naming Test; TOPF, Test of Premorbid Functioning.

P: probability of difference between Young and Old adults, Mann–Whitney non-parametric test (n.s., non-significant).

3.2.3 Apparatus

Stimuli were created and presented through Presentation (16.5, Neurobehavioural systems, Albany, CA, United States of America), run on a Dell Optiplex 990 computer with a 23-inch ViewSonic VA2342-LED screen (resolution 1920 x 1080 pixels, refresh rate 100 Hz). Participants were seated in a dimly lit room, approximately 63 cm away from the monitor. Responses were collected using a standard keyboard.

3.2.4 Stimuli and experimental design

Each experiment consisted of a speeded RT task and an RSVP task. In the speeded RT task (Figure 1a), participants were instructed to respond as quickly as they could to a green circular patch, which appeared at the center of the screen. In the non-speeded RSVP task (Figure 1b), participants were instructed to identify a target letter ('X' or 'O') embedded in a stream of distractor letters. In both tasks, the pitch of an auditory cue preceding the target indicated the likelihood of the target item occurring after a short (540 ms) or long (1580 ms in the speeded RT task and 1620 ms in the RSVP task) temporal interval (75% validity). Participants were instructed to maintain central fixation throughout the tasks and to do their best to use the temporal information provided to them by the auditory cues to help them to predict when the target was most likely to appear.

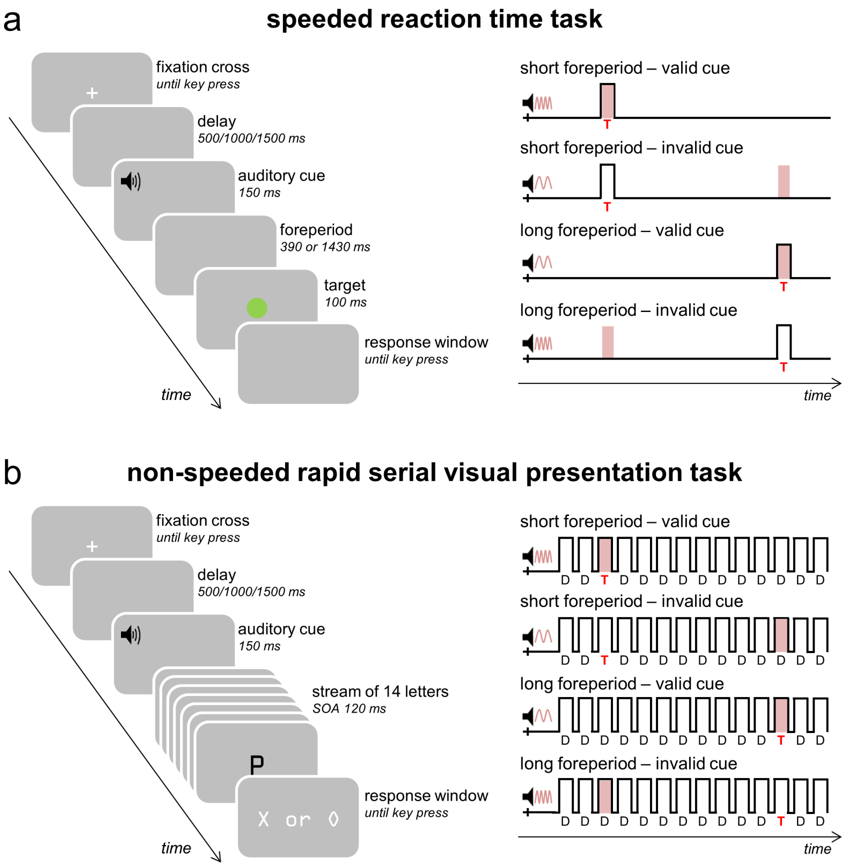

Figure 3.1 Schematic illustration of the speeded RT task and the RSVP task. Auditory cues predicted when target events were more likely to occur. (a) Speeded RT task. Targets consisted of green circular patches presented foveally. Participants were instructed to respond as quickly as possible to the green patch by pressing the left arrow key on a standard keyboard with their right index finger. (b) RSVP task. Targets were either an X or an O that was presented foveally. Participants were instructed to hold off on responding until the end of the trial, and to press the left arrow key if they thought they saw an X and the right arrow key if they thought they saw an O.

Both tasks followed the same basic design (Figure 1). Stimuli appeared superimposed against a uniform grey background (RGB values: 128, 128, 128), and a fixation point remained visible in the center of the screen (width: 0.46°; height: 0.46°). Each trial commenced following a participant-initiated key press. After a short delay lasting 500 ms (50% probability), 1000 ms (25% probability) or 1500 ms (25% probability), an audio cue was presented for 150 ms. In Experiments 1 and 2, the audio cue was either a high pitch (1100 Hz) or a low pitch (600 Hz) beep indicating a short or a long foreperiod, respectively. The cue was valid in 75% of the trials. Participants were informed that the audio cues would help them to predict when the target would appear. In Experiment 3, we again used a high pitch (1600 Hz) and a low pitch (400 Hz) beep indicating a short or a long foreperiod with 75% validity. In addition, we introduced an audio cue with an intermediate pitch (1000 Hz) as a neutral cue that provided no information about the duration of the foreperiod.

In the speeded RT task, participants were asked to respond as quickly as possible with their right index finger to a green circular patch (diameter: 1.82°), which was presented foveally after either a short (stimulus-onset asynchrony (SOA) of 540 ms) or a long foreperiod (SOA 1580 ms) (Figure 1a). In the non-speeded RSVP task*,* the audio cue was followed by a stream of 14 black letters (font: OCR A Extended; width: 0.9°; height: 1.92°) presented foveally and in rapid succession (duration 100 ms; inter-stimulus interval 20 ms). The SOA between the audio cue and the first letter was 300 ms. Thirteen letters were distractors and one was a target letter (Figure 1b). The target letter, either an 'X' or an 'O', appeared either early (on the 3rd location, after 540 ms) or late (on the 12th location, after 1620 ms). The distracter stimuli were randomly sampled without replacement from a set of letters [A,B,E,F,G,H,I,J,L,M,P,Q,R,T,U,W]. Following the presentation of the letter stream, participants made a non-speeded, delayed discrimination response with their right hand using the left (for 'X') and right (for 'O') arrow keys on a standard keyboard. In order to minimize the motor component of the perceptual discrimination task, participants responded after the offset of the visual stream during a designated response window. Participants were under no time pressure to provide a response and were informed that only the accuracy of the response would be taken into account.

3.2.5 Data Analysis

Statistical analysis was performed using MATLAB and SPSS. For the speeded RT task, our primary outcome variable was the mean RT on correct responses for each condition. Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT. The average number of outlying trials was low (1%) and did not differ between young and old adults (Table 3.3). To ensure that age-related effects were not related to general slowing of older compared to younger adults, we also calculated for each foreperiod a 'cueing index'. For Experiments 1 and 2, the index was calculated by taking the difference between the mean RT in the invalid condition and the mean RT in the valid condition, and dividing this difference by the mean RT in the valid condition. For Experiment 3, we calculated one index reflecting validity benefits (mean RT in the valid condition minus the mean RT in the neutral condition, divided by the mean RT in the neutral condition), and one index reflecting invalidity costs (mean RT in the invalid condition minus the mean RT in the neutral condition, divided by the mean RT in the neutral condition). In a supplementary analysis, we analyzed the proportion of anticipatory responses (see Appendix).

For the non-speeded RSVP task, our primary outcome variable was a measure of perceptual sensitivity (*d'*). Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT (Table 3.3). In addition, although response speed was de-emphasized, we also analyzed the mean RTs on correct responses for each condition for the sake of completeness (see Appendix).

For each measure, we excluded from the analysis data from participants who scored more than three standard deviations away from the mean value in at least one condition.

To examine how sensitivity to temporal prediction changed with age, we ran a 3-way mixed-design analysis-of-variance (ANOVA) with foreperiod (short, long) and cue validity (Experiments 1 and 2: valid, invalid; Experiment 3: valid, invalid, neutral) as within-subjects factors, and age group (young, old) as a between-subjects factor for each task. When sphericity could not be assumed (Mauchly's sphericity test: $p < .05$), p-values were adjusted using the Greenhouse-Geisser correction (G-G correction).

As part of a supplementary set of analyses, in order to assess whether differences in performance depended on whether the auditory cues were blocked, we ran a 4-way analysis of variance with experimental design ('blocked design', 'trial-by-trial design') as between-subjects factor. Only older participants who participated in Experiment 1 and in Experiment 2 were included in the analysis ($n = 13$) (see Appendix).

Finally, to account for the possibility of unequal trial numbers or power between the trial conditions or groups, we conducted a series of non-parametric permutation tests to analyze the strength of the validity effects for each experiment (Ernst, 2004; Maris, Schoffelen, & Fries, 2007; see also Rohenkohl, et al, 2014). To this end, we performed repeated-measures ANOVAs separately for young and old adults. Statistical tests used a critical alpha level of 0.05. Following the data analysis procedure employed in Rohenkohl et al. (2014), we assessed the significance of the observed results by comparison to a null distribution generated via Monte Carlo simulation with 10,000 repetitions. The null distribution was created by randomly shuffling the condition labels within each participant's data in each repetition. The statistical test (F) was then performed, and the resulting value was entered into the null distribution. The permutation p value was determined as the proportion of random partitions that resulted in a larger test statistic than the observed one.

Table 3.3

The number of excluded outlying trials per experiment (n.b. with RT *values more than 3 standard deviations away from the mean* RT *of a participant classified as 'outlying'). The average number of outlying trials did not differ between both age groups, according to two-sample t-tests.*

	Old adults			Young adults			
Experiment	Mean	Min	Max	Mean	Min	Max	Two-sample *t*-test
Speeded RT task							
Experiment 1	5.83	1	11	5.16	1	10	$t(34) = .77, p = .44$
Experiment 2	5.50	1	11	7.17	2	10	$t(36) = -1.91, p = .06$
Experiment 3	6.64	1	12	7.06	2	21	$t(33) = -.33, p = .76$
RSVP task							
Experiment 1	7.78	1	13	7.72	4	13	$t(34) = .06, p = .95$
Experiment 2	7.55	1	13	7.00	2	11	$t(36) = .56, p = .58$
Experiment 3	8.74	1	15	9.00	4	16	$t(35) = -.98, p = .33$

3.3 Experiment 1: Temporal Orienting in a Blocked Design

3.3.1 Method

Eighteen younger participants (M_{age} = 26.8 years, $M_{\text{education}}$ = 21.5 yrs, 10 females) and 18 older participants (M_{age} 65.5 years, $M_{\text{education}}$ = 18.0 yrs, 10 females) took part in the experiment. In this experiment, the pitch of the audio cue was manipulated between blocks. In half of the blocks, a high-pitched auditory cue was presented on every trial indicating that the target would appear after a short interval with a probability of 75%. In the other blocks, a low-pitched auditory cue occurred indicating that the target would appear after a long interval with a probability of 75%. Participants performed four blocks consisting of 96 trials each for each task. Two blocks of the speeded RT task were alternated with two blocks of the RSVP task. A short practice block was given before each set of two blocks. The order of the tasks was counterbalanced across participants.

3.3.2 Results

3.3.2.1 Speeded RT task

After removing the anticipatory responses, performance was at ceiling (<1% misses) for all four conditions in both age groups. Before analyzing the between-group differences, two participants (one young, one old) with response times more than 3 standard deviations (SD) above the average response time of all the other participants were removed from the analysis.

The key results of the ANOVA are listed in Table 3.4. The main finding was that both younger and older adults showed significant and equivalent effects of cued temporal expectations on speeded detection of targets appearing at the short interval. We observed main effects of age, foreperiod, and cue validity; as well as a foreperiod-by-validity interaction on the RTs (ps < .001). Older participants responded more slowly to the target compared to younger individuals (Figure 2a). Post-hoc paired-sample t-tests were conducted to inform the foreperiod-by-validity interaction, which was significant within each age group (young adults: $F(1,16) = 54.42$, $p < .001$, F-test permutation $p < .001$; old adults: $F(1,16) = 59.837$, $p < .001$, F-test permutation $p < .001$). Participants reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid versus invalid temporal information ($t(33) = -11.92$, $p < .001$). The effect size was very large in both age groups (young adults: Cohen's $d = 1.78$; old adults: Cohen's $d = 2.32$) (Figure 2a). In contrast, the validity of the auditory cue did not modulate RTs in trials with a long foreperiod ($t(33) = 1.76$, $p = .09$). To ensure that the absence of any age-related differences in the validity effect was due to old adults responding more slowly than young adults, we additionally analysed the 'cueing index' that was corrected for the mean RT of each individual. We did not observe a main effect of age ($F(1,32) = .22$, $p = .64$) or an interaction between foreperiod and age ($F(1,32) = .18$, $p = .67$). In summary, both younger and older participants experienced the expected asymmetric cueing benefit for short versus long foreperiods.

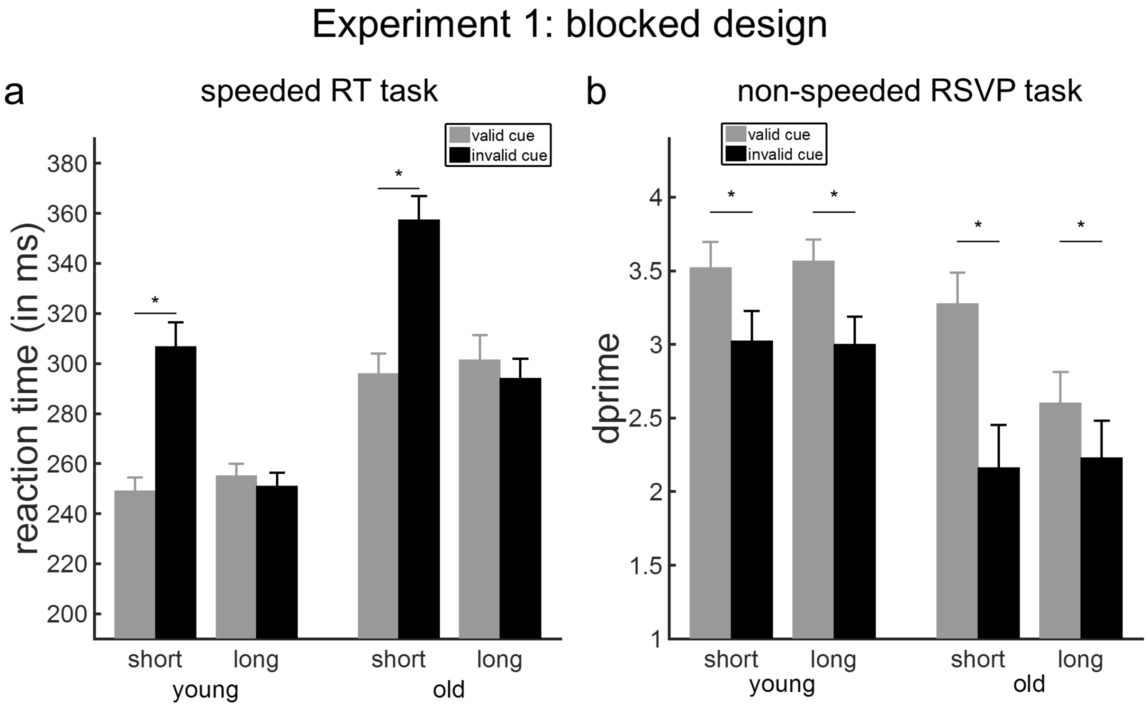

Figure 3.2 Temporal orienting effects in Experiment 1 (blocked design). (a) Effects of temporal expectations on reaction time values (ms) in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

3.3.2.2 RSVP task

No participant performed more than three SD's beyond the mean for any condition on perceptual discrimination, so all participants were included in the analysis. Analysis of *d'* revealed significant and equivalent effects of blocked cued temporal expectations for detecting targets at the short and long intervals in both younger and older adults. We observed main effects of age and cue validity on the *d'* values ($ps \leq .006$, see Table 3.5). The main effect of cue validity was significant in each age group (young adults: $F(1,17) = 19.94$, $p < .001$, *F*-test permutation $p < .001$; old adults: $F(1,17) = 23.61$, $p < .001$, *F*-test permutation $p < .001$). As shown in Figure 2b, the target letter was identified better when the cue correctly predicted its position in the RSVP stream compared to when the cue was invalid. Although in general the performance of older participants was worse than that of younger participants, the size of the cue validity effect was large in both age groups (young adults: Cohen's $d = 1.05$; old adults: Cohen's $d = 1.15$).

In summary, in contrast to previous reports (e.g., Zanto et al., 2011), the results of Experiment 1 provide the first behavioral demonstration that cued temporal orienting can be preserved in healthy ageing. Importantly, our experimental design differed from Zanto and colleagues, who manipulated temporal cues on a trial-by-trial basis. An event-related design may be more sensitive to pick up subtle deficits in the flexibility of cued temporal orienting, as participants need to change their temporal expectation on a trial-by-trial basis. In a second experiment, we therefore intermixed cues predicting short and long intervals. This allowed us to examine the extent to which executive functions related to encoding and updating the meaning of the cue might have contributed to the temporal expectation deficits observed in previous studies.

3.4 Experiment 2: Temporal Orienting in a Trial-by-Trial Design

3.4.1 Method

Eighteen young (M_{age} 25.0, $M_{\text{education}}$ = 18.0 yrs, 11 females) and 20 older (M_{age} 66.8, $M_{\text{education}}$ = 17.85 yrs, 12 females) volunteers took part in the experiment. In this experiment, high- and low-pitched auditory cues were randomly intermixed within each block. Participants completed for each task four blocks of 96 trials each. Two blocks of the speeded RT task were alternated with two blocks of the RSVP task. A short practice block was given before each set of two blocks. The order of the tasks was counterbalanced across participants.

The use of trial-by-trial cueing also permitted the analysis of sequential effects. Sequential effects refer to how the order of the foreperiod intervals can influence performance (Los, 2010). Previous studies found asymmetrical sequential effects, showing that RTs are lengthened when the previous foreperiod was longer than the current foreperiod (e.g. Capizzi, et al., 2013; Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn, et al., 2008; Vallesi & Shallice, 2007). Performance on valid trials was analyzed using a 3-way mixed-design ANOVA with current foreperiod (‘short’, ‘long’) and previous foreperiod (‘short’, ‘long’) as within-subjects factors, and age group (‘young’, ‘old’) as a between-subjects factor. Only validly cued trials preceded by a validly cued trial were included in this analysis.

3.4.2 Results

3.4.2.1 Foreperiod effects

Speeded RT task. No participants were excluded from the RT analysis. Extending the results of the blocked-design version of the task in Experiment 1, significant and equivalent effects on the speed of detecting targets occurring at the short interval were also conferred by fully intermixed temporally predictive cues in both younger and older adults. Analysis of RTs revealed main effects of foreperiod and cue validity, and a significant interaction between foreperiod and cue validity (*p*s < .001, Table 3.4). We did not observe any significant difference between the age groups (Table 3.4). Post-hoc paired-sample *t*-tests were conducted to inform the foreperiod-by-validity interaction, which was significant in young adults ($F(1,17) = 22.53$, $p < .001$, *F*-test permutation $p < .001$) and in old adults ($F(1,19) = 23.64$, $p < .001$, *F*-test permutation $p < .001$). Responses to targets appearing after a short foreperiod were faster when preceded by a valid compared to invalid auditory cue ($t(37) = -7.27$, $p < .001$) (Figure 3a). The size of this effect was large and of similar magnitude within each age group (young adults: Cohen's $d = 1.21$; old adults: Cohen's $d = 1.22$). There was no significant difference in RTs between the validly and invalidly cued targets appearing after a long foreperiod ($t(37) = .74$, $p = .47$). Analysis of the 'cueing index' did not reveal a main effect of age ($F(1,36) = 1.64$, $p = .21$) or an interaction between foreperiod and age ($F(1,36) = .004$, $p = .88$).

Figure 3.3 Temporal orienting effects in Experiment 2 (trial-by-trial design). (a) Effects of temporal expectations on reaction time values (ms) in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

RSVP task. No participant performed more than three SD's beyond the mean for any condition on perceptual discrimination, so all participants were included in the analysis.

As in the blocked-design version of the task in Experiment 1, significant and equivalent effects on discriminating targets at short and long intervals were conferred by fully intermixed temporally predictive cues in both younger and older adults. Analysis of *d'* revealed main effects of foreperiod and cue, as well as a foreperiod-by-validity interaction (*p*s $\leq .007$). Age did not affect perceptual discrimination performance in this experiment (Table 3.5), and there was a foreperiod-by-validity interaction in young ($F(1,18) = 3.71$, $p = .07$, *F*-test *permutation* $p < .05$) and in old adults ($F(1,19) = 4.45$, $p < .05$, *F*-test permutation $p = .04$). As shown in Figure 3b, identifying the target letter was easier when the cue correctly predicted its timing in the RSVP stream compared to when the cue was invalid. This was true for targets appearing after a short interval ($t(37) = 4.22$, $p < .001$) and for targets appearing after a long interval ($t(37) = 2.55$, $p = .02$), although the size of this effect was significantly larger for targets appearing at the short foreperiod (Cohen's *d* for young adults: .68, old adults: .69) compared to long foreperiods (Cohen's *d* for young adults: .39; old adults: .51) (Figure 3b).

3.4.2.3 Sequential Effects

Speeded RT task. Analysis of sequential effects was limited to trials with a valid auditory cue preceded by trials with a valid auditory cue in the trial-by-trial speeded RT task.

Analysis of the RTs revealed robust and equivalent sequential effects for detecting targets at the short interval for both younger and older adults. The ANOVA yielded a main effect of previous foreperiod and an interaction between current and previous foreperiod (*p*s

$< .001$) (see Table 3.6 for the key results of the ANOVA). Post-hoc paired-sample *t*-tests were used to inform the interaction between current foreperiod and previous foreperiod, which was significant in each age group (young adults: young adults: $F(1,19) = 46.06$, $p < .001$, *F*-test permutation $p < .001$; old adults: $F(1,19) = 56.90$, $p < .001$, *F*-test permutation $p < .001$). Responses were faster when a short foreperiod was preceded by a short compared to a long foreperiod. The effect was very large in both young (Cohen's $d = 1.72$) and old (Cohen's $d = 1.43$) adults. RTs were unaffected in trials with a long foreperiod ($t(37)= -1.04$, $p = .30$).

RSVP task. Analysis of *d'* values revealed a main effect of current foreperiod ($p < .008$), with better perceptual discrimination performance for short compared to long foreperiods, and an interaction between previous foreperiod and age ($p = .008$) (see Table 3.6). Separate ANOVAs were run for trials with a preceding short versus long foreperiod. No main effect of age was observed when the preceding foreperiod was long ($F(1,36) = .01$, $p = .91$). In contrast, when the previous foreperiod was short, younger adults tended to perform better than older adults ($F(1,36) = 3.16$, $p = .08$) (Figure 4b).

In Experiment 2, we replicated the findings observed in Experiment 1 and showed that temporal expectations conferred by temporal cues can be preserved in older adults, even if older adults have to adjust their expectation from trial to trial. Although the sizes of the cued temporal expectations were equivalent in younger and older adults in both tasks across the two experiments, it is not possible to conclude that both groups of participants are affected by temporal cues in the same way. The use of only valid and invalid temporally predictive cues precludes the separation of validity benefits from invalidity costs. It is possible, for example, that younger participants proactively use cues to anticipate targets and optimise performance, whereas older adults remain more reactive and show further deficits in reorienting attention when cues are invalid. In order to compare the pattern of cued temporal orienting effects in the two age groups, we conducted an additional experiment. In Experiment 3, we extend the blocked-design version of the tasks to include non-informative, neutral audio cues. By comparing performance after valid and invalid temporally predictive cues relative to these neutral cues, it becomes possible to titrate the contribution of validity benefits and invalidity costs, respectively, to the overall effect of temporal orienting.

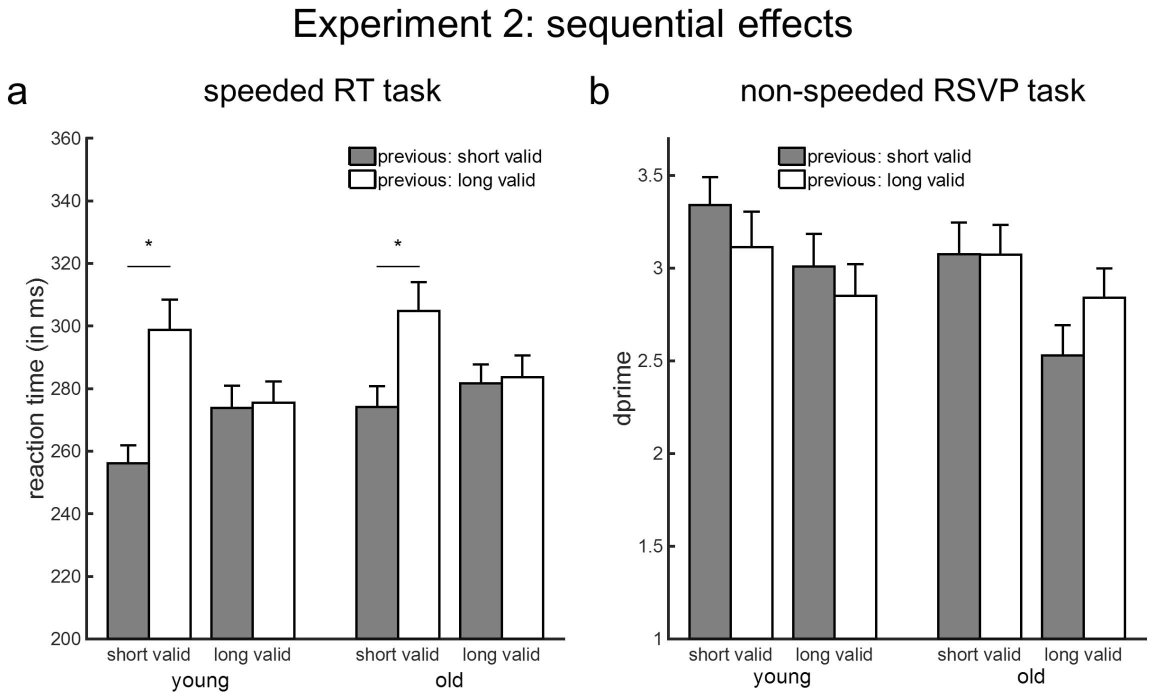

Figure 3.4 Sequential effects for the speeded RT task and RSVP task. Error bars represent SEM. The analysis was limited to validly cued targets preceded by validly cued targets. (a) Reaction time values (ms) in the speeded RT task. (b) Sensitivity scores (*d'*) in the RSVP task.

3.5 Experiment 3: Benefits and Costs of Temporal Cues

3.5.1 Method

Eighteen young (M_{age} 22.3, $M_{\text{education}}$ = 17.8 yrs, 12 females) and 20 older (M_{age} = 68.0, $M_{\text{education}}$ = 15.6 yrs, 12 females) volunteers took part. One older subject had to be excluded because of a score on the MOCA that indicated a Mild Cognitive Impairment (MCI), and two additional older participants had to be excluded from the speeded RT task due to technical difficulties during data acquisition. In this experiment, we replicated the design of Experiment 1, but we added to each task two 'neutral' blocks consisting of 48 trials each. In these blocks, targets appeared with equal probability after a short or long foreperiod, and a middle-pitched audio cue was used, which did not convey any information about the length of the upcoming foreperiod. Based on the effect sizes in younger adults observed in Experiment 1, an *a priori* power analysis suggested that we needed at least 5 participants in the speeded RT task and 10 participants in the RSVP task to achieve 80% power at two-sided 5% significance level to observe a significant difference between performance after valid and invalid cues (G-power: Faul & Erdfelder, 1992).

3.5.2 Results and Discussion

3.5.3.1 Speeded RT task

After removing the anticipatory responses, performance was at ceiling (<1% misses) for all four conditions in both age groups. One older participant was excluded from the RT analysis.

The findings indicated that blocked temporally predictive cues conferred both benefits and costs for detecting targets at the short interval in both age groups. We observed main effects of age, foreperiod, and cue validity; as well as a foreperiod-by-validity interaction on the RTs ($ps \leq .006$) (Table 3.4). Post-hoc paired-sample *t*-tests were conducted to inform the foreperiod-by-validity interaction, which was significant within each age group (young adults: $F(1.16,19.81) = 15.66$, G-G adj. $p = .001$, *F*-test permutation $p < .001$; old adults: $F(1.39,20.85) = 22.58$, G-G adj. $p < .001$, *F*-test permutation $p < .001$). Participants reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid versus neutral temporal information ($t(33) = -3.89$, $p < .001$). The benefit of having valid temporal information was associated with a medium effect size, both in young participants (Cohen's $d = .61$) and in old participants (Cohen's $d = .74$) (Figure 5a). In addition, participant responses were slowed down by the audio cue when it contained invalid versus neutral temporal information ($t(33) = 5.98$, $p < .001$). The cost of having invalid temporal information was associated with a large effect size, both in young participants (Cohen's $d = .97$) and in old participants (Cohen's $d = 1.24$) (Figure 5a). The validity of the auditory cue did not modulate RTs when the foreperiod was long (valid versus neutral: $t(33) = .68$, $p = .50$; neutral versus invalid: $t(33) = -1.01$, $p = .32$).

Analysis of the 'cueing index' for validity benefits and invalidity costs did not reveal a main effect of age (benefits: $F(1,32) = .21$, $p = .65$; costs: $F(1,32) = 2.53$, $p = .12$) or an interaction between foreperiod and age (benefits: $F(1,32) = .21$, $p = .65$; costs: $F(1,32) = .00$, $p = .98$).

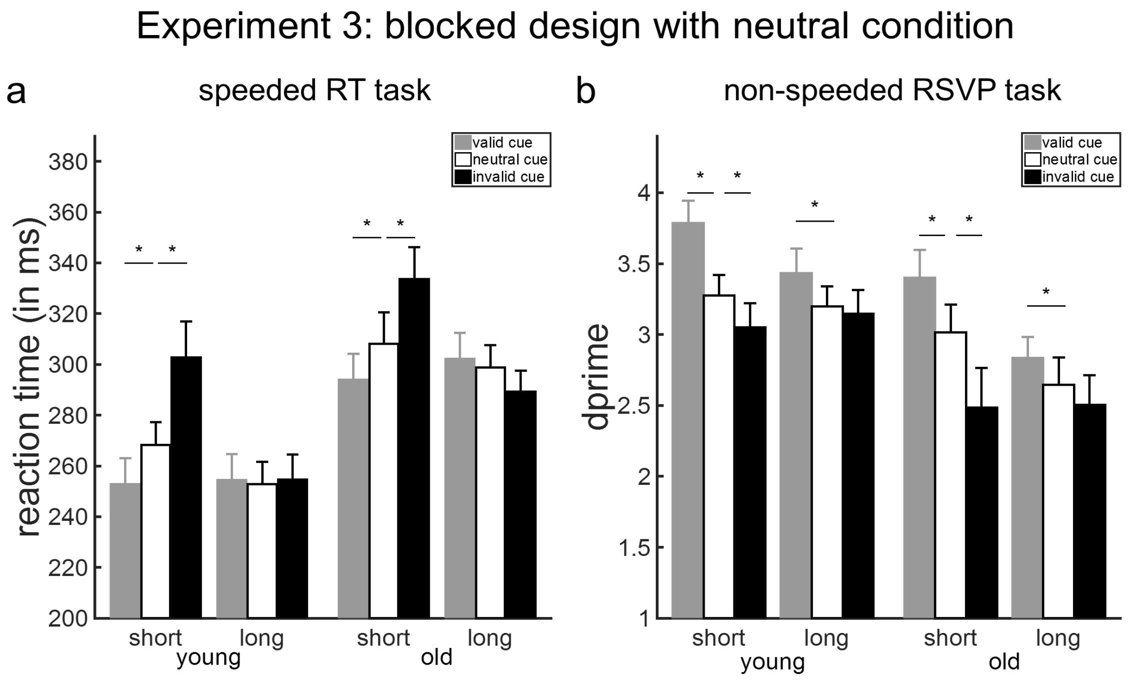

Figure 3.5 Temporal orienting effects in Experiment 3. (a) Effects of temporal expectations on reaction time values (ms) in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

3.5.3.2 RSVP task

No participant performed more than three SD's beyond the mean for any condition on perceptual discrimination, so all participants were included in the analysis. The results showed an equivalent pattern of costs and benefits for temporally predictive cues.

A three-way ANOVA on *d'*-values showed main effects of age, foreperiod, and validity; and a foreperiod-by-validity interaction (*p*s ≤ .01, see Table 3.5). There were no interactions involving age (*p*s ≥ .56, see Table 3.5). Post-hoc *t*-tests were run to inform the foreperiod-by-validity interaction. When the foreperiod was short, perceptual discrimination of a target was better when the audio cue was valid relative to when it was neutral ($t(36) = 3.37$, $p = .002$) (Cohen's *d* for young adults: .68, for old adults: .40), and worse when it was invalid compared to when it was neutral ($t(36) = -2.21$, $p = .03$) (Cohen's *d* for young adults: .35, for old adults: .40).

For long foreperiods, we also observed a performance benefit for valid compared to neutral audio cues ($t(36) = 2.42$, $p = .02$) (Cohen's *d* for young adults: .45, for old adults: .34). No significant difference was observed in perceptual discrimination performance between invalid versus neutral cues ($t(36) = -.72$, $p = .48$).

In summary, the introduction of blocks with non-informative neutral cues revealed that the pattern of benefits and costs conferred by blocked temporally predictive cues was equivalent for both types of task in younger and older participants. The findings suggest that older individuals are able to use temporally predictive cues proactively to anticipate targets and enhance their performance in both tasks that emphasize motor preparation and perceptual discrimination. The temporal orienting effects do not seem, therefore, to be restricted to deficits linked to excessive inflexibility or inability to reorient attention in time.

Table 3.4

Analysis of variance (ANOVA) on RT values from the speeded RT task

Effect	df1	df2	*F*	*p*	η^2
Experiment 1					
Age*	1	32	23.82	<.001	.42
Foreperiod*	1	32	55.56	<.001	.64
Foreperiod x Age	1	32	.31	.58	
Validity*	1	32	79.97	<.001	.71
Validity x Age	1	32	.001	.97	
Foreperiod x Validity*	1	32	114.25	<.001	.78
Foreperiod x Validity x Age	1	32	.33	.57	
Experiment 2					
Age	1	36	1.70	.20	
Foreperiod*	1	36	55.10	<.001	.64
Foreperiod x Age	1	36	2.33	.14	
Validity*	1	36	52.68	<.001	.60
Validity x Age	1	36	2.31	.14	
Foreperiod x Validity*	1	36	43.37	<.001	.55
Foreperiod x Validity x Age	1	36	1.35	.25	
Experiment 3					
Age*	1	32	8.62	.006	.32
Foreperiod*	1	32	24.16	<.001	.43
Foreperiod x Age	1	32	.57	.46	
Validity*	1.66	53.25	20.91	<.001†	.43
Validity x Age	1.66	53.25	2.18	.13†	
Foreperiod x Validity*	1.25	39.91	36.47	<.001†	.53
Foreperiod x Validity x Age	1.25	42.05	.03	.98†	

Note. * = significant effects; † = Greenhouse-Geisser adjusted *p*-value

Table 3.5

Analysis of variance (ANOVA) on d' values from the RSVP task

Effect	df1	df2	F	p	η^2
Experiment 1					
Age*	1	34	8.44	.006	.20
Foreperiod	1	34	2.00	.17	
Foreperiod x Age	1	34	2.29	.14	
Validity*	1	34	43.26	<.001	.56
Validity x Age	1	34	1.19	.28	
Foreperiod x Validity	1	34	2.41	.13	
Foreperiod x Validity x Age	1	34	3.43	.07	
Experiment 2					
Age	1	36	.09	.77	
Foreperiod*	1	36	10.99	.002	.23
Foreperiod x Age	1	36	1.06	.31	
Validity*	1	36	13.38	.002	.27
Validity x Age	1	36	.35	.56	
Foreperiod x Validity*	1	36	8.12	.007	.18
Foreperiod x Validity x Age	1	36	.02	.90	
Experiment 3					
Age*	1	35	7.23	.01	.17
Foreperiod*	1	35	5.37	.03	.13
Foreperiod x Age	1	35	1.18	.28	
Validity*	1.83	63.92	13.67	<.001†	.28
Validity x Age	1.83	63.92	.42	.64†	
Foreperiod x Validity*	1.66	58.25	4.11	.03†	.11
Foreperiod x Validity x Age	1.66	58.25	.19	.79†	

Note. * = significant effects; † = Greenhouse-Geisser adjusted *p*-value

Table 3.6

Experiment 2: Analysis of variance (ANOVA) on the sequential effects

Effect	df1	df2	*F*	*p*	η^2
Speeded RT task					
Age	1	36	1.08	.31	
Current Foreperiod	1	36	2.74	.11	
Current Foreperiod x Age	1	36	.47	.50	
Previous Foreperiod*	1	36	64.90	<.001	.64
Previous Foreperiod x Age	1	36	1.44	.24	
Current Foreperiod x Previous Foreperiod*	1	36	99.34	<.001	.73
Current Foreperiod x Previous Foreperiod x Age	1	36	3.23	.09	
RSVP task					
Age	1	36	.95	.34	
Current Foreperiod*	1	36	14.66	<.001	.29
Current Foreperiod x Age	1	36	.26	.62	
Previous Foreperiod	1	36	.09	.77	
Previous Foreperiod x Age*	1	36	8.02	.008	.18
Current Foreperiod x Previous Foreperiod	1	36	2.64	.11	
Current Foreperiod x Previous Foreperiod x Age	1	36	1.08	.31	

Note. * = significant effects.

3.6 Discussion

We investigated the effectiveness of predictive cues in driving temporal expectations in older adults. We found no evidence that temporal orienting of attention was compromised in healthy older adults. Rather, we found robust evidence that healthy older adults generate and use temporal expectations to improve performance both in tasks that emphasize motor preparation and those that emphasize perceptual discrimination. Analysis of the blocked and trial-by-trial cue designs confirmed that young and older participants benefited similarly from temporal expectations conferred by auditory cues to guide speeded responses (RT task) and perceptual discrimination (RSVP task). Inclusion of blocks with non-informative, neutral cues in the third and final experiment further demonstrated that the effects of temporal orienting in older adults come about through a similar pattern of validity benefits and invalidity costs as in the younger group. Although the benefits of temporal orienting are now very well established (for a review, see Nobre & Rohenkohl, 2014), our data represent the first demonstration of its robust preservation in ageing. Our findings, therefore, question the generality of the age-related deficits reported by Zanto et al. (2011) in tasks using visual temporal orienting cues. Indirectly, our findings also constrain interpretations of age-related deficits in tasks that manipulate general temporal preparation for imperative stimuli by introducing or manipulating foreperiods (Bherer & Belleville, 2004; Gottsdanker, 1982; Vallesi, et al., 2009; Wilkinson & Allison, 1989), suggesting that these should not be equated with temporal orienting deficits. Taken together, the findings support the growing notion that there may be several sources of temporal information acting upon stimulus processing through non-coextensive mechanisms to influence performance (see Nobre & Rohenkohl, 2014).

In our first, blocked-design experiment, the performance of older adults was on the whole less accurate and slower than that of the younger cohort, replicating previous findings (Drag & Bieliauskas, 2010; Kok, 2000; Salthouse, 2000; Vallesi al., 2009; Woodrow, 1914). Nevertheless, we observed strong cueing effects in both young and old participants in the speeded RT task, as well as in the perceptual discrimination task. Our results are consistent with previous temporal orienting studies that cue to only two moments in time (Correa et al., 2005; Coull, et al., 2000; Griffin et al., 2001), wherein the cue benefit is found to be larger in the short-foreperiod trials than in the longer-foreperiod trials. This is attributed to the predictive power of the unidirectional flow of time itself (Coull & Nobre, 1998; Nobre, 2001; Nobre, et al., 2007). In other words, as time passes, if the target does not occur at the short interval then participants know that it must occur at the longer one, allowing them to re-orient their attention accordingly. Importantly, in our study we replicate this asymmetric cueing benefit in our speeded RT task and demonstrate that this finding is of a similar magnitude in both age groups.

In the speeded RT task, there is also evidence of the use of cues in the supplementary analyses of anticipatory responses (see Appendix), with participants making more anticipatory responses when they are anticipating the target to occur after a short foreperiod. Both age groups made the majority of their anticipatory responses in the invalid-cueing condition in which they expected the target to appear after a short interval, but target presentation was delayed to the long interval. These results provide converging evidence that older adults are capable of internalizing temporal expectations to aid performance.

Puzzled by the contrast between the robust temporal orienting effects in older adults in our first study, and the absence of these effects across Zanto et al.'s (2011) three task conditions, we considered whether deficits in updating information about the cue prediction on a trial-by-trial basis could have masked their temporal expectation effects. We therefore ran a trial-by-trial version of our blocked experiments to test the hypothesis that older individuals might experience a deficit in dynamically and repeatedly encoding the cue information in order to orient their attention to the relevant time point, rather than a deficit in using temporal information to improve performance *per se*. Support for the claim that the executive demands imposed by fully intermixing temporally predictive cues can contribute to an expectation deficit in older adults would have occurred if older participants demonstrated a validity effect in the blocked design, but not in the trial-by-trial design. The results of our second experiment, however, convincingly replicated the primary findings from our first experiment. Again, we found reliable cue validity effects for both the speeded RT task and the perceptual discrimination task.

In addition to the replication of our blocked-design results, the trial-by-trial experiment allowed us to examine sequential foreperiod effects, which also tap into the consequences of temporal structure in the environment on performance (Los, 2010). Following previous studies (Capizzi et al., 2013; Drazin, 1961; Los & Van Den Heuvel, 2001; Steinborn et al., 2008; Vallesi & Shallice, 2007), our results in the speeded RT task indicated that response times on valid trials were improved when the current foreperiod was identical to the foreperiod used in the previous trial, but only when the foreperiod was short. This asymmetrical sequential effect was present in both age groups. That is, participant RTs to early targets were faster if the previous foreperiod was short as compared to when it was long; whereas, there were similar RTs for late targets independent of whether the previous interval was short or long. The strength of the foreperiod effects in our study is all the more surprising when one considers that the effects survived the delay between trials, which included self-initiation of each trial.

Recently, it has been argued that different types of temporal expectation can be distinguished — for example, separating the effects of the sequential effects carried over across trials from other temporal orienting effects (Correa et al., 2004; Los & Van Den Heuvel, 2001). As it was argued in Chapter 1 where similar sequential effects were discovered, one possible interpretation is that these effects may arise from non-overlapping mechanisms (Capizzi et al., 2012; Triviño et al., 2010; Triviño, Arnedo, Lupiáñez, Chirivella, & Correa, 2011), whereby the observed sequential effects may be dependent on more basic and automatic mechanisms (see Vallesi et al., 2009). If this is true, then the older participants here should be thought of as having multiple types of temporal expectations intact.

The abovementioned results in the blocked and trial-by-trial studies do not support sweeping deficits in top-down control or expectations in older adults. Instead, both younger and older adults demonstrated an ability to orient their attention in time. Though older participants may be slightly slower and slightly less accurate in some contexts, our results clearly suggest that temporal expectations can be spared. This left us to question why our findings differed from those previously reported. One important difference was our use of valid versus invalid cues as compared to Zanto et al.'s (2011) use of valid versus neutral cues. The different cue-validity conditions used in our first two experiments left open the possibility that our sample of older participants did not benefit from temporal expectations conferred by the cues, but instead were hindered by breaches of expectation.

Our third experiment explored whether our findings reflected primarily invalidity costs, rather than cueing benefits. The results of our third experiment, which included neutral cues, replicated the findings in our first two experiments, confirming that older adults are able to make use of temporal cues to optimize behavioural performance — as evidenced by enhanced motor and perceptual abilities. Support for the claim that the behavioural benefits we observed in our first experiment were solely down to the costs of invalid cues would have been garnered had we found no significant difference between valid and neutral trials. Instead, our results confirmed the presence of reliable cue-validity benefits. Invalidity costs were also observed, with a similar pattern across both age groups. Our results, therefore, provide strong evidence for comparable orienting of attention in time between age groups.

Whereas researchers have argued that older participants may have deficits in inhibitory control (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Hasher, Zacks, & Rahhal, 1999), the participants in our three studies were no worse than young participants in making anticipatory responses. In fact, older adults were marginally better at inhibiting responses, with younger adults making more anticipatory responses in the late invalid conditions (see Appendix). In contrast to Pincham, Killikelly, Vuillier, & Power (2012), who argue that Zanto et al.'s (2011) results might be evidence of a deficit in proactive control, rather than expectation, the older adults in our studies seem to be less impulsive in our two blocked design speeded RT tasks than their younger counterparts. Compared to the younger adults, the older adults in our study are more inhibited and less reactive.

In line with the age differences observed in the RT effects on our blocked design experiments, these results are at least somewhat consistent with the research that reports an age-related slowing on speeded RT tasks (Salthouse, 1996), and are consistent with the suggestion that older adults tend to be more cautious (Lindenberger & Mayr, 2014). However, the precise explanation for these age-related differences in the number of anticipatory responses remains difficult to pinpoint, and could reflect a mixture of age-related differences: in overall impulsivity and inhibition (Connelly & Hasher, 1993; Hasher, Stoltzfus, Zacks, & Rypma, 1991; Tipper, 1991); the extent to which the two age groups internalise predictions by the cues (e.g. reflecting differences in top-down control, see Zanto & Gazzaley (2014) for review); the rate or efficiency with which the groups can orient or re-orient attention (see Cona, Bisiacchi, Amodio, & Schiff, 2013); and/or the faster speed of young participants' responses constraining the ability to withhold a prepotent response.

It is important to consider the possible influence of our task parameters in unveiling cued temporal expectation effects in the older participants. Traditionally, the ageing literature focuses almost exclusively on unimodal paradigms (e.g. visual or auditory) when comparing young and old performance (for review see Guerreiro, Murphy, & Van Gerven, 2010). In contrast, our task design used auditory cues to guide visual temporal orienting. It may be that auditory cues are more intuitive or more efficient at guiding temporal predictions. Alternatively, visual cues may cause interference with the visual target, whereas auditory cues do not engage the visual system and are therefore less disruptive. Some support for this can be seen from data showing that older adults take longer to disengage from visual stimuli compared to younger adults (e.g., Cona et al., 2013) and age-related performance declines due to distraction are minimal (if at all) when presented with relevant/irrelevant stimuli in different modalities (i.e., auditory and visual) (reviewed in Guerreiro et al., 2010). By increasing task demands, or experimenting with different types of cues, future studies could look to separate these effects and explore the extent to which the salience and task appropriateness of the cue might contribute to differences in behavioural outcomes. To the extent that extraneous task variables have deleterious effects, it would be prudent to revisit other types of expectation deficits in the elderly.

Finally, task performance in different age groups may vary as a consequence of different strategies or state variables, such as attentional time-sharing (e.g. decreased divided attention), fatigue, or boredom (Lustig, 2003; Lustig & Meck, 2001). It is possible, although somewhat speculative, that our participants were less fatigued than those in Zanto et al.'s (2011) study, which involved a lengthier set-up time for EEG investigation. Demographic variables, such as years of education, have also been suggested to influence the preservation of certain cognitive abilities — though this is in itself debatable (Anstey & Christensen, 2000; Zahodne et al., 2011). On the surface, our older cohort had similar levels of education and performance levels on neuropsychological tests as those in Zanto et al.'s study (2011), though it remains possible that subtle differences in some other demographic or neuropsychological factor might contribute to the different nature of our findings.

Being able to use top-down control proactively to stay focused and optimise performance in the task at hand is essential to cognitive well-being. Building on our promising findings, it will be important to continue to explore the boundaries of conditions that enable older adults to make use of temporal cues. Moreover, given that we have identified a task in which both older and younger adults are able to utilize temporal information to orient their attention and suppress irrelevant or distracting information (i.e. in the case of the perceptual discrimination task), future studies could use our paradigm to explore the neural mechanisms involved in temporal expectation, the degree to which they are separable, and their preservation in healthy ageing.

3.7 Conclusion

If age-related differences in temporal expectation exist, it is probably too early to conclude that older adults suffer from a categorical deficit. The deviation of our findings from Zanto et al.'s (2011) suggests that more work ought to be done to uncover the conditions for an expectation deficiency. That is, to the extent that research into temporal expectation in ageing is motivated by designing ageing-friendly environments, ageing research must involve an investigation into the boundaries of ageing-related shifts in internal-to-external processing. For instance, the use of simple cues that provide intuitive stimulus driven associations may be more appropriate as an aid to guide behaviour in various adaptive contexts. Our results provide the first demonstration that temporal expectation can work on its own to enhance behavioural performance well into old age. More work ought to be done to ascertain the point at which temporal orienting of attention declines in healthy ageing, and to uncover the limits of this effect.

While demonstrating that temporal orienting can be preserved in healthy older adults, Chapter 2 and 3 are unable to offer any insight into the brain regions and mechanisms responsible for the preservation of this ability. In the following set of experiments, I take this investigation further by testing whether or not temporal orienting can be preserved when there is dysfunction in subcortical structures known to be involved in temporal processing.

4 Temporal orienting in Parkinson's disease

Chapter Abstract

Failure to orient attention to moments in time can lead to impaired behavioural performance. As we have seen in the previous chapters, flexible cue-based temporal expectations can be used to enhance behavioural performance and modulate perceptual functions in healthy old and young adults. In patients with Parkinson's disease (PD), studies have reported significant deficits in temporal processing and temporal preparation abilities. To investigate the generality of these deficits, participants with PD and healthy older adults were invited to take part in a study investigating temporal expectation at the interval time scale. As in Chapter 3, a reaction time (RT) task emphasizing speeded responding and a non-speeded rapid-serial-visual-presentation (RSVP) task emphasizing visual discrimination are used to assess temporal orienting ability. The performance of eighteen participants with PD 'off' dopaminergic medication is compared to the behavioural performance of eighteen age-matched controls. In both tasks, auditory cues indicate the likelihood of a target item occurring after a short or long temporal interval (foreperiod; 75% validity). In line with previous findings, results show that healthy controls are able to benefit from auditory temporal cues to improve their motor responses and perceptual discrimination. In contrast, whereas cued temporal expectation conferred performance advantages for participants with PD on a speeded-RT test, there is no significant improvement in perceptual judgements on the RSVP task. Overall, this suggests that PD patients can benefit from cue-based temporal expectation, but these behavioural advantages may be constrained by task- and domain-relevant factors. Further research should be done to determine whether there are distinct neural networks being used to orient attention in time for enhancement of motor responses and optimizing perceptual discrimination.

4.1 Introduction

In his book *Awakenings*, Oliver Sacks (1990) depicts what it may be like to live with Parkinson's disease (PD), and highlights the astonishing distortions of space and time that such patients are liable to experience. To illustrate the type of spatial distortions in perception that can occur, Sacks summarizes the challenges faced by one patient with PD named Frances. In her own words:

> It's not as simple as it looks. I don't just come to a halt, I am still going, but I *have run out of space to move in*…You see, *my* space, *our* space, is nothing like *your* space: our space gets bigger and smaller, it bounces back on itself, and it loops itself round till it runs into itself (p. 339).

This, and other examples given by Sacks (1990), suggests that our subjective experiences of space *and* time can become unreliable — warped by some underlying pathology. While there may be reasons to suppose that *our time* (i.e. a healthy person's perception of time) can be rendered unlike the temporal experience of those with PD, neuropsychological research into the subject has only recently been able to provide us with some insight into the underlying aetiology of this distortion.

PD is recognized as a neurodegenerative disorder that primarily affects the basal ganglia through dopamine (DA) depletion in the striatum (Allman & Meck, 2012; Jones & Jahanshahi, 2014). As reviewed in Chapter 1 (section 1.3.3), a number of important neuroscientific findings have helped to characterise the underlying mechanisms and brain structures implicated in temporal processing. These experiments have shown that the basal ganglia and the associated subcortical dopaminergic system play an important role in temporal processing (Buhusi & Meck, 2005; Meck, 1996; 2005) and in interval timing in particular (for reviews, see: Coull, Cheng, & Meck, 2011; Matthews & Meck, 2016; Meck & Benson, 2002; Meck, et al., 2008; Merchant & Harrington, 2013). Given the basal ganglia's association with interval timing, and PD's pattern of neurodegeneration, participants with PD represent an ideal model to study the effects of basal ganglia dysfunction on temporal aspects of attention.

In this chapter I was interested in testing whether PD could lead to deficits in temporal expectations. Before outlining the experimental procedures that I have used to measure temporal orienting in this clinical group, it is worth reviewing some of the research that has demonstrated deficits related to temporal aspects of cognition. To begin, I will provide a brief overview of relevant findings related to motor timing deficits in PD. From there, I will summarize some of the results taken from studies that have examined non-motor deficits, such as deficits in temporal perception, which could impinge on the ability to make use of temporal cues to enhance perceptual performance. I will then conclude with an introduction to the experimental procedures that were used to examine whether temporal orienting cues can be used to enhance motor responses and perceptual judgement within this clinical group. While deficits in timing are commonly observed across motor and perceptual domains in PD (Jones & Jahanshahi, 2014), whether it is possible to improve behavioural performance within these attentional domains using cue-based temporal expectations is still unresolved.

4.1.1 Motor deficits

All movement is necessarily extended in time, and, as such, it is inherently a temporal process. This claim is easily intuited if one reflects on how motor coordination fundamentally relies on various muscles having to be activated in the correct sequences at the appropriate moments in time (e.g. consider again the example of catching a ball in section 1.2).[7] In the case of PD, disruption in coordinated movement and general motor deficits are often reported (O'Boyle, Freeman, & Cody, 1996), and these deficits — subsuming deficits in timing — have been tied to dopaminergic dysfunction within the basal ganglia (Meck, 2005; Wiener, Lohoff, & Coslett, 2011). While DA in the basal ganglia regulates the precision of temporal preparation of motor responses in healthy participants (Jones & Jahanshahi, 2014; Tomassini, Ruge, Galea, Penny, & Bestmann, 2016) — and plays an important role in the initiation, planning, and programming of movement — for people with PD, the DA depletion in the striatum and motor areas of the cerebral cortex contributes to a breakdown in temporal preparation and the accurate timing of a motor responses (Gaspar, Duyckaerts, Alvarez, Javoy-Agid, & Berger, 1991; Malapani et al., 1998). As a result, the basal ganglia are rendered unable to support the synchronization of the output elements of the motor cortex (Braunlich & Seger, 2013). With the breakdown of this subcortical input, activity in the motor cortex — and thus the pattern of muscle discharge — can become arrhythmic (Brown & Marsden, 1998; Jurkowski, Stepp, & Hackley, 2005; Praamstra & Pope, 2007; Salenius, Avikainen, Kaakkola, Hari, & Brown, 2002) leading to some of the cardinal symptoms of PD, such as movement difficulties including: bradykinesia (slowness in movement initiation and execution), akinesia (lack of movement), muscle rigidity, muscle weakness, and tremors at rest (see Sheridan, Flowers, & Hurrell, 1987).

The consequences of PD and the associated damage to the basal ganglia on motor responses and timing are also evident across a number of reaction time and movement-related studies. These studies have found that sufferers of PD tend to experience a number of motor impairments, including: increased manual reaction times (Bloxham, Dick, &

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[7] The connection of timing to action and/or motor coordination is reviewed in section 1.3.2 — see also Coull (2014) and recent research by Morillon and colleagues (2016).

Moore, 1987; Evarts, Teräväinen, & Calne, 1981); increased speech production times (Lieberman, Kako, Friedman, & Tajchman, 1992; Volkmann, Hefter, Lange, & Freund, 1992); impairment in the production of simultaneous and sequential movements (Benecke, Rothwell, Dick, Day, & Marsden, 1986; 1987); consistent difficulties in being able produce the temporal components of movement, e.g. in planning and synchronizing motor activity required to maintain a fixed rhythm (Freeman, Cody, & Schady, 1993; Nagasaki & Nakamura, 1978; Nakamura & Nagasaki, 1978; O'Boyle et al., 1996; Wing, Keele, & Margolin, 1984); and profoundly deficient temporal preparation abilities in rhythmic tasks (see Praamstra & Poper, 2007). Many of these deficits are also evident in 'beat-based' timing tasks, in which the timing of motoric responses to a specific rhythm is found to be significantly less accurate in participants with PD than healthy controls for metric simple rhythms (Grahn & Rowe, 2009). (Incidentally, beat-based timing has been consistently shown to activate the basal ganglia (Grahn & Brett, 2007; Grahn & Rowe, 2013), and has been found to worsen with the severity of the disease (Cameron, Pickett, & Earhart, 2016).)

The finding that DA depletion and degradation of the basal ganglia contribute to impaired motoric responses has led to increased exploration of whether there is a fundamental timing disturbance in PD that could underlie the observed motor slowness and deficits in synchronizing movement. While it seems to be the case that patients with PD are deficient in reproducing the temporal components of movement (Malapani et al., 1998), there has been some uncertainty as to whether this reflects a deficit related to temporal processing or is simply a reflection of a more general motor deficit. Although the independence of temporal processing deficits and motor deficits is debateable — and likely relies on significant overlap — Levit-Binnun and colleagues (2007) demonstrated that the timing processes involved in controlling the tapping movement (i.e. using a finger tapping task) and the motor processes in charge of execution of the motor commands can be dissociated, ultimately relying on distinct neural systems.

In sum, degeneration of the basal ganglia in PD seems to result in motor-related symptoms, and deficits in motor timing are common. As PD progresses, these effects often worsen. Though motor coordination is inherently a temporal process, the extent to which there may be non-motor related timing processes underlying the observed motor deficits remains a matter of debate.

4.1.2 Non-motor timing deficits

Over the years that PD has been studied, it has become clear that it cannot be wholly described as motor disorder (Chaudhuri & Schapira, 2009). In addition to the more common motor deficits observed in PD that have come to characterise the disease, non-motor timing-related deficits have also been widely reported. These deficits include: impaired temporal discrimination of stimuli in visual and auditory modalities (Artieda, Pastor, Lacruz, & Obeso, 1992); impaired time estimation (Lange, Tucha, Steup, Gsell, & Naumann, 1995)[8]; and deficits in the reproduction and verbal estimation of temporal intervals (Pastor, Artieda, Jahanshahi, & Obeso, 1992).

It has been hypothesized that the compromised fronto-striatal connectivity in PD may also have a negative effect on the processes that underpin perceptual timing judgments (Perbal, et al., 2005; Wild-Wall, Willemssen, Falkenstein, & Beste, 2008), leading to deficits on perceptual timing tasks in the interval timing range (Koch et al., 2008; Rammsayer & Classen, 1997; Smith, Harper, Gittings, & Abernethy, 2007) that worsen as the disease

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[8] In contrast, Riesen & Schnider (2001) have claimed that the time estimation (or the 'feeling of the flow of time') is normal in PD patients despite the observation that there may be an impairment when it comes to discrimination of brief intervals in the range of seconds.

progresses (Pastor, Artieda, Jahanshahi, & Obeso, 1992; Wearden et al., 2008). However, perceptual timing deficits can often be ameliorated by dopaminergic medication or deep brain stimulation (DBS) of the subthalamic nucleus (STN) (Guehl et al., 2008; Koch et al., 2004; Wojtecki et al., 2011).

If the basal ganglia did not play an important role in timing, or if timing was more distributed, one might not expect timing deficits on perceptual tasks. However, taken together with the deficits in the motor domain, concomitant deficits in temporal perception and non-motor timing-related tasks provide evidence for a more generalized timing deficit in PD.

4.1.3 Overview of investigation

As we have seen in previous chapters, temporal expectations that involve extracting temporal predictions and regularities from the environment are used to facilitate various aspects of cognition, from preparing and executing motor responses to perceptual discrimination. However, the extent to which temporal expectations (explicit or implicit) can be used to improve motor and perceptual performance in PD is only just beginning to be studied.

At the time of writing, external cues (both auditory and visual) have been shown to aid PD patients on a variety of tasks related to timing. For instance, rhythmic auditory cues have shown great promise in improving gait impairments in PD, which are otherwise difficult to treat with pharmacological interventions (Baker, Rochester, & Nieuwboer, 2007; Rochester, et a., 2007; Rochester, et al., 2010; Rubinstein, Giladi, & Hausdorff, 2002; Lim et al., 2005; te Woerd, Oostenveld, Bloem, de Lange, & Praamstra, 2015; Warlop, et al, 2015). These rhythmic cueing-based interventions usually require patients to synchronize footsteps to metronome cues (for reviews, see Keus, Bloem, Hendriks, Bredero-Cohen, & Munneke, 2007; Rubinstein, et al., 2002; Spaulding et al., 2012), but musical rhythms have also been shown to facilitate movement in PD (Nombela, Hughes, Owen & Grahn, 2013). In addition to auditory cues leading to benefits in gait, it has also been found that coupling gait to rhythmic auditory cues can improve motor and perceptual timing (Benoit, et al., 2014). Moreover, auditory cues have also been used to help PD patients synchronize finger tapping (Freeman, et al., 1993) and visual stimuli (i.e. symbolic arrow cues) have been used as an aid in improving movement initiation (Praamstra, Stegeman, Cools & Horstink, 1998).

While these studies highlight the possibility of using temporal cues to improve behavioural performance in PD in some contexts (mostly motor), comparatively few investigations have examined the utility of external cues to improve perceptual performance. As we examined in Chapter 1, temporal information coded implicitly plays a central role in adaptive behaviour and there are many types of temporal expectations, which may rely on different mechanisms. Mechanisms related to explicit timing have been proposed to differ substantially from mechanisms related to using timing implicitly to guide other forms of perceptual or motor acts (for review, see Coull & Nobre, 2008). In a recent study that investigated temporal expectations implicitly in PD by measuring the latency of anticipatory eye movements in a target pursuit task, de Hemptinne and colleagues (2013) found that PD patients made fewer anticipatory eye movements, but the timing of the anticipation of target motion reversal was similar to controls. In other words, anticipatory eye movements and the implicit timing of salient events seemed to be largely unaffected by PD. These results were interpreted as supporting the hypothesis that implicit and explicit timing are differently affected by basal ganglia dysfunction.

Though many of the highlighted findings in the preceding sections evince motor and non-motor timing-related deficits caused by PD, none of the experiments were specifically designed to measure the effects of cue-based temporal orienting. While there seems to be some indication of temporal expectation deficits in PD in rhythmic tasks (e.g. Praamstra, et al., 2007), it remains unclear whether these timing-related deficits generalise to the implicit use of temporal information to guide perception and action. In both the motor and perceptual domain it is plausible that attentional cues could be used to direct one's attention to specific moments in time to optimize behavioural performance.

In the following chapter, I question whether temporal deficits extend to the use of temporal predictions to optimise the efficiency of motor responses and perceptual functions in PD. As with other studies that have used cues to help participants make predictions about when the environment will change (i.e. when to pay attention) or when a motor action is required (e.g. Coull & Nobre, 1998; Nobre, et al., 2007), the investigation herein explores the performance of PD patients and healthy older adults on tasks that use temporal information to manipulate attention. As in Chapter 3 (*Experiment 1*) participants completed two tasks: a reaction-time task that emphasized speeded responding and a non-speeded RSVP task that emphasized visual discrimination. Auditory cues indicated the likelihood of a target item occurring after a short or long temporal interval (foreperiod) (75% validity). In the speeded-RT task, participants were asked to respond as quickly as they could to a green circle that appeared at the centre of the screen. Reaction times were measured in order to examine whether benefits were conferred by temporal expectation. In the non-speeded perceptual discrimination task, participants were asked to make a judgment about whether they saw an 'X' or an 'O' in a stream of rapidly presented letters. Using *d*-prime as a measure of perceptual sensitivity, discrimination performance for the target letter was assessed. This experiment was conducted alongside a much larger investigation utilizing MEG and fMRI to record brain activations of the participants as they completed computerised motor-response tasks. For the purposes of this chapter, however, only the behavioural findings from the temporal orienting tasks will be presented. Given the reduction of dopaminergic neurons in the basal ganglia in PD (Jahanshahi et al., 2010), and the presumed influence of the basal ganglia on temporal processing tasks (Meck, 2005), it is expected that participants with PD (when 'off' medication) will evince a deficit in temporal orienting abilities. However, given that external cues have been found to improve behavioural performance in PD across other motor domains, it is possible that temporal orienting cues can be used to ameliorate deficits.

4.2 Methods

4.2.1 Participants

All experimental methods received ethical approval from the Oxfordshire Research Ethics Committee as part of the National Research Ethics Service (NRES) (Reference number: 12/SC/0650). Eighteen patients with idiopathic PD ($M_{\text{age}} = 68.9$, $M_{\text{education}} = 13.8$, 8 F) and 18 age- and education-matched healthy controls ($M_{\text{age}} = 67.3$, $M_{\text{education}} = 15.1$, 9 F) were invited to participate in the study following a screening procedure. The healthy participants in the control group were an independent sample compared to those in other chapters. The screening procedure was aimed at excluding any volunteer with metal implants in their body that would cause artefacts in the MEG and MRI recordings or with claustrophobia. In addition, participants were excluded if they were active participants in a clinical drug trial; if they were taking psychotropic, hypertensive or vasoactive medication; or if they self-reported neurological, head injury, or psychiatric history (other than a history of PD for the clinical group). Since PD participants were asked to withdraw from taking their PD medication the night before participating in both experimental sessions, volunteers were excluded from participating if they could not tolerate coming off their PD medication.

All participants provided informed consent. Most participants were right handed except for one participant in the PD group and two participants in the control group who were left handed; and all participants had normal or corrected-to-normal vision. PD participants were asked to withdraw from their dopaminergic medication at 19:00 hr the night before the experiment, so that the duration of time they withdrew from their medication (i.e. between 15 and 20 hours) was comparable across all other participants in the PD group. The amount of time PD participants were off their medication is comparable to other studies that have investigated the effects of PD on timing-related experiments (e.g., O'Boyle et al., 1996).

PD participants were recruited with the help of the Dementias and Neurodegeneration (DeNDRoN) Specialty and fulfilled the UK PD Brain-Bank criteria for probable Parkinson's disease (Hughes, Daniel, & Kilford, 1992). When requesting names of participants from DeNDRoN to invite to participate in the study, it was asked that all adhere to the following set of criteria: (i) diagnosed within 5 years of the participation date, (ii) native English speaker, and (iii) above the age of 50. Healthy older adults were recruited from the Oxford Dementia and Ageing Research database (Friends of OxDARE: http://www.oxdare.ox.ac.uk/become-a-friend), and names were selected based on being similar in age and education to PD participants.

4.2.2 Neuropsychological Evaluation

The neuropsychological evaluation consisted of tests designed to assess general cognitive function (Montreal cognitive assessment (MoCA, version 7.1; Nasreddine et al., 2005; Hoops, et al., 2009), attention/task switching (Trail making test (TMT); Reitan, 1958; Reitan & Wolfson, 1985; Tombaugh, 2004), executive function (Rey-Osterrieth Complex Figure test (RCF); Fastenau, Denburg, & Hufford, 1999; Osterrieth, 1944; Rey, 1941), semantic memory (Category fluency—names of animals 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, Freed, Williams, & Henderson, 1992), verbal working memory (Digit span; Wechsler, 2008), premorbid intelligence quotient (Test of premorbid functioning (TOPF); Wechsler, 2009), and motor function (Purdue Pegboard; Desrosiers, Hebert, Bravo, & Dutil, 1995). The test scores are summarized in Table 4.1.

To verify PD diagnosis and confirm that healthy controls did not present PD symptoms, 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 when participants were off medication at the beginning of the first and/or second phase of the study as outlined in section 4.2.5 of this chapter. (Importantly, high levels of test-retest reliability have been reported in patients with advanced PD for the UPDRS measure (Metman, et al., 2004)). In addition, the severity of the disease was evaluated using the motor subscale of the unified Parkinson's disease rating scale, the Hoehn and Yahr (1967) scale, which is a subset of the UPDRS-III. The H&Y scale ranks the symptoms of PD from 1 to 5, where 5 is most severe (e.g. 'confinement to bed'). Since symptom dominance tends to be asymmetrical in PD (van der Hoorn, Bartels, Leenders, &

de Jong, 2011; van der Hoorn, Burger, Leenders, & de Jong, 2012), left/right dominance of symptoms were examined using the UPDRS III lateral scores and the Purdue Pegboard responses. It is important to note, however, that the Purdue Pegboard values may not be ideal to measure symptom lateralisation, since dominance of handedness may affect these values. Symptom Asymmetry Scores (SAS) were therefore calculated by summing the left/right scores on sections 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.15, 3.16 and 3.17 of the UPDRS-III, then subtracting the left and right lateralisation values and dividing by the sum of left and right lateralisation values (i.e. (L-R)/(L+R)). Scores on examination and test scores relevant for PD are summarized in Table 4.2.

Table 4.1.

Mean scores from the neuropsychological evaluation conducted in participants with PD and healthy controls.

	PD (*n* = 18, 8F)				Controls (*n* = 18, 9F)				
	Mean	Range	SE	> 2 SD*	Mean	Range	SE	> 2 SD*	P
Age	68.9	54 - 79	1.6	n.a.	67.3	60 - 76	1.1	n.a.	n.s.
Education	13.8	10 - 23	0.8	n.a.	15.1	10 - 20	0.9	n.a.	n.s.
MoCA	26.2	18 - 29	0.7	4.0	28.3	26 - 30	0.3	0.0	<.05
TMT: A (s)	36.0	14.81 - 56.61	2.9	0.0	28.5	15.15 - 50.34	2.3	1.0	n.s.
TMT: B (s)	86.7	29 - 214	12.2	2.0	57.5	23.22 - 188	8.8	1.0	< .05
ROCFT									
Copy (out of a possible 36)	29.1	5 - 36	1.7	2.0	31.5	17.5 - 36	1.2	2.0	n.s.
Immediate (out of a possible 36)	16.6	1.5 - 28	1.7	1.0	18.5	5.5 - 33	1.7	1.0	n.s.
Delay (out of a possible 36)	15.0	2.5 - 25.5	1.7	2.0	19.7	4.5 - 31	1.9	0.0	n.s.
Category Fluency	20.9	13 - 29	1.2	n.a.	22.1	14 - 31	1.0	n.a.	n.s.
HVLT-R									
Trial 1	4.6	3 - 7	0.3	n.a.	5.6	3 - 9	0.4	n.a.	<.05
Trial 2	6.1	3 - 9	0.4	n.a.	7.6	3 - 11	0.5	n.a.	<.05
Trial 3	7.2	3 - 11	0.6	n.a.	8.9	5 - 12	0.5	n.a.	<.05
Learning	2.6	-4 - 6	0.6	3.0	3.3	-1 - 7	0.6	4.0	<.05
Sum of 1-3	17.9	9 - 26	1.0	1.0	22.1	15 - 32	1.1	0.0	n.s.
Delayed Recall	5.3	0 - 11	0.7	4.0	7.9	0 - 12	0.7	1.0	<.05
Percent Retained (%)	73.1	0 - 233**	12.1	n.a.	87.0	0 - 120	6.1	n.a.	<.05
True Positives	10.3	6 - 13	0.4	n.a.	10.8	8 - 12	0.3	n.a.	n.s.

False Positives	1.6	0 - 4	0.2	n.a.	1.1	0 - 3	0.2	n.a.	n.s.
Discrimination Index	8.7	3 - 11	0.5	2.0	9.7	7 - 12	0.4	0.0	n.s.
BNT	14.4	12 - 15	0.2	0.0	14.8	14 - 15	0.1	0.0	n.s.
Digit Span (Scaled Score)	9.4	4 - 13	0.7	1.0	11.3	7 - 16	0.6	0.0	n.s.
Purdue Pegboard Right	11.1	4 - 15	0.7	6.0	13.1	8 - 16	0.4	1.0	<.05
Purdue Pegboard Left	10.1	6 - 15	0.5	3.0	12.8	9 - 15	0.3	1.0	<.001
Purdue Pegboard Both	8.6	4 - 13	0.5	5.0	10.6	8 - 14	0.3	0.0	<.01
Purdue Pegboard Sum	29.7	19 - 42	1.4	7.0	36.4	25 - 42	0.9	1.0	<.001
Purdue Pegboard Assembly	19.6	10 - 36	1.7	5.0	28.0	20 - 37	1.3	0.0	<.001
TOPF - FSIQ	110.0	89.2 - 129	3.0	0.0	114.1	89.3 - 134.3	3.3	0.0	n.s.
UPDRS - III	33.2	11-81	4.01	n.a.	1.3	0-4	.4	n.a.	<.001
H & Y	1.78	1-3	.15	n.a.	0	0	0	n.a.	<.001

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 Fig. 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 patients and healthy controls, Mann–Whitney non-parametric test (n.s., non-significant).

Table 4.2

Clinical details of the PD group.

Patient	Gender	Age (years)	Handedness	SAS	LS	Purdue Pegboard (R)			Purdue Pegboard (L)			HY	UPDRS-III	YSD	LEDD
						Score	Norm Mean	Norm SD	Score	Norm Mean	Norm SD				
P1	F	68	R	-.29	L	14	14.3	1.3	9	13.7	1.3	3	49	2	400
P2	M	67	R	.11	R	9	12.7	1.5	8	12.7	1.5	2	51	2	400
P3	F	63	R	-.05	L	15	14.3	1.3	14	13.7	1.3	2	23	1	300
P4	M	68	R	.38	R	4	12.7	1.5	11	12.7	1.5	1	43	2	400
P5	M	73	R	.06	L	7	11.2	1.9	8	10.7	2.1	2	48	2	300
P6	M	54	R	-1.0	L	15	n.a.	n.a.	10	n.a.	n.a.	1	15	2	0
P7	M	59	L	.54	R	12	n.a.	n.a.	15	n.a.	n.a.	1	17	2	400
P8	M	72	R	.25	R	13	11.2	1.9	8	10.7	2.1	2	30	1	300
P9	F	62	R	.33	R	9	14.3	1.3	9	13.7	1.3	2	37	4	380
P10	M	74	R	-.24	L	9	11.2	1.9	9	10.7	2.1	2	27	4	900
P11	F	73	R	-.39	L	11	12.7	1.8	9	11.8	1.8	2	23	4	888
P12	F	77	R	-.06	L	14	12.7	1.8	12	11.8	1.8	1	30	4	750
P13	F	65	R	-1.0	L	10	14.3	1.3	10	13.7	1.3	1	11	4	600
P14	M	74	R	-.2	L	9	11.2	1.9	6	10.7	2.1	3	81	4	650
P15	F	75	L	-.63	L	13	12.7	1.8	11	11.8	1.8	1	19	2	0
P16	F	66	R	.31	R	13	14.3	1.3	12	13.7	1.3	2	38	2	320
P17	M	79	R	.29	R	11	11.2	1.9	10	10.7	2.1	2	21	4	300
P18	M	71	R	-.24	L	11	11.2	1.9	10	10.7	2.1	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/days

n.a. = relevant normative data not available.

4.2.3 Apparatus

Stimuli for the behavioural tasks were created and presented through Presentation software (16.5, Neurobehavioural systems, Albany, CA, United States of America). The experiment was run on an ASUS Notebook M50SV Series Notebook PC, Intel(R) Core(TM)2 Duo CPU, HDD NVIDIA GeForce 9500M GS, with a 15.4 inch screen (resolution 1440 x 900 pixels, refresh rate 60 Hz). Participants were seated in a dimly lit room, approximately 55 cm away from the monitor. Responses were collected using a standard keyboard.

4.2.4 Stimuli and experimental design

Performance data were recorded using a shorter version of Experiment 1, outlined in Chapter 3.2.3. Each assessment consisted of a speeded RT task and a non-speeded RSVP task. Participants completed two blocks of each task (192 trials each). In the speeded-RT task, participants were instructed to respond as quickly as they could to a green circular patch, which appeared at the centre of the screen. In the RSVP task, participants were instructed to identify a target letter ('X' or 'O') embedded in a stream of fourteen rapidly presented letters and to provide a non-speeded response at the end of the trial.

Both tasks followed the same basic design (Figure 3.1). Participants were instructed to maintain central fixation throughout the tasks and to do their best to use the temporal information provided to them by the auditory cues (as a reminder of the block that they were in) to help them to predict when the target was most likely to appear. Stimuli appeared superimposed against a uniform grey background (RGB values: 128, 128, 128), and a fixation point remained visible in the centre of the screen (width: 0.52°; height: 0.52°). Each trial commenced following a participant-initiated key press. After a short delay lasting 500 ms (50% probability), 1000 ms (25% probability) or 1500 ms (25% probability), an audio cue was presented for 150 ms. The audio cue was either a high pitch (1100 Hz) or a low pitch (600 Hz) beep indicating a short or a long foreperiod, respectively. The cue was valid in 75% of the trials. In the speeded RT task, participants were asked to respond as quickly as possible with their right index finger to a green circular patch (diameter: 1.89°), which was presented foveally after either a short (stimulus-onset asynchrony (SOA) of 540 ms) or a long SOA of 1580 ms). In the non-speeded RSVP task, the audio cue was followed by a stream of 14 black letters (font: OCR A Extended; width: 0.83°; height: 1.77°) presented foveally and in rapid succession (duration 100 ms; inter-stimulus interval 20 ms). The SOA between the audio cue and the first letter was 300 ms. Thirteen letters were distractors and one letter was a target letter. The target letter, an 'X' or an 'O', appeared either early (on the 3rd location, after 540 ms) or late (on the 12th location, after 1620 ms). The distracter stimuli were randomly sampled without replacement from a set of letters [A,B,E,F,G,H,I,J,L,M,P,Q,R,T,U,W]. Following the presentation of the letter stream, participants in both groups made a non-speeded, delayed discrimination response using their right hand using the left (for 'X') and right (for 'O') arrow keys on a standard keyboard. Participants were encouraged to take as much time as they needed before responding during the response window. Participants were under no time pressure to provide a response and were informed that only the accuracy of the response would be taken into account.

4.2.5 Procedure

The study was administered across two sessions that took place on separate days (days between sessions: mean = 10.2; range = 0 to 30). The first session consisted of the neuropsychological evaluation and one MEG scan, and took place at the Oxford Centre for Human Brain Activity (OHBA) at the Warneford Hospital, Oxford. Upon arrival at OHBA, informed consent was obtained and participants were then invited to complete standardized neuropsychological tests (see 4.2.2). This took place in advance of the scan, and was conducted in order to characterise individual differences that may contribute to behaviour across behavioural tasks. In total, the neuropsychological tests took approximately 45 mins and the MEG scan took approximately one hour.

The second session consisted of two computerized tasks and an MRI scan, both of which took place at the Oxford Centre for Magnetic Resonance (OCMR) at the John Radcliffe Hospital. Upon arrival at OCMR, participants were invited to take part in the motor and perceptual temporal orienting tasks as described in 4.2.4. These computer tasks took approximately 1 hour to complete. Following this, one MRI brain scanning session (45 minutes total) was performed. Again, PD participants were scanned and tested following overnight withdrawal of PD medication.

4.2.6 Data analysis

Statistical analyses were performed using custom-made scripts in MATLAB version 7.14 (R2012a, 32-bit) and SPSS version 22.0.

4.2.6.1 Primary analysis

For the speeded RT task, the primary outcome variable was the mean RT on correct responses for each condition. Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT across all condition. The average number of outlying trials was low (<2%) and did not differ between PD participants and healthy controls (Table 4.3).

For the non-speeded RSVP task, the primary outcome variable was a measure of perceptual sensitivity (*d'*). Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT across all conditions (Table 4.3). For each measure, participants who scored more than three standard deviations away from the average value within each group in at least one condition were excluded from the analysis. To examine how PD affected temporal orienting, a 3-way mixed-design analysis of variance (ANOVA) was conducted with foreperiod (short, long) and cue validity (valid, invalid) as within-subjects factors, and group (PD, Control) as a between-subjects factor for each task.

In addition, in order to control for possible biases in the statistics due to difference in power between valid and invalid conditions, a series of non-parametric permutation tests were conducted to analyse the strength of the validity effects for each experiment (Ernst, 2004; Maris, Schoffelen, & Fries, 2007; see also Rohenkohl, Gould, Pessoa, & Nobre, 2014). To this end, repeated-measures ANOVAs were performed separately for PD and control participants (see Table 4.4 and 4.5.). Statistical tests were two-sided and used a critical alpha level of 0.05. The significance of the observed results was assessed by comparison to a null distribution generated via Monte Carlo simulation with 10,000 repetitions. This null distribution was generated by randomly shuffling the condition labels within each participant's data in each repetition. The statistical test (*F*) on the mean difference between the conditions of interest was then performed, and the resulting value was entered into the null distribution. The permutation *p*-value was determined as the proportion of random partitions that resulted in a larger test statistic than the observed one.

To examine the effect sizes, Cohen's d was calculated (Cohen, 1988) using an online Effect Size Calculator (2014). Cohen's d was calculated by taking the difference between two means divided by the standard deviation. To correct for the dependence among means, and enable a direct comparison of effect sizes between groups, the correlation between the two means was added to the equation (see Equation 8 in Morris & DeShon (2002)).

To help investigate the differences in the strength of the validity effect (e.g. in the case of two-way interactions), a 'cueing index' was calculated for each foreperiod. For the speeded RT task, the index was calculated by taking the difference between the mean RT in the invalid condition and the mean RT in the valid condition, and dividing this difference by the mean RT in the valid condition. For the non-speeded RSVP task, the index was calculated by taking the difference between the mean *d'* scores in the valid condition and the mean *d'* scores in the invalid condition, and dividing this difference by the mean *d'* score in the valid condition.

4.2.6.2 Supplementary analyses

Previous studies show that general cognitive functioning can become increasingly disrupted when the dopaminergic system is compromised (Brown & Marsden, 1990; Dubois & Pillon, 1996; Kehagia et al., 2010; Owen et al., 1992; Zgaljardic et al., 2003). In order to exclude the possibility that group differences in temporal orienting effects could be attributed to reduced cognitive abilities in PD participants compared to healthy controls, an analysis of covariance (ANCOVA) was conducted including the MoCA scores (meancentred across the two groups) as a covariate. If the covariate was non-significant and did not interact with other factors in the initial analysis, the results from the ANOVA without the covariate were reported.

Disease severity, which can be approximately indexed by duration of illness and a participant’s UPDRS-III score (Fahn & Elton, 1987; see Jones & Jahanshahi, 2014), has been shown to be related to timing scores (Cameron et al., 2016). To assess whether the (in)ability to orient attention in time was related to disease severity, a Pearson product-moment correlation coefficient between the reaction time values on the speeded RT task and *d’* values on the RSVP task on the one hand, and disease severity (UPDRS-III) on the other, was computed. UPDRS scores were also compared to validity effects for the short foreperiod trials as measured by a cueing index score. Cook’s distances were calculated to identify outliers and quantify the influence of each observation on the fitted response values. Correlations were then re-calculated after removing the individual data points that were three times the mean of Cook’s distance (Cook, 1977).

Table 4.3

The number of excluded outlier trials per experiment. RT values were considered outliers if more than 3 standard deviations away from the mean RT of a participant.

	PD patients (18)			Controls (18)			
Experiment	Mean	Min	Max	Mean	Min	Max	Two-sample t-test
Speeded RT task	3.3	0	5	3.6	1	6	$t(34) = -.40$, $p = .69$
RSVP task	2.9	1	5	3.7	1	7	$t(34) = -1.50$, $p = .14$

Note. The average number of outlier trials did not differ between both groups, according to two-sample t-tests.

4.3 Results

4.3.1 Speeded RT task

After removing the anticipatory responses, performance accuracy was at ceiling (<1% misses) for all conditions in both groups. Before analysing the between-group differences, individual participants scoring more than 3 standard deviations (SD) above or below the average performance of all the other participants were removed from the analysis. As a result, one control participant was excluded from the analysis.

The main results of the 3-way mixed ANOVA on RTs are summarized in Table 4.4. The main finding was that both groups showed significant and equivalent effects of cued temporal expectations on speeded detection of targets appearing at the short interval. Between-group analyses indicated main effects of group, foreperiod, and cue validity; as well as a foreperiod-by-validity interaction on the RTs (all other *p*s > .20). The pattern of these results did not change when including the MoCA scores as a covariate of no interest. Overall, PD participants responded more slowly (*M*±*SD* = 405±139 ms) to the target compared to control participants (319±29 ms) (Figure 4.1a).

Post-hoc paired-sample *t*-tests were conducted to inform the foreperiod-by-validity interaction, which was significant within each group (controls: F(1,16) = 17.48, p < .001, *F-test permutation p* < .001; PD participants: F(1,17) = 8.84, p < .001, F-test *permutation p* < .001). Participants reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid (*M*±*SD* = 356±103 ms) compared to invalid (*M* = 425, *SD* ± 143 ms) temporal information (*t*(34) = -5.55, *p* < .001). The effect size was very large in both groups (controls: Cohen's $d = 1.61$; PD patients: Cohen's $d = 1.01$). In contrast, the validity of the auditory cue did not modulate RTs significantly in trials with a long foreperiod, though there was a trend driven by marginally faster RTs for long invalid ($M \pm SD = 342 \pm 86$ ms) compare to long valid trials ($M \pm SD = 359 \pm 123$ ms), ($t(34) = 1.80$, $p = .08$).

For completeness, the validity effect for short and long foreperiods was also directly compared between groups using the cueing index, which was corrected for the mean RT of each individual. There was again a main effect of foreperiod ($F(1,33) = 27.22$, $p < .001$, $\eta^2 = .45$), but no main effect of group ($F(1,33) = .23$, $p = .64$) or an interaction between foreperiod and group ($F(1,33) = .66$, $p = .42$).

In summary, both participants with PD and healthy older participants experienced an asymmetric cueing benefit for short versus long foreperiods (Figure 4.1a). As expected, PD participants were significantly slower than control participants, but this did not interact with any experimental condition of interest.

Table 4.4

Analysis of variance (ANOVA) on RT (ms) values from the speeded RT task

Effect	df1	df2	*F*	*p*	η^2
Between group effects					
Group*	1	33	6.28	<.05	.16
Foreperiod*	1	33	50.51	<.001	.61
Foreperiod x Group	1	33	.19	.67	
Validity*	1	33	48.16	<.001	.59
Validity x Group	1	33	.42	.55	
Foreperiod x Validity*	1	33	17.19	<.001	.34
Foreperiod x Validity x Group	1	33	1.70	.20	
Within group effects: Controls					
Foreperiod*	1	16	46.47	<.001	.74
Validity*	1	16	54.41	<.001	.77
Foreperiod x Validity*	1	16	17.48	<.001	.52
Within group effects: PD					
Foreperiod*	1	17	19.48	<.001	.53
Validity*	1	17	18.42	<.001	.52
Foreperiod x Validity*	1	17	8.84	<.01	.34

Note. * = significant effects.

4.3.2 RSVP task

No participant performed more than 3 SD's beyond the mean for any condition on perceptual discrimination, so all participants were included in the analysis.

The main results of the 3-way mixed ANOVA on *d'* are presented in Table 4.5. Analyses of *d'* revealed main effects of foreperiod, cue validity, and an interaction between validity and group (all other *p*s > .09). The pattern of these results did not change when including the MoCA scores as a covariate of no interest.

Separate ANOVAs for PD participants versus healthy controls were conducted to inform the validity-by-group interaction. The main effect of cue validity was significant in healthy controls (F (1,17) = 21.21, $p < .001$, η^2 =0.56; F-test *permutation,* $p < .0001$), but not in the PD group (F (1,17) = 2.48, $p = .13$; F-test *permutation,* $p = .13$). Control participants responded with greater sensitivity to the target when the preceding cue contained valid information ($M \pm SD$=3.23±.68) compared to invalid temporal information ($M \pm SD$=2.38±1.14). There was also a very large effect size of cue validity in the control participants (Cohen's d = .96). Conversely, PD participants did not respond with significantly greater sensitivity to validly cued targets ($M \pm SD$=2.44± 1.08) than to invalidly cued targets ($M \pm SD$ = 2.19±1.08). While the effect of cue validity was not significant in the PD cohort, it is worth noting that the pattern of results is qualitatively similar to the control group.

In summary, while healthy older participants exhibited a perceptual advantage for validly cued information, this effect was not significant in participants with PD. As shown in Figure 4.1b, the target letter was most effectively discriminated in the control group when the cue correctly predicted its position in the RSVP stream compared to when the cue was invalid, replicating previous findings (see Chapters 2 and 3).

Table 4.5

Analysis of variance (ANOVA) on d' values from the speeded RT task

Effect	df1	df2	*F*	*p*	η^2
Between group effects					
Group	1	34	3.13	.09	
Foreperiod*	1	34	13.20	<.001	.28
Foreperiod x Group	1	34	.15	.70	
Validity*	1	34	19.16	<.001	.36
Validity x Group*	1	34	4.65	<.05	.12
Foreperiod x Validity	1	34	1.01	.32	
Foreperiod x Validity x Group	1	34	2.08	.16	
Within group effects: Controls					
Foreperiod*	1	17	4.48	<.05	.21
Validity*	1	17	21.21	<.001	.56
Foreperiod x Validity	1	17	12.53	.13	
Within group effects: PD					
Foreperiod*	1	17	9.83	<.01	.37
Validity	1	17	2.48	.13	
Foreperiod x Validity	1	17	.18	.74	

Note. * = significant effects.

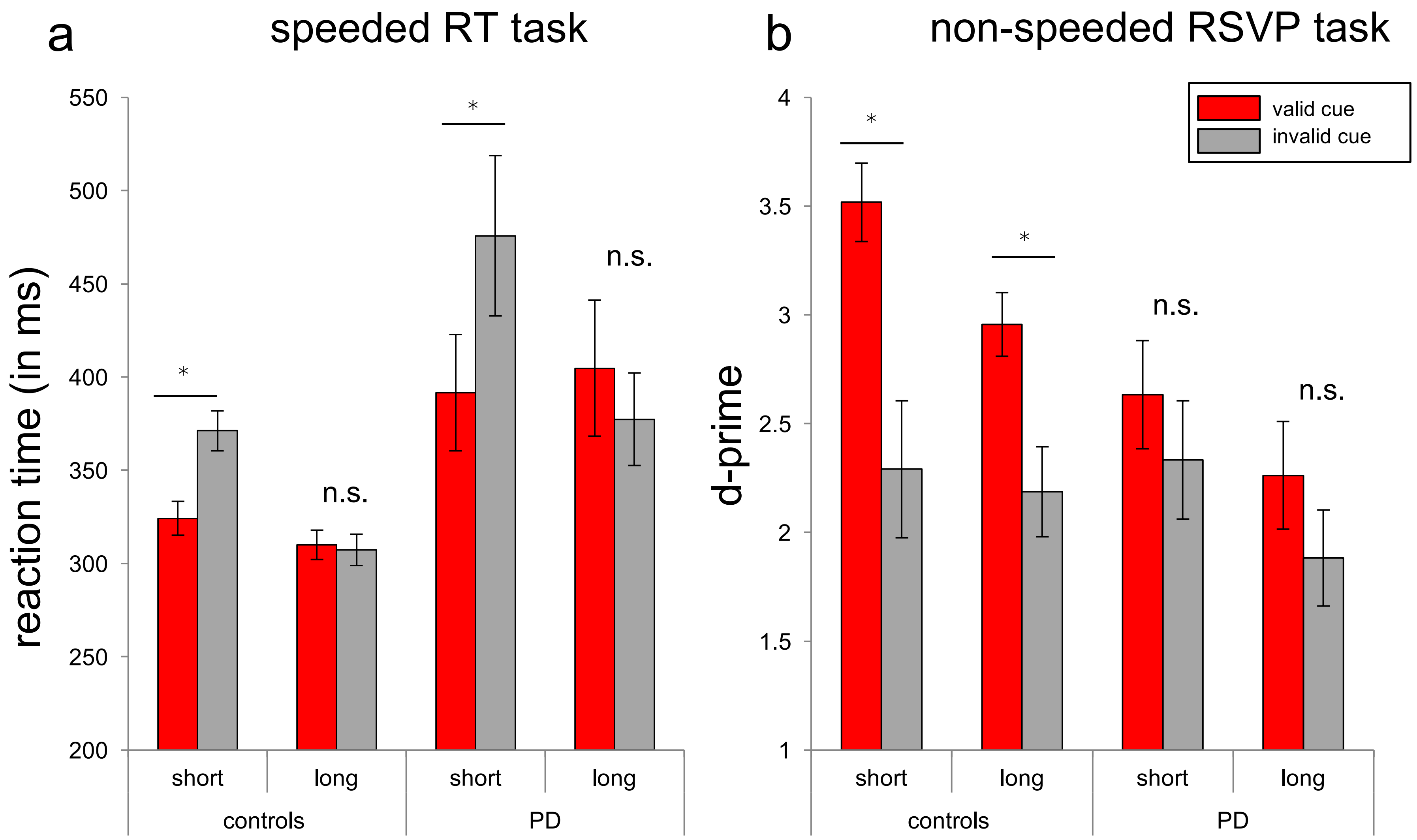

Figure 4.1 Temporal orienting effects for targets appearing after a short and long duration of time, for expected (valid) and unexpected (invalid) targets. (a) Effects of temporal orienting on reaction time values (ms) in the speeded RT task. (b) Effects of temporal orienting on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent standard errors of the means (SEM).

4.3.2 Correlation between effects of behavioural performance and PD symptom severity

As part of an exploratory analysis, Pearson product-correlation coefficients were computed to assess the relationship between the performance on the experimental tasks and the severity of symptoms for PD participants. All p-values are uncorrected for multiple comparisons. UPDRS scores ('off' medication) significantly covaried with overall reaction times for the speeded motor timing task. Pearson correlation showed that UPDRS scores (*n.b.* higher scores mean higher severity) and mean reaction-time values (averaged over all trials or only valid trials) positively correlated (all trials: $r = .65, p < .01$; valid trials only: $r = .68, p < .01$). However, there was no relationship with discrimination performance (d') values on the non-speeded RSVP task (overall: $r = -.15, p = .55$; valid trials only: $r = -.18, p = .49$). Validity effects for the short trials on the speeded RT task ($r = -.08, p = .75$) and the RSVP task ($r = .02, p = .95$) also did not correlate with UPDRS scores. After removing the five PD participants who scored <26 on the MoCA ($n = 13$), UPDRS scores and mean reaction time values (averaged over all trials or only valid trials) were positively correlated (all trials: $r = .62, p < .05$; valid trials only: $r = .61, p < .01$). However, there was still no relationship with discrimination performance (d') values (overall: $r = -.12, p = .48$; valid trials only: $r = -.13$, p = .66) on the non-speeded RSVP task.

To investigate the potential effect of outliers on the relationship between UPDRS scores and reaction time values on the original sample ($n = 18$), Cook's distances were calculated in order to determine the influence of each participant's response values on the positive correlation. Three participants were removed from the original sample ($n = 15$). Pearson correlation showed that UPDRS scores and mean reaction-time values (averaged over all trials or only valid trials) did not correlate (all trials: $r = .37$, $p = .18$; valid trials: $r = .32$, $p = .16$) after these outliers were removed.

4.4 Discussion

In the present study, the influence of PD on temporal orienting was examined on a reaction-time task that emphasized speeded responding and a non-speeded RSVP task that emphasized visual discrimination. As in previous chapters (see Chapter 2 and 3), temporal orienting of attention was preserved in healthy older adults. Intriguingly, participants with PD and healthy controls benefited similarly from cue-based temporal expectations to improve performance in a task that emphasized motor preparation and speeded responding. In contrast, participants with PD did not benefit significantly from temporal expectations for perceptual discrimination. The absence of significant temporal orienting effects in the RSVP task was not driven by the reduced cognitive abilities characteristic of PD. Though participants with PD were overall slower than control participants, the data presented herein show that cue-based temporal expectations can be used as an external aid to modulate and enhance motor performance in individuals with PD. These findings imply divergent degrees of ability to successfully integrate temporal information to improve task performance in some contexts but not others.

In the speeded RT task, the finding that individuals with PD are able to make use of temporal cues to speed up responses is in line with evidence demonstrating that external timing signals can be used to strengthen internalized expectations for motor responses. As reviewed in the introduction (section 4.1.1), temporal cues have been shown to confer a behavioural advantage across a number of motor tasks in PD. For example, symbolic cues relevant for motor responses have been found to speed responses by facilitating the initiation of movement (Praamstra et al., 1998) and rhythmic auditory cues can improve motor and perceptual timing (Benoit, et al., 2014). Understood in the context of these findings, the observed boost in motor performance is perhaps unsurprising. However, since no neutral control condition was used, we cannot be sure that the gains reflect a validity benefit or a cost of invalidity.[9]

Though temporal cues were seen to enhance motor performance in PD, it is worth highlighting that they were still significantly slower relative to healthy controls on the speeded RT task. PD participants also exhibited a correlation with general RT scores and UPDRS scores, which points to motor deficits in PD (i.e. severity of PD contributes to slower responses overall). The comparatively slower responses were also observed on neuropsychological measures that involved measurements of RT, such as the TMT (B) and the Purdue Pegboard (see Table 4.1). This pattern of results is consistent with the research demonstrating a general slowing of motor timing in PD and suggests an underlying motor-response impairment (e.g. Bloxham, Dick, & Moore, 1987; Evarts, Teräväinen, & Calne, 1981).

In contrast to the observed boost in temporal orienting abilities on the speeded RT task for the PD group, temporal orienting conferred by auditory cues failed to produce behavioural benefits on the perceptual discrimination task. However, the additional attentional and executive demands in the RSVP task over and above the requirement for perceptual discrimination may have played a role in this result. For example, the RSVP task may have required greater executive control in comparing incoming items to a working memory (WM) template (i.e. decision-making), and a greater need for inhibiting distractors to gate responses — both of these functions, incidentally, have been shown to be associated

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[9] However, see Chapter 1, section 1.2.2, where invalidity costs have been found to be negligible in previous experiments that have used temporal orienting tasks.

with the basal ganglia and may have interacted to influence the effects observed herein. As reviewed by McNab and Klingberg (2008), the basal ganglia play an important role in allowing information to enter WM, and previous research has highlighted the importance of the basal ganglia in sensory gating (Schneider, 1984; Hazy, Frank, & O'Reilly, 2007). It has also been proposed that top-down control of attention can serve as a gatekeeper for WM by biasing the encoding of information toward items that are most relevant (Awh, Vogel, & Oh, 2006). Since WM capacity is predicted by prefrontal and basal ganglia activity (McNab & Klingberg, 2008), it is also possible that PD-related dysfunction of the basal ganglia is linked to the inability of our participants to effectively inhibit distracting information in the RSVP task. Furthermore, given that the basal ganglia are implicated in WM, and the functional and neural overlap of temporal processing and WM is an area of debate (Lustig et al., 2005), further research will need to be conducted in order to understand how temporal expectations interact with WM, temporal processing, and other attention-related networks.[10]

Another important difference between the RSVP task and the speeded RT task is that there is uncertainty about the identity of the target (X or O) in the RSVP task. In other words, the RSVP is more akin to a dual-task paradigm than the speeded RT task and may be more sensitive to picking up deficits. Thus, WM may already be filled up with the identity of the two targets ('X' and 'O') leaving little processing resources to also take into consideration the temporal cue. In addition, distractor items may take up 'slots' in visual short-term memory reducing the WM capacity even further.

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[10] As recognized by Manohar et al. (2013), some attention deficits in PD may be explainable as a failure of 'braking' or inhibition. Previous research has shown that PD increases errors on go/no-go tasks in a complexity dependent manner (Cooper, Sagar, Tidswell, & Jordan, 1994). Further, it is also noteworthy that early PD patients who perform within normal limits on go/no-go tasks exhibit increased prefrontal and basal ganglia activation compared to healthy people (Baglio, et al., 2011). This suggests greater involvement of these structures in order to exert similar levels of control. A trial-by-trial, more demanding version of the speeded RT task (such as in Chapter 3, Experiment 2) would help to demonstrate the importance of these mechanisms in temporal orienting. If PD participants exhibit deficits in such a task, this may help to clarify the results.

Alongside the above interpretations of the findings, it is important to consider that — while PD is perhaps best characterized as a movement disorder — as the disease progresses, and the mesocortical dopaminergic system becomes compromised, attentional and cognitive deficits (among others) tend to occur (Brown & Marsden, 1990; Chaudhuri & Schapira, 2009; Dubois & Pillon, 1996; Kehagia, et al., 2010; Owen, et al., 1992; Zgaljardic, Borod, Foldi, & Mattis, 2003; Zgaljardic, Foldi, & Borod, 2004). Ultimately, there is likely a complex relationship between the cognitive decline attributed to the observed neural degeneration and the weakened performance on the perceptual discrimination task in PD. Though lower MoCA scores were not found to interact with performance on either of the temporal orienting tasks, and thus generic cognitive performance does not seem to be driving the observed effects, it is remains possible that the ability to orient one's attention in time to aid perception may be undermined in PD by differences in cognitive abilities and attention — such as differences in selective, sustained and divided/executive attention (Manohar, Bonnelle, & Husain, 2013). Future experiments should look at disambiguating cognitive deficits from general timing deficits, which may independently contribute to temporal orienting abilities (Jones & Jahanshahi, 2014).

Importantly, it is also conceivable that temporal expectations may be embedded within partially separate task-related circuits rather than always having the same, common neural cause. In this case, some of the demands in the RSVP task may be more compromised in PD participants. For example, it is possible that the networks involved in perceptual enhancement are part of a distinct, higher level control system responsible for the control of perceptual variables, which may be independent from the sensorimotor-cortico-basal ganglia network critical for controlling movement speeds at a lower level (for a review of the control hierarchy in the basal ganglia, see Yin, 2014). Though it is known that there is tremendous heterogeneity in the connectivity of different cortical, striatal and pallidal regions (Gerfen & Wilson, 1996; O'Reilly, et al., 2008; Yin, 2014), extensive experimental work will need to be undertaken to determine how these regions and related circuits integrate and make use of temporal information for motor performance and perceptual enhancement.

The inability of PD participants to internalize temporal information and filter distracting information to improve their perceptual performance may be underpinned by some combination of impairment in executive control and damage to mechanisms related to task-related networks. As such, another explanation for the dissociation in performance between tasks may come down to how the temporal information is encoded between tasks. Strictly speaking, both tasks are examples of using implicit timing; however, this does not rule out a possible contribution of participants generating explicit timing to aid them in the task. For instance, it may be that the temporal expectation effects in the RSVP task rely more heavily on participants creating an explicit representation of the possible timing of targets[11] than the speeded RT task, which may in comparison rely on more implicit timing mechanisms. Previous research indicates that the basal ganglia are critical in explicit timing tasks, and are less essential for implicit timing measures (e.g., Coull & Nobre 2008 review). If the RSVP task performance indeed relied upon more explicit timing, the difference in the behavioural results may have been partially influenced by the explicit timing deficits known to occur in PD.

In addition to differences in cognitive abilities and differences in internalised representation of the temporal information, other factors, such as heterogeneity in PD symptoms, may have also contributed to the participants inability to use temporal cues to improve perceptual judgement. PD is recognized as a disease with a broad phenotype,

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[11] n.b. This may also be dependent upon WM or available processing resources.

including a range of motor and non-motor symptoms, which subsume (*inter alia*) neuropsychiatric, autonomic, and cognitive symptoms (Chaudhuri, et al., 2006; Chaudhiru & Shapira, 2009). More generally speaking, in considering patients as a homogenous group — a practice that seems to be common in PD studies — researchers tend to ignore effects that may be particular to clinical subtypes, such as predominantly akineto-rigid patients and tremor-predominant patients (Jankovic, McDermott, Carter, & Gauthier, 1990). In addition, the severity of the disease and the medications being used to treat the most common symptoms (e.g. the motor symptoms) introduce yet another source of variance across patient groups. The different types of medications, and the amount used, may have consequences for cognition (or other non-motor timing abilities) that linger even when patients are 'off' medication. Given the range of possible sources of variation in PD performance, further investigation is needed to account for the plausible influence of clinical heterogeneity on temporal expectation abilities before determining whether there is a categorical deficit in being able to use temporal information to enhance perceptual judgment. Indeed, identifying the sources of variation will no doubt be instrumental to understanding the determinants of deficits in timing-related performance associated with PD. In previous studies, PD sufferers have been shown to be much more variable on temporal processing tasks compared to healthy controls (Elsinger, et al., 2003). Since the pattern of effects on the RSVP task was similar to the control group, it is worth considering whether PD variability may have been a particularly important determinant in the lack of effects observed herein.

In the future, better characterization of the manipulations that distinguish PD from healthy control groups will serve to broaden our understanding of the precise nature of the temporal deficits found in people with PD. Task factors, including the choice of paradigm and stimulus features, can have an impact on orienting attention in time to improve perceptual performance in PD. Further, comparison tasks that control for the potential confounds associated with executive demands and differences in cognitive abilities should be considered. It is also imperative that researchers pay careful attention to the effects associated with asymmetrical symptoms, which seem to be very common among PD patients (van der Hoorn et al., 2011) and consider this in the task design. Though symptom asymmetry scores (SAS) were not found to interact with the findings reported in the current investigation, the behavioural tests used required participants to make their responses using their right hand only, which may still have subtly impacted results (n.b. these could also have contributed to variability in the group, which may have masked effects.)

In sum, if it is true that there is real distinction to be made between deficits in temporal orienting for motor and perceptual performance, then it is worth considering what might be behind these observed differences. At present it remains unclear whether the observed impairment in temporal orienting in perception is underpinned by dysfunction in the basal ganglia *per se* (e.g. related to functional changes in the striatum), connections to cortical sites — which are insufficiently activated — or the result of dysfunction/degeneration in some other brain regions or processes. Additional research is required to determine the sources of the observed deficit in using temporal cues to aid perceptual performance in PD, and to ascertain the precise role of the basal ganglia across different types of temporal orienting tasks and intervals. This can be investigated through brain imaging that allows for the characterization of the patterns of dysfunctional brain activity during timing-related tasks, and/or by looking at the behavioural effects of stroke survivors with lesions in the basal ganglia and other brain structures implicated in timing. Though additional evidence is needed, the findings in the present investigation raise the possibility that separate mechanisms may be involved in motor- and perception- related temporal expectation, and further affirms that there may be multiple sources of temporal information that constrain stimulus processing (see Nobre & Rohenkohl, 2014). These findings also suggest that the context in which temporal expectations are deployed also matter.

4.5 Conclusion

Falling short of being able to locate ourselves in time effectively has implications for almost all behaviour that we engage in, and, as such, identifying when impairments in temporal expectation occur is hugely important. We often use external cues and artefacts in the environment to prompt us to act at particular times. Just as motor timing can often be enhanced in PD patients when environmental aids are present, the findings presented herein leave open the possibility of temporal cues being used as an aid to enhance behavioural performance in the context of neurodegeneration. This suggests that different types of external cues might be exploited to greater or lesser benefit in physical and cognitive therapies, depending on task relevance. Whether different types of attentional cues can be used to optimize perceptual performance in ecologically valid contexts, however, is still unclear (Robertson & O'Connell, 2014).

Timing in cognition does not occur in isolation; rather, it is frequently associated with other executive demands, such as those that involve working memory, selective attention, and decision making (Wiener, Turkeltaub, & Coslett, 2010). Future investigations should look to disambiguate the conditions for temporal expectation impairments in PD, and determine the extent to which other extraneous factors, such as those related to task design, differences in cognitive abilities, or patient heterogeneity, may explain some of the differences observed in temporal orienting ability. Such considerations will be crucial in developing a thoroughgoing understanding of the role of the basal ganglia (among other brain structures) in timing more generally.

While the mechanisms involved in temporal expectations used to enhance motor responses and perceptual judgement are still being debated, by investigating whether temporal orienting exists in stroke survivors with similarly affected brain regions as those affected in PD, it may be possible to pull apart the mechanistic and structural contributions of the subcortical structures implicated in different types of temporal expectation. It is to this subject that we now turn in Chapter 5.

5 Temporal orienting of attention in participants with basal ganglia damage

Chapter Abstract

Neuroimaging studies have consistently implicated the basal ganglia in temporal processing. The aim of this chapter is to assess the causal involvement of the basal ganglia in the ability to allocate attention to moments in time. Specifically, I tested whether temporal orienting of attention is compromised in patients with brain damage to this region. Seven chronic stroke survivors with basal ganglia damage and 18 age-matched healthy controls participated in the study. Two temporal orienting tasks were used: a speeded reaction-time task and a non-speeded perceptual discrimination task using rapid serial visual presentation (RSVP). In both tasks, auditory cues (high or low pitch) indicated the likelihood of a target stimulus appearing after a short or long temporal interval (75% validity). In the speeded RT task, participants were instructed to use the cues to help them respond as quickly as they could to seeing a green patch appear at the fovea. In the RSVP task, participants were instructed to use the cues to discriminate a target letter in a stream of rapidly presented distracting letters. Compared to healthy controls, patients with basal ganglia damage did not benefit from temporal cues to enhance perceptual performance in the RSVP task. In contrast, their ability to use temporal information to speed up performance was preserved in the speeded response task. Together with the previous findings, these results suggest that deficits in temporal orienting caused by basal ganglia dysfunction can be modulated according to the task context and the domain in which temporal expectations operate.

5.1 Introduction

While neuroimaging research has endeavoured to characterize the neural mechanisms and regions involved in temporal expectations (for review, see Nobre & Rohenkohl, 2014), neuropsychological research has hitherto been unable to demonstrate a causal relationship between the basal ganglia and temporal orienting (Triviño, et al., 2010). As ascertained by PET and fMRI studies, and reviewed in Chapter 1, the neuroanatomical correlates of temporal expectations include a range of brain regions, such as the left posterior parietal cortex along the IPS, the left inferior premotor cortex, , left inferior prefrontal cortex, and left and right cerebellum (Cotti, et al., 2011; Coull & Nobre, 1998; Coull et al., 2000; Coull et al., 2013; Coull, Cotti, & Vidal, 2016; Davranche, et al., 2011). These regions seem to tap into fronto-parietal networks associated with the control of action more generally (Coull, 2014; Griffin, Miniussi, & Nobre, 2002; Nobre, 2001), but engage a qualitatively distinct sensorimotor circuit from oculomotor control (Nobre & Rohenkohl, 2014). The left hemispheric dominance, the engagement with the sensorimotor circuit, and the systematic activation of prefrontal structures for motor control, suggest that temporal orienting is part of a strategic process that involves planning for and control of action.

In addition to the brain regions implicated in temporal orienting, the basal ganglia (and cortico-striato-thalamo-cortical system (CSTCS) more generally) have been found to be linked to a number of timing functions, including interval timing, and distortions of time perception (e.g. Allman & Meck, 2012; Allman, Teki, Griffiths, & Meck, 2014; Coull, et al., 2011; Ivry & Spencer, 2004; Jones & Jahanshahi, 2009; Matell & Meck, 2000; 2004; Meck, 2005; Meck & Benson, 2002; Meck & Malapani, 2004; Merchant et al., 2013; Schwartze & Kotz, 2013). As part of its role in subserving temporal processing, the basal ganglia interacts with a much broader network of neural mechanisms and brain regions, including the SMA and the right inferior frontal cortex (e.g., Harrington, Zimbelman, Hinton, & Rao, 2010; Livesey, Wall, & Smith, 2007; Coull, et al., 2004; Ferrandez et al., 2003). These regions have been purported to be part of a more general timing system that spans core regions of the motor network, including the basal ganglia, cerebellum, the inferior olive, supplementary motor areas, and the premotor cortex, which interact with higher-level regions such as the prefrontal cortex (Meck, 2005). More recently, this timing system has been refined, and an integrative view of time perception based on coordinated activity in the core striatal and olivo-cerebellar networks, which are interconnected with each other and with the cerebellar cortex through multiple synaptic pathways, has been put forward (Allman & Meck, 2012; Allman et al., 2014; Teki et al., 2011; 2012).[12]

The finding that the basal ganglia are part of a more general timing system has led some researchers to hypothesize that damage to the basal ganglia could affect temporal orienting (Triviño, et al., 2010) — e.g. a lesion in this structure may affect how one estimates the passage of time, which may in turn have consequences for temporal orienting. To date, however, few researchers have investigated whether these brain areas are causally involved in temporal orienting by examining the effects of temporal orienting in populations with focal lesion damage to regions implicated in temporal processing. Instead, most studies, including the many that have been outlined above, have sought to investigate the neuroanatomical correlates of temporal orienting using neuroimaging techniques. It is important to note that while brain imaging studies are useful in highlighting the brain areas that may be involved in a given task, and determining how they functionally interact, these methods are unable to clarify whether a given brain region is *required* or causally involved in a particular function

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[12] As a cursory note, it has been proposed that timing in this model may involve serial beat-based striatal activation followed by absolute olivocerebellar timing mechanisms (for review, see also Cope et al., 2013; Merchant et al., 2013).

(see Rorden & Karnath, 2004; Müller & Knight, 2006). Moreover, when it comes to investigating the neural correlates of temporal orienting (and the related effects of timing) imaging technologies are limited for other reasons too. As summarized in Nobre and Rohenkohl (2014), haemodynamic measures are slow and struggle to account for the rapid pace of temporal cueing experiments, complicating the ability of researchers to dissect out activations associated with temporal processing. So far, brain-imaging studies have been unable to isolate the neural activations specifically triggered by temporal cues (Nobre & Rohenkohl, 2014). By providing additional insight into the role of specific brain regions and the neural substrates of temporal orienting, brain disruption techniques present a complementary approach to these methods.

Moving beyond neuroimaging data, Triviño and colleagues (2010) were the first to investigate temporal orienting in patients with focal damage to the basal ganglia and to the PFC. In their experiment, temporal orienting ability was assessed using a speeded RT task that involved using a visual cue to direct the participants' attention to either an early (400 ms) or late (1400 ms) target item (an 'X' or 'O'). In contrast to what might have been expected, given the role of basal ganglia in timekeeping (Praamstra & Pope, 2007) and temporal preparation tasks (Jurkowski et al., 2005), it was found that the group of patients with basal ganglia lesions exhibited no deficit in temporal orienting. By comparison, patients with right prefrontal damage exhibited deficits in temporal orienting but showed preserved sequential effects, whereby RTs for detecting a target were facilitated when the previous cue-target interval was short rather than long. These findings suggest that at least some types of temporal expectations can be preserved in patients with lesions in the basal ganglia. Additional results replicating the preservation of temporal orienting effects in individuals with lesions to the basal ganglia therefore would be highly desirable.

Triviño et al.'s (2010) investigation suggests that temporal orienting can be used to enhance motor responses for participants with focal lesions in the basal ganglia. However, the researchers did not explore whether perceptual processes could also be modulated by temporal expectations in the same patient group. Therefore, whether temporal orienting effects can be observed at the perceptual level for participants with basal ganglia damage remains unresolved. Discrimination tasks demand a more detailed perceptual analysis than detection tasks, which (independent of visual features) only demand a speeded response (Correa et al., 2005). As a result, we cannot know whether the temporal orienting effects preserved in a target detection task (e.g. as in Triviño et al.'s study) are generalizable to tasks that pose greater perceptual demands. While it could be the case that temporal orienting is subserved by coextensive mechanisms in tasks that emphasize either motor or perceptual levels of analysis, recent assessment runs contrary to this line of reasoning (Nobre & Rohenkohl, 2014). Instead, it is possible that temporal expectations are dissociable based on task demands and context, and can therefore influence motor or perceptual processing through separate, non-coextensive mechanisms.

This study builds on the experiments in the previous chapter, in which the role of basal ganglia-related neural systems in temporal orienting was investigated in individuals with PD. Separate tasks were used to interrogate the ability to orient attention to cued intervals in tasks with high motor versus perceptual demands. The results of Chapter 4 showed that participants with PD can use temporal information to enhance their motor responses in a speeded RT task, but they could not use temporal expectations to improve their perceptual judgements. While suggestive, it is difficult to attribute the pattern of findings to damage in the basal ganglia in particular, since PD is a neurodegenerative condition that affects the brain at the network level (Grosset, Grosset, Okun & Fernandez, 2011). For example, the particular pattern of findings could also result from dysfunction to areas other than the basal ganglia in PD patients, such as the prefrontal cortex or cerebellum. Moreover, it is also important to note that there is generalised neuronal degeneration in PD, and thus the dysfunction in PD is not primarily degeneration of the striatum, but includes an uneven loss of its dopaminergic input (Kish, et al., 1988; for review, see Cope et al., 2014).

The current experiments therefore attempt to examine temporal orienting effects at both the motor and perceptual level, using a speeded RT task and a RSVP perceptual discrimination task in individuals with focal lesions involving the basal ganglia. For the RSVP task, the speed of the participants' response was not of interest. Instead, target sensitivity (*d'*) was measured to see if expectation could enhance perceptual discrimination ability. Lesion mapping was used to delineate the lesions and to assess whether or not the basal ganglia are critical for temporal orienting in different task domains (Rorden, et al., 2007). In line with what was found in Chapter 4, it was hypothesized that participants would experience an enhancement of motor preparation, but damage to the basal ganglia would have a negative impact on temporal orienting for perceptual discrimination.

5.2 Methods

5.2.1 Participants

All experimental methods received ethical approval from the Central University Research Ethics Committee of the University of Oxford (Reference number: MSD-IDREC-C1-2013-41). The investigation was carried out on a group of seven chronic stroke survivors with focal lesions that involved the basal ganglia (M_{age} = 65.71, $M_{\text{education}}$ = 11.86, 2 F) and 18 age-matched neurologically intact control participants (M_{age} = 65.9, $M_{\text{education}}$ = 18.0, 10 F). All participants provided informed consent. Most were right handed, with the exception of two participants in the control group, who were left-handed, and all participants had normal or corrected-to-normal vision. Further sample characteristics with regard to age, education, gender, lesion aetiology and lesion location of included participants are given in Table 5.1.

All participants took part in the experiment at the Oxford Cognitive Neuropsychology Centre (CNC). Patients with unifocal ischemic lesions involving the basal ganglia were recruited through the CNC. Lesions were primarily confined to the basal ganglia but in some cases compromised the insula or inferior frontal cortex. Exclusion criteria included the following: age above 80 years old, extensive white matter lesions, lesions excluding the basal ganglia, and multiple lesions. Exclusion for the control participants was based on the outcome of their neuropsychological evaluation. All control participants were required to have Montreal Cognitive Assessment (MoCA) scores equal to or above 26 to be included, since a score below that value is an indication of a mild cognitive impairment (Nasreddine, et al., 2005). In addition, control participants were excluded if they were active participants in a clinical drug trial; if they were taking psychotropic, hypertensive or vasoactive medication; or if they self-reported neurological, head injury, or psychiatric history.

Table 5.1

Demographic and neuropsychological data.

Group	Age in years	Years of Education	Sex	Type of stroke	Average time elapsed from lesion (months) to neuropsych exam	Average time elapsed from lesion (months) to experiment	Lateralisation of the lesion
Basal ganglia	65.71 (11.07)	11.86 (3.45)	5M, 2F	Ischemic Stroke	9.8	29.8	6 R, 1 L
Controls	65.89 (5.4)	18 (3.93)	8M, 10F	-	-	-	-

Data are averaged for group and standard deviation (in parenthesis) is included. M = male; F = female; R = Right, L = Left.

5.2.2 Neuropsychological Evaluation

Control participants underwent a neuropsychological evaluation that consisted of tests designed to assess general cognitive function (MoCA, version 7.1; Nasreddine, et al., 2005)), attention/task switching (Trail Making Test (TMT); Reitan, 1958; Reitan & Wolfson, 1985; Tombaugh, 2004), executive function (Rey-Osterrieth Complex Figure test (RCF); Fastenau, et al., 1999; Osterrieth, 1944; Rey, 1941), semantic memory (Category fluency—names of animals 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). All neuropsychological tests were completed in a single sitting. The test scores are summarized in Table 5.2.

Patients were not given the same battery of neuropsychological tests as the controls. Instead, all patients took part in the neuropsychological screening procedure regularly delivered at the CNC. During this procedure, participants were asked to complete the Birmingham Cognitive Screen (BCoS) (Humphreys, Bickerton, Samson, & Riddoch, 2012), which is given over a 1-hour testing session. The BCoS is an extensive stroke-specific test battery, which — in contrast to the neuropsychological evaluation administered to the control participants — has the advantage of being inclusive (i.e. neglect and aphasia friendly). The BCoS provides a cognitive profile across a range of cognitive processes, which indicates a clinical impairment (related to norms) in five primary domains of cognition: (1)

attention and executive function, (2) language, (3) memory, (4) number skills praxis, and (5) action. The test scores are summarized in Table 5.3.

Table 5.2

Neuropsychological evaluation conducted in control participants.

	Mean	Range	SE	> 2SD*
Age	65.9	61-82	1.3	
Education	18.0	12-29	0.8	
MOCA	27.7	26-29	0.2	
TMT: A (s)	34.7	26-68	1.9	
TMT: B (s)	71.2	43-160	5.2	
ROCFT				
Copy (out of a possible 36)	34.1	30-36	0.4	
Immediate (out of a possible 36)	20.5	3.5-34	1.4	1.0
Delay (out of a possible 36)	18.8	2.5-34	1.4	
Category Fluency	20.7	15-33	0.9	
HVLT-R				
Trial 1	5.6	3-7	0.2	
Trial 2	8.1	3-12	0.4	
Trial 3	9.5	6-12	0.3	
Learning	4.1	2-7	0.3	
Sum of 1-3	23.1	13-29	0.8	
Delayed Recall	8.3	4-12	0.4	
Percent Retained (%)	85.4	40-110	3.4	
True Positives	11.2	8-13	0.2	
False Positives	0.7	0-3	0.2	
Discrimination Index	10.6	8-13	0.3	
BNT	14.7	13-15	0.1	
Digit Span (Scaled Score)	9.9	6-14	0.5	
Purdue Pegboard Right	12.2	10-15	0.3	
Purdue Pegboard Left	12.2	9-17	0.4	1.0
Purdue Pegboard Both	10.1	8-13	0.3	
Purdue Pegboard Sum	34.4	28-44	0.8	
Purdue Pegboard Assembly	25.2	15-33	1.0	
TOPF - FSIQ	119.9	102.6-134.9	1.8	

Note. *This column contains 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 Fig. Test; HVLT-R, Hopkins Verbal Learning Test-Revised; BNT, 15-Item Boston Naming Test; TOPF, Test of Premorbid Functioning

Table 5.3

Summary of results for Birmingham Cognitive Screen (BCoS) conducted on stroke survivors

				Case ID						
DOMAIN	**Subdomain**	**Function**	**Max**	1	2	3*	4	5	6	7
MEMORY	**Long Term**	Personal	0-8	8	8	8	8	8	8	8
		Time Space	0-6	6	6	6	6	6	6	6
		Recall	0-15	11	**0**	6	13	6.5	10	13
		Recognition	0-15	15	14	13	15	13	15	15
	Short term	Recall	0-15	11	9.5	**3**	10.5	7	7.5	11
		Recognition	0-15	14	13	**11**	15	14	14	15
	Episodic	Task Recognition	0-10	10	10	**8**	10	10	10	10
LANGUAGE	**Spoken**	Picture Naming	0-14	13	12	14	14	14	14	14
		Reconstruction	0-8	8	**7**	**7**	8	8	8	8
	Comprehension	Comprehension	1-3	3	3	NT	3	3	3	3
		Sentence Reading	0-42	42	**40**	42	42	42	42	42
	Writing	Non-Word Reading	0-6	6	4	5	6	6	6	6
		Writing	0-5	5	3	NT	5	5	5	5
ATTENTION	**Spatial neglect**	Overall	0-50	45	47	49	47	42	43	**41**
		Page Asymmetry	0-20	1	2	0	2	0	2	2
		Object Asymmetry	0-50	0	0	1	0	0	0	0
	Spatial extinction	Visual Left	0-8	8	8	8	8	8	8	8
		Visual Right	0-8	8	8	8	8	8	8	8
		Tact Left	0-8	8	**1**	8	8	8	8	8
		Tact Right	0-8	8	7	8	8	8	8	8
	Executive function	Rule Accuracy	0-18	10	6	**2**	12	9	11	11

	Total Rules	0-3	3	**0**	**1**	3	3	**2**	3
Auditory attention	Total Accuracy	0-54	47	47	52	53	47	53	47
	Working Memory	0-3	2	**1**	3	3	2	3	3
	Sustained Attention		0	**5**	0	1	**6**	-1	1
PRAXIS	Object Use	0-12	12	12	12	11	11	12	11
	Gesture Production	0-12	12	12	12	12	12	12	**12**
	Gesture Recognition	0-6	6	5	5	6	6	5	6
	Imitation	0-12	12	6	12	11	12	11	12
	Figure Copy	0-47	43	**36**	NT	44	41	44	45
CALCULATION	Reading	0-9	9	9	9	9	8	9	9
	Writing	0-5	5	**2**	NT	5	5	4	5
	Calculation	0-4	4	**1**	3	4	3	4	4
LESION INFORMATION	Lesion Size (in cm^3)	-	21.62	27.78	3.08	68.53	3.90	24.48	3.51
	Lesion Side	-	R	L	R	R	R	R	R

Note: Underlined scores are abnormal as compared to normative scores (Humphreys et al., 2012); NT = Not Tested.

* Participant could not write due to motor weakness in the right hand.

5.2.3 Neuroimaging

All patients included in the study had unilateral lesions as a result of ischaemic stroke demonstrated by magnetic resonance (*n* = 4) or computerized tomography scans (*n* = 3). Magnetic resonance images (MRI) were acquired on a 3-Tesla TIM Trio scanner at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). For each patient, a high-resolution 3D whole-brain T1-weighted MRI scans using a magnetization-prepared rapid gradient echo sequence (MPRAGE) (repetition time 3000 ms, echo time 4.7 ms, flip angle 8 degrees, 1 mm isotropic resolution) and a fluid rapid attenuated inversion recovery (FLAIR) image (repetition time = 5000 ms, echo time = 397, in-plane resolution 1 mm, slice thickness 1.5 mm) was acquired. The boundary of the lesion was delineated by a member of the CNC on the individual FLAIR image (*n* = 4, cases 4, 5, 6 & 7) or CT image (*n* = 3, cases 1, 2 & 3) for every transverse slice with MRIcron (Rorden, Karnath, & Bonilha, 2007) and a graphics tablet (Wacom Intuos Pro Medium, Vancouver, Washington, USA). Subsequently, both the anatomical images and the lesions were mapped onto stereotaxic space using the "Clinical Toolbox" (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) implemented in the Statistical Parametric Mapping 8 (SPM8) software package (Wellcome Department of Cognitive Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk). See Figure 5.1 for summary of lesion mapping.

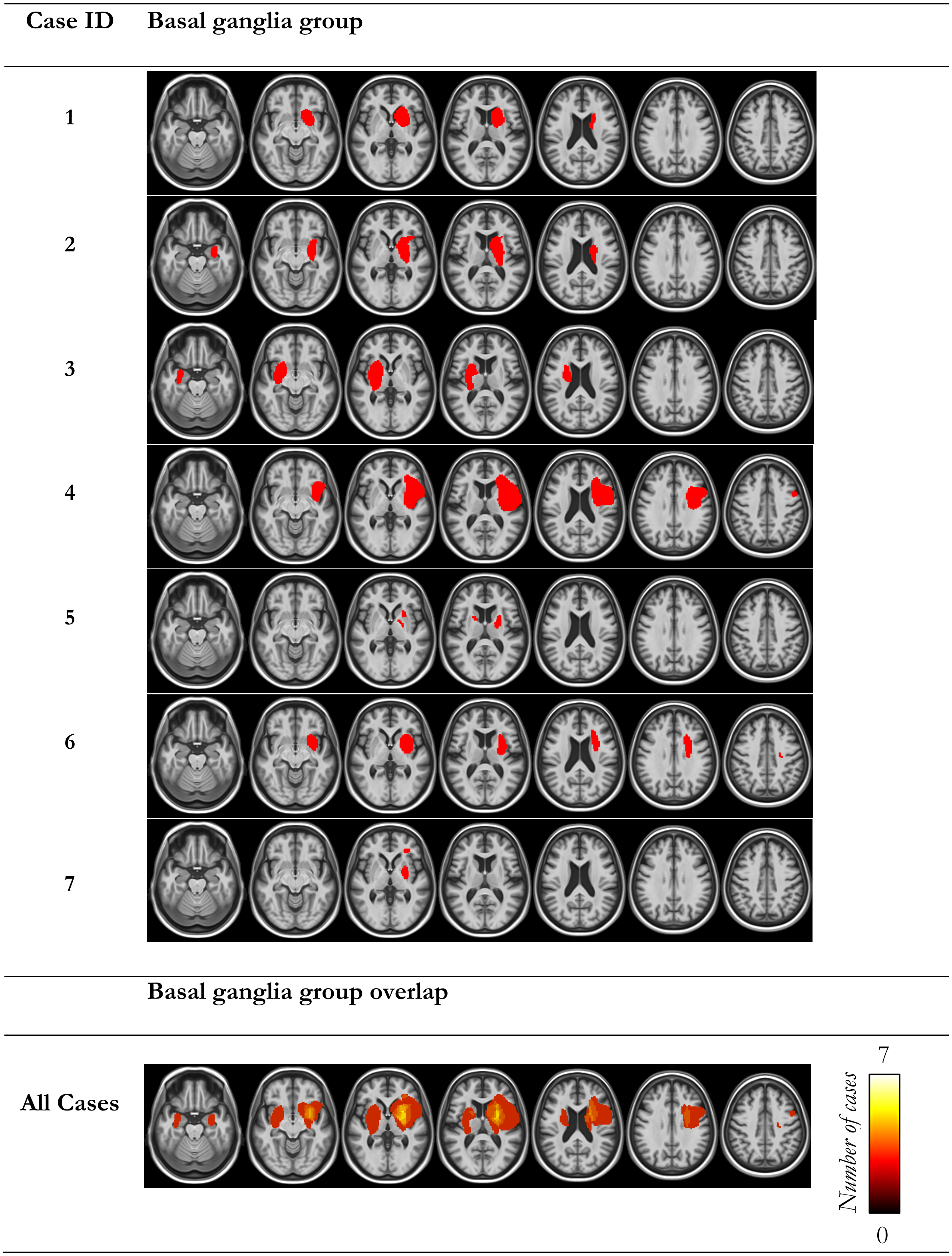

Figure 5.1 Neuroanatomy of lesions. Left hemisphere is represented in the left side of the images (neurological convention). Lesions are projected on a standard template.

5.2.4 Apparatus

Stimuli were created and presented through Presentation (16.5, Neurobehavioural systems, Albany, CA, United States of America), run on a Dell Optiplex 990 computer with a 23-inch ViewSonic VA2342-LED screen (resolution 1920 x 1080 pixels, refresh rate 60 Hz). Participants were seated in a dimly lit room, approximately 63 cm away from the monitor. Responses were collected using a standard keyboard.

5.2.5 Stimuli and experimental design

As in Chapter 4, performance data were recorded using a shorter version of Experiment 1 outlined in Chapter 3.2.3. Each study consisted of a speeded RT task and a non-speeded RSVP task (see Figure 3.1). Participants completed two blocks of each task (192 trials each). A short practice block was given before each set of two blocks. Whether the participant performed the speeded RT or the RSVP task first was alternated between participants. In the speeded RT task, participants were instructed to respond as quickly as they could to a green circular patch, which appeared at the centre of the screen. In the RSVP task, participants were instructed to identify a target letter ('X' or 'O') embedded in a stream of fourteen rapidly presented letters. The primary manipulation of temporal expectation in each case was blocked. Across a block of trials, cues consistently predicted the target would occur after a short or long interval. The blocked design was selected for three primary reasons: (1) blocked designs have been shown to produce more robust temporal orienting effects as compared to trial-by-trial manipulations (Correa et al., 2006; Trivino et al., 2010); (2) there was limited amount of time for testing participants in a single session (i.e. because of fatigue and/or demands on their time by other experimenters at the CNC); and (3) piloting determined that it was easier for patients to understand task instructions for a blocked design.

Both tasks followed the same basic design (see Chapter 3). Participants were instructed to maintain central fixation throughout the tasks and to do their best to use the temporal information provided to them by the auditory cues to help them to predict when the target was most likely to appear. Stimuli appeared superimposed against a uniform grey background (RGB values: 128, 128, 128), and a fixation point remained visible in the center of the screen (width: 0.46°; height: 0.46°). Each trial commenced following a participant-initiated key press. After a short delay lasting 500 ms (50% probability), 1000 ms (25% probability) or 1500 ms (25% probability), an audio cue was presented for 150 ms. The audio cue was either a high pitch (1100 Hz) or a low pitch (600 Hz) beep indicating a short or a long foreperiod, respectively. The cue was valid in 75% of the trials. Participants were informed that the audio cues would help them to predict when the target would appear.

In the speeded RT task, participants were asked to respond as quickly as possible with their right index finger[13] to a green circular patch (diameter: 1.82°), which was presented foveally after either a short (stimulus-onset asynchrony (SOA) of 540 ms) or a long foreperiod (SOA 1580 ms) (Figure 3.1a). In the non-speeded RSVP task, the audio cue was followed by a stream of 14 black letters (font: OCR A Extended; width: 0.9°; height: 1.92°) presented foveally and in rapid succession (duration 100 ms; inter-stimulus interval 20 ms). The SOA between the audio cue and the first letter was 300 ms. Thirteen letters were distractors and one was a target letter (Figure 3.1b). The target letter, either an 'X' or an 'O', appeared either early (on the 3rd location, after 540 ms) or late (on the 12th location, after 1620 ms). The distracter stimuli were randomly sampled without replacement from a set of

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[13] All patients and controls used their right index finger with the exception of Case ID #3. This participant exhibited motor weakness in the right hand and therefore used the left index finger instead.

letters [A,B,E,F,G,H,I,J,L,M,P,Q,R,T,U,W]. Following the presentation of the letter stream, participants made a non-speeded, delayed discrimination response with their right hand using the left (for 'X') and right (for 'O') arrow keys on a standard keyboard. In order to minimize the motor component of the perceptual discrimination task, participants responded after the offset of the visual stream during a designated response window. Participants were under no time pressure to provide a response and were informed that only the accuracy of the response would be taken into account.

5.2.6 Procedure

The study was administered for control participants over a single two-hour session at the CNC in Oxford. Upon arrival at the CNC, informed consent was obtained and participants were then invited to complete standardized neuropsychological tests (see 5.2.2). This took place in advance of the behavioural tasks, and was conducted in order to ensure that all participants were cognitively healthy. In total, the neuropsychological test took approximately 45 minutes and the behavioural task took a little over an hour to complete. All control participants did double the number of experimental trials as the patients. However, only the only the first two blocks for each task (192 trials) were used for analyses in this chapter so that nuisance variables such as the degree of familiarity with the task fatigue could be equated (see Chapter 3, Experiment 1).

All participants with basal ganglia lesions were invited to take part in both experimental tasks over a single session, which took approximately one hour. Prior to being invited to take part in the study, all stroke survivors gave informed consent to take part in experiments at the CNC. In all but one patient, the neuropsychological evaluations took place within 7 months of suffering a stroke. Case ID #6 was self-referred, and therefore BCoS was not admitted in the acute phase after stroke.

5.2.7 Data analysis

Statistical analyses were performed using custom-made scripts in MATLAB version 7.14 (R2012a, 32-bit) and SPSS version 22.0.

5.2.7.1 Primary analyses

For the speeded RT task, the primary outcome variable was the mean RT on correct responses for each condition. Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT across all conditions. The average number of outlying trials was low (<4%) and did not differ between patients and healthy controls (Table 5.4). For the non-speeded RSVP task, the primary outcome variable was a measure of perceptual sensitivity (*d'*). Trials were excluded from the analysis if the RT was more than three standard deviations above the mean RT across all conditions, and groups were compared using the Mann-Whitney U-test to account for unequal sample sizes.

As a first step with the analyses, the data from the group of stroke survivors with chronic basal ganglia lesions (n = 7) and the group of controls (n = 18) were analysed using separate two-way mixed-design analyses of variance (ANOVAs) with foreperiod (short, long) and cue validity (valid, invalid) as factors. For each measure, all participants who scored more than three standard deviations away from the average value within each group in at least one condition were excluded from the analysis. To examine how basal ganglia lesions affected temporal orienting, the ANOVA was conducted with non-parametric p-values (via a Monte Carlo simulation, described below) in order to account for the small sample size. Interaction effects were then followed up with non-parametric Wilcoxon signed-rank tests. Participant data from the control group was kept separate and analysed using a two-way ANOVA in order to ensure that the results were normal and replicated previous findings where longer tasks were used (see Chapter 3).

In order to control for possible biases in the statistics due to difference in power between valid and invalid conditions, a series of non-parametric permutation tests were conducted (Ernst, 2004; Maris, et al., 2007; see also Rohenkohl, et al., 2014). To this end, repeated-measures ANOVAs were performed separately for stroke survivors and control subjects. The significance of the observed results was assessed by comparison to a null distribution generated via Monte Carlo simulation with 10,000 repetitions. This null distribution was generated by randomly shuffling the condition labels within each participant's data in each repetition. The statistical test (*F*) on the mean difference between the conditions of interest was then performed, and the resulting value was entered into the null distribution. The permutation *p* value was determined as the proportion of random partitions that resulted in a larger test statistic than the observed one. Statistical tests were two-sided and used a critical alpha level of 0.05.

To help investigate the differences in the strength of the validity effect (e.g. in the case of two-way interactions), a 'cueing index' was calculated for each foreperiod. For the speeded RT task, the index was calculated by taking the difference between the mean RT in the invalid condition and the mean RT in the valid condition, and dividing this difference by the mean RT in the valid condition. For the non-speeded RSVP task, the index was calculated by taking the difference between the mean *d'* scores in the valid condition and the mean *d'* scores in the invalid condition, and dividing this difference by the mean *d'* score in the valid condition.

To examine the effect sizes, Cohen's d was calculated (Cohen, 1988) using an online Effect Size Calculator (2014). Cohen's d was calculated by taking the difference between two means divided by the standard deviation. To correct for the dependence among means, and enable a direct comparison of effect sizes between groups, the correlation between the two means was added to the equation (see Equation 8 in Morris & DeShon (2002)).

Table 5.4

The number of excluded outlier trials per experiment. RT values were considered outliers if more than 3 standard deviations away from the mean RT of a participant.

	Basal Ganglia Group			Controls			
Experiment	Mean	Min	Max	Mean	Min	Max	Mann-Whitney U test
Speeded RT task	2.57	1	5	3.71	1	7	U = 34.5, p = .10
RSVP task	2.85	1	4	3.06	1	5	U = 53.0, p = .54

Note. The average number of outlier trials did not differ between both groups, according to two-sample t-tests.

5.2.7.2 Secondary analyses

In a secondary analysis, the performance of each participant with a lesion in the basal ganglia was individually investigated. This was done by taking each stroke survivor's individual scores and comparing them to the distribution of results in all age-matched controls (i.e. comparing normalised z-scores) using Crawford & Garthwaite's (2002) single-case investigation method. Specifically, each patient had their overall performance for cueing indices contrasted with all healthy age-matched controls. Statistical tests were two-sided and used a critical alpha of 0.05.

5.3 Results

5.3.1 Speeded RT task

After removing the anticipatory responses, performance accuracy was at ceiling (<1% misses) for all conditions in both groups. Before analysing the between-group differences, individual participants scoring more than 3 standard deviations (SD) above or below the average performance of all the other participants were removed from the analysis. As a result, one control participant was excluded from the analysis.

5.3.1.1 Within-group results for basal ganglia and control groups

Separate two-way ANOVAs for the healthy control group and the basal ganglia group were conducted.

For healthy controls, the main effect of foreperiod was significant (*F* (1,16) = 15.89, $p < .001$, η^2 =0.5; *F*-test *permutation, p* < .0001), with RTs faster when the foreperiod was long (*M*±*SD* = 299±42 ms) than when it was short (*M*±*SD* = 309±28 ms). There was also a main effect of cue validity (*F* (1,16) = 38.59, $p < .001$, η^2 =0.71; *F*-test *permutation, p* < .0001), with RTs faster for valid (*M*±*SD* = 299±35 ms) than invalid (*M*±*SD* = 323±32 ms) trials. Of note, there was a significant interaction between foreperiod and validity (*F* (1,16) = 40.36, $p < .001$, η^2 =0.72; *F*-test *permutation, p* < .0001). In order to clarify the two-way interaction, post-hoc paired samples *t*-tests were conducted comparing the validity effects within groups for each foreperiod. Overall, control participants reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid (*M*±*SD* = 297±28 ms) compared to invalid (*M* = 350, *SD* ± 33 ms) temporal information (*t*(16) = -9.96, $p < .001$). The effect size was very large (Cohen's d = 2.46). In contrast, the validity of the auditory cue did not modulate RTs significantly in trials with a long foreperiod (*t*(16) = .46, $p = .65$).

For the basal ganglia group, a two-way mixed-design ANOVA was also conducted, however, due to the small sample size, only non-parametric p-values from the Monte Carlo simulation are reported. While there was no main effect of foreperiod (*F*-test *permutation* (1,6) = .94, $p = .41$), there was a main effect of cue validity (*F*-test *permutation* (1,6) = 4.46, $p < .0001$), with RTs faster for valid (*M*±*SD* = 409±90 ms) than invalid (*M*±*SD* = 486±146ms) trials. Of note, there was a significant interaction between foreperiod and validity (*F*-test *permutation* (1,6) = 12.59, $p < .0001$). In order to clarify the two-way interaction, post-hoc Wilcoxon signed-rank tests were conducted comparing the validity effects for each foreperiod. Overall, participants in the basal ganglia group reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid (*M*±*SD*

= 382±68 ms) compared to invalid (*M*±*SD* = 438±144 ms) temporal information (Z = -2.37, $p < .05$). In contrast, the validity of the auditory cue did not modulate RTs significantly in trials with a long foreperiod (Z = -1.86, p = .06).

In summary, as is common on temporal orienting tasks, each participant group exhibited an asymmetric cueing benefit for short versus long foreperiods. As shown in Figure 5.2, the target letter was most effectively discriminated in both groups when the cue correctly predicted the timing of the target stimulus to when the cue was invalid for the short foreperiod, replicating previous findings (see Chapters 2, 3 and 4).

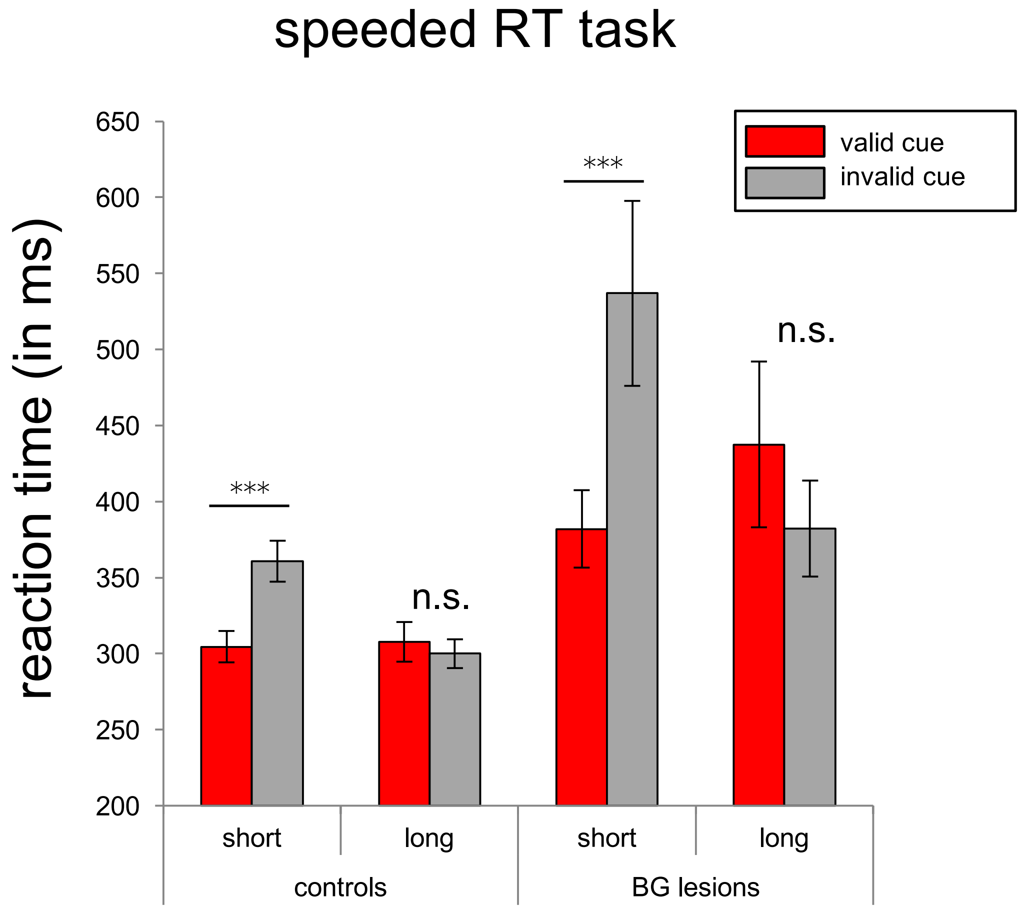

Figure 5.2 Temporal orienting effects for targets appearing after a short and long duration of time, for expected (valid) and unexpected (invalid) targets. Effects of temporal orienting on reaction time values (ms) in the speeded RT task. Error bars represent standard errors of the means (SEM).

5.3.1.2 Analyses of cueing index in individual cases

To compare the pattern of results between each individual member of the basal ganglia group, and the control group, the cueing index scores were individually compared to the age-matched group of controls for each condition (Figure 5.3). When the foreperiod was short, three of the seven basal ganglia participants (Case ID: 1, 4, and 7) showed a cueing index that was significantly larger than the average cueing index in healthy controls, with Case #4 having the largest cueing index (Table 5.5). (Of note, Case 4 was the only participant to have a lesion that extended into the insula and IFG). When the foreperiod was long, only one basal ganglia participant (Case ID: 1) showed a cueing index value that was significantly larger than the average cueing index score for healthy controls.

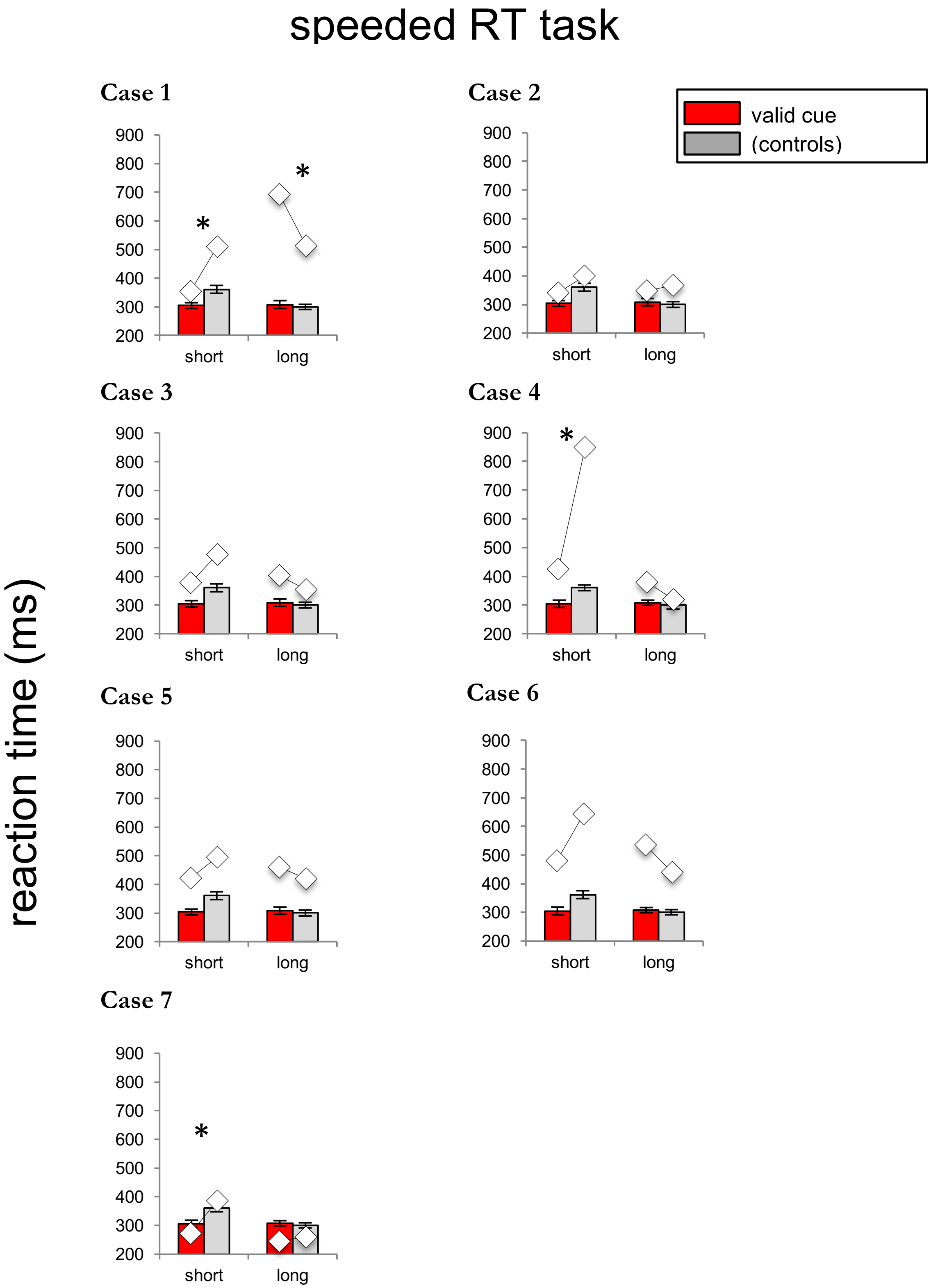

Figure 5.3 Temporal orienting effects for targets appearing after a short and long duration of time, for expected (valid) and unexpected (invalid) targets. Mean RT (ms) performance on the speeded RT task for each BG lesion participant (white diamonds) plotted over control group mean performance (*n* = 17). Error bars represent standard errors of the means (SEM). Asterisks indicate significant difference from controls according to cueing index.

Table 5.5

Behavioural performance on speeded RT task (ms) of individual members of basal ganglia group compared to all age-matched controls (n = 17)

#	Lesion Type	Short Cue Index*	Long Cue Index*
1	right basal ganglia	**0.44**	**-0.26**
2	Right basal ganglia, insula	0.17	0.05
3	left basal ganglia and thalamus	0.26	-0.12
4	right basal ganglia, insula, IFG	**1.00**	-0.16
5	right putamen	0.17	-0.08
6	right basal ganglia	0.34	-0.18
7	right basal ganglia	**0.42**	0.06
	Controls†	.18 (.08)	-.004(.09)

Note. All contrasts based on modified single case *t*-test by Crawford & Garthwaite (2002). Bold values correspond to significance at **$p < .05$**, bold and underlined values correspond to significance at **$p < .025$**.

* Short Cue Index = (Short Invalid – Short Valid) / (Short Valid); Long Cue Index = (Long Invalid – Long Valid) / (Long Valid).

† Mean and standard deviation (in parenthesis), averaged over all healthy control participants.

5.3.2 RSVP task

No participant performed more than 3 SD's beyond the mean for any condition on perceptual-discrimination task, so all participants were included in the analysis.

5.3.2.1 Comparing basal ganglia and control groups

Separate two-way ANOVAs for the healthy control group and the basal ganglia group were conducted.

For healthy controls, there was a significant main effect of cue validity (*F* (1,17) = 34.36, $p < .001$, $\eta^2 = 0.67$; *F*-test *permutation, p* < .01), with participants demonstrating greater sensitivity when trials were valid (*M*±*SD* = 2.74±.65) than when they were invalid (*M*±*SD* = 1.86±.98). There was a large effect size of cue validity (Cohen's d = .80). The interaction between validity and foreperiod was also significant in controls (*F* (1,17) = 8.52, $p < .01$, $\eta^2 = 0.33$; *F*-test *permutation, p* < .01), but there was no main effect of foreperiod (*p* = .12).

Post-hoc paired-sample *t*-tests were conducted to inform the foreperiod-by-validity interaction for control participants. Participants reacted significantly more quickly to targets appearing after a short foreperiod when the preceding cue contained valid (*M*±*SD* = 3.22±.7) compared to invalid (*M* = 1.72, *SD* ± 1.12) temporal information (*t*(17) = 5.43, $p < .001$). It was also found that the validity of the cue enhanced behaviour in the late trials. Control participants reacted significantly more quickly to targets appearing after a long foreperiod when the preceding cue contained valid (*M*±*SD* = 2.44±.8) compared to invalid (*M* = 1.96, *SD* ± .87) temporal information (*t*(17) = 5.43, $p < .001$). While there was a validity effect in both short and long conditions, by contrasting the cueing index for both conditions, it was found that the validity effect was much stronger in the short ($M \pm SD$ = .47±.40) compared to long (M = .14, SD ± .45) foreperiod condition ($t(17) = 2.67$, $p < .05$).

For the basal ganglia group, a two-way mixed-design ANOVA was also conducted, however, due to the small sample size, only non-parametric p-values from the Monte Carlo simulation are reported. There was no main effect foreperiod (F-test *permutation* (1,6) = .79, p = .40) or of cue validity (F-test *permutation* (1,6) = .82, p = .40). There was also no significant interaction between foreperiod and validity (F-test *permutation* (1,6) = .32, p =.59).

In summary, participants with basal ganglia lesions did not exhibit a perceptual advantage for validly cued information. As shown in Figure 5.4, the target letter was most effectively discriminated in the control group when the cue correctly predicted its position in the RSVP stream compared to when the cue was invalid, replicating previous findings (see Chapters 2, 3 and 4).

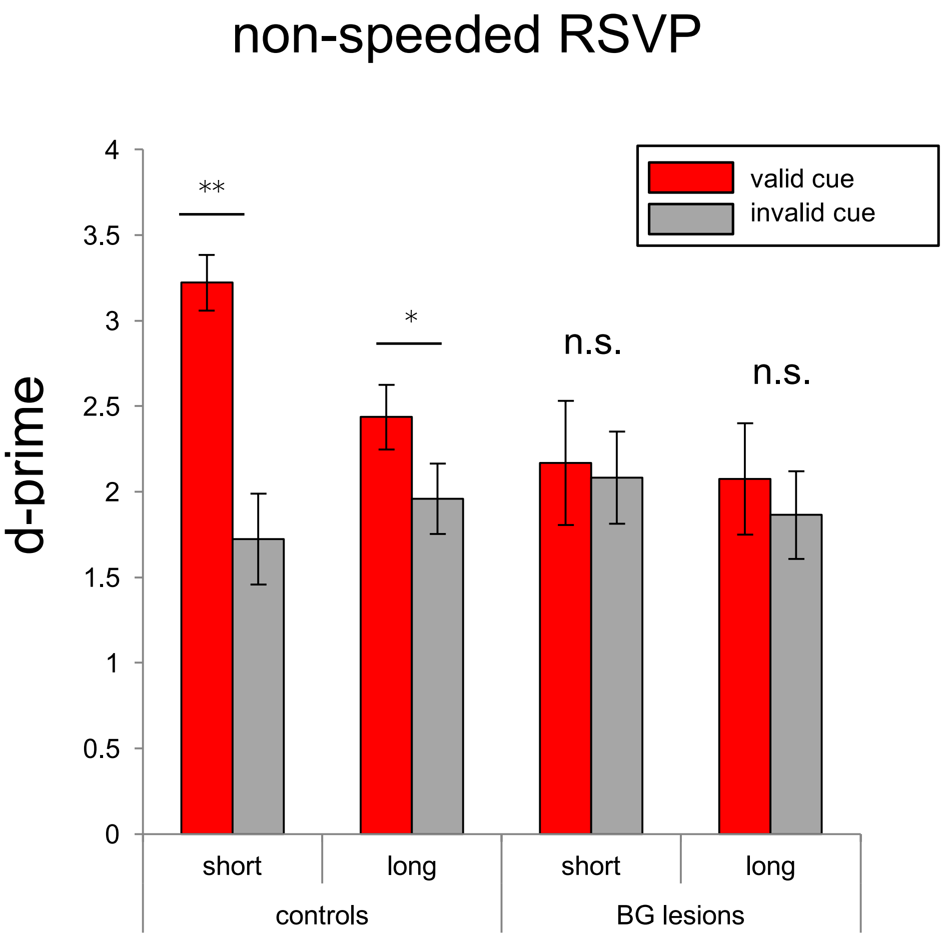

Figure 5.4 Temporal orienting effects for targets appearing after a short and long duration of time, for expected (valid) and unexpected (invalid) targets. Effects of temporal orienting on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent standard errors of the means (SEM).

5.3.2.2 Individual case comparisons

To examine deficits in temporal orienting in the RSVP task on a case-by-case basis, the cueing index scores were individually compared to the age-matched group of controls. According to the cueing index scores, all of the 7 basal ganglia participants showed a significant deviation from the performance of control participants for the short foreperiod, indicating a deficit at the single-case level (see Table 5.7). There was no difference between basal ganglia and control participants for the long foreperiod cueing index. As depicted in Figure 5.5, all participants in the basal ganglia group demonstrated cueing index values that were significantly smaller than control participants.

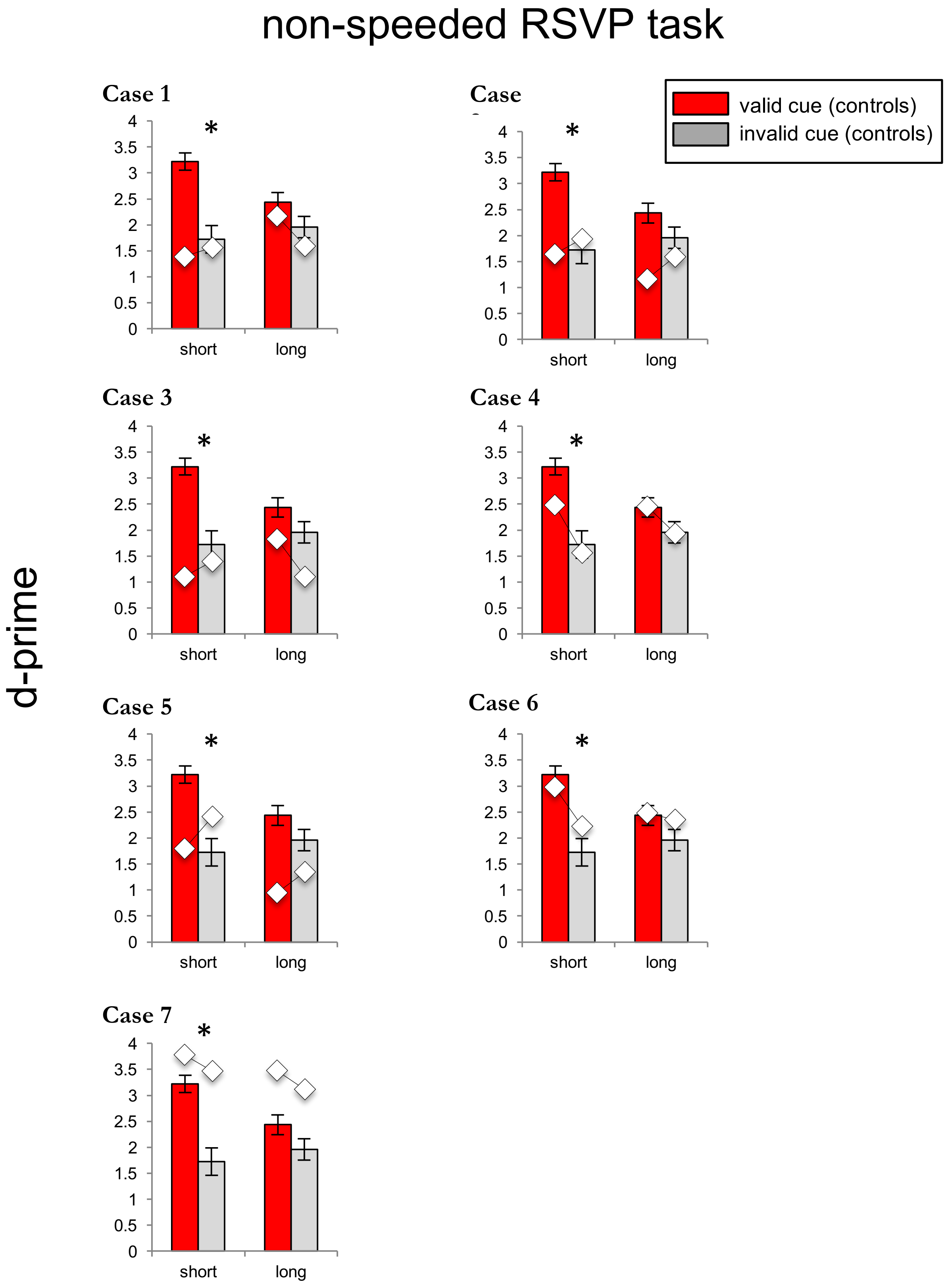

Figure 5.5 Temporal orienting effects for targets appearing after a short and long duration of time, for expected (valid) and unexpected (invalid) targets. Mean sensitivity score (*d'*) on the non-speeded RSVP task for each BG lesion participant (white diamonds) plotted over control group mean performance (n = 18). Error bars represent standard errors of the means (SEM). Asterisks indicate significant difference from controls according to cueing index.

Table 5.7

Behavioural performance on non-speeded RSVP task (d') of individual members of basal ganglia group compared to all age-matched controls (n = 18)

#	Lesion Type	Short Cue Index*	Long Cue Index*
1	right basal ganglia	**-0.13**	0.27
2	right insula, basal ganglia	**-0.18**	-0.36
3	left basal ganglia and thalamus	**-0.26**	0.40
4	right insula, basal ganglia, IFG	**0.37**	0.21
5	right putamen	**-0.34**	-0.43
6	right basal ganglia	**0.25**	0.05
7	right basal ganglia	**0.08**	0.10
	Controls†	.83 (.07)	.14 (.45)

Note. All contrasts based on modified single case *t*-test by Crawford & Garthwaite (2002). Bold values correspond to significance at p **< .05**, bold and underlined values correspond to significance at **p < .025**.

* Short Cue Index = (Short Valid – Short Invalid) / (Short Valid); Long Cue Index = (Long Valid – Long Invalid) / (Long Valid).

† Mean and standard deviation (in parenthesis), averaged over all healthy control participants.

5.4 Discussion

In the current study, the influence of the basal ganglia on temporal orienting was examined using a reaction-time task that emphasized speeded responding and a non-speeded RSVP task that emphasized visual discrimination. As previously shown, temporal orienting of attention can be preserved in healthy older adults. Given the presumed role of the basal ganglia in subserving temporal cognition, focal damage (or neurodegenerative changes) was hypothesized to contribute to deficits in temporal orienting. Interestingly, both stroke survivors with damage to the basal ganglia and controls benefited from cue-based temporal expectations to improve performance in a task that emphasized speeded responding. In contrast, individuals with stroke damage to the basal ganglia were unable to use temporal expectations to modulate perceptual performance in the perceptually demanding RSVP task. In line with the previous findings in Chapter 4, these results open the intriguing possibility that effects of temporal orienting can be dissociable depending on its target of modulation: temporal expectations can be used to enhance motor performance in a group of individuals with basal ganglia lesions, but are unable to modulate processing at the perceptual level. Additionally, or alternatively, the results may suggest that other demands or features of the RSVP task interact with the ability of orienting attention to enhance performance.

5.4.1 Temporal orienting for motor responses

The finding that temporal orienting can be used to modulate motor responses and improve reaction times in participants with basal ganglia lesions replicates previous findings (Triviño et al. 2010). This suggests that external timing signals can be used to strengthen internalized expectations for motor responses in participants with damage to the basal ganglia. Or put less hypothetically, temporal cues (in this case, auditory) can act as an external aid in improving motor performance.

Despite previous evidence demonstrating that patients with damage to the basal ganglia experience a generalized timing deficit (i.e., motor and non-motor), the findings of the current study demonstrate that temporally predictive contexts in which a given pre-target interval dominates combined with auditory cues can still be used to enhance motor responses. This is in line with previous studies that have shown how external cues can be used to offset a dysfunctional cortico-striato-thalamo-cortical system and improve performance on motor tasks. Consistent with our findings, it has been shown that temporally predictable auditory signals can help improve walking and gait to become better synchronized in patients with basal ganglia dysfunction (Benoit et al., 2014; Bella, Benoit, Farrugia, Schwartze, & Kotz, 2015). Moreover, these findings also align with studies on basal ganglia dysfunction that have shown how external auditory cues can be used to remediate dysfunctional internal beat perception in music (e.g., Grahn & Rowe, 2013) and improve speech perception (e.g., Kotz, Schwartze, & Schmidt-Kassow, 2009; Kotz & Schmidt-Kassow, 2015). While it is important to point out that these external cues involve a variety of task contexts, the finding in the present study could be seen as providing further support for the general benefit of external sensory cues to enhance behavioural performance in cases of basal ganglia dysfunction across contexts.

While the facilitation of motor responses by temporal orienting in the basal ganglia group provides an important replication of Triviño, et al.'s study (2010), these results should not be interpreted to mean that there is no motor or timing deficit in this group of individuals. Indeed, it is important to note that while patients were able to use implicit cues to improve their reaction times, they were still slower than control participants overall. This pattern of results supports the now well-established claim that the basal ganglia plays an integral role in coordinating motor actions (e.g. Braunlich & Seger, 2012). It is also consistent with the interpretation that basal ganglia deficits lead to a slowing of the internal clock (Ivry, 1996; Meck, 1996; Meck & Benson, 2002).

5.4.2 Temporal orienting for perception

Temporal orienting effects have been consistently found to enhance perceptual sensitivity, which suggests that temporal expectations can enhance early perceptual processing in a non-clinical population (Correa et al., 2005). While temporal expectations were shown to modulate behavioural performance for motor responses in a participant group with basal ganglia lesions, they were unable to modulate performance at the perceptual level in the RSVP task. These findings replicate and extend those of the study in Chapter 4, in which a similar pattern of results was revealed for individuals with PD. Specifically, participants with PD were unable to use temporal expectations to improve perceptual judgments. Confirmation of this pattern of results suggests that the basal ganglia, and not just other areas that might be affected in PD, are causally involved in temporal orienting in the RSVP task. Note, however, brain lesions in some of the individuals in the basal ganglia group also extended into insular and inferior frontal cortex. In addition, chronic basal ganglia lesions may also have affected interconnected brain areas through diaschisis (Carrera & Tonini, 2014). At the same time, the integrity of temporal orienting in the speeded RT task may mean that other brain regions have compensated for the basal ganglia lesion through reorganization (see Gillebert & Mantini, 2013). Future research should evaluate the possibility of temporal orienting deficits in participants with basal ganglia lesions being correlated with or being more pronounced when concomitant frontal damage is present.

The finding that temporal orienting is able to modulate performance at the motor level (*n.b.* the effect size was still smaller in the basal ganglia group) but not at the perceptual level invites some critical reflection. There are at least three possible interpretations of these findings:

(1) One possible interpretation is that temporal orienting for motor responses and perception rely on non-coextensive mechanisms (Nobre & Rohenkohl, 2014). In this case, deficits in temporal orienting caused by basal ganglia lesions can be modulated according to the task context and domain in which temporal expectations operate within, leading to the preservation of temporal orienting at the motor level but not at the perceptual level of processing.

(2) Conversely, a second plausible explanation is that temporal orienting is impaired in patients with basal ganglia dysfunction/damage, but that the speeded RT task was not sensitive enough to pick up on it. By virtue of the blocked nature of the design, the temporal orienting manipulation used was extremely strong, combining effects of cueing with those of hazard functions. The motor response demands were also very simple. Perhaps tasks that emphasise motor speed within more elaborate or coordinated action requirements would reveal subtler deficits. As such, the strength and preservation of the orienting effect in the speeded RT task should be interpreted with caution. Future research should examine whether the results would be maintained if task demands were increased.

(3) Or, thirdly, features of the RSVP task unrelated to temporal expectations may have prevented effects of temporal orienting to become manifest. If this is the case,

temporal orienting might still confer benefits for perceptual judgement in individuals with basal ganglia lesions in a different, more suitable task. Performance in the RSVP task may rely heavily on other functions, which may be compromised by basal ganglia lesions. For example, the observed difference may be better explained by a deficit in distractor inhibition. Functions related to distractor inhibition may have interacted with the ability of temporal predictions from the context (hazard rates) or cues to facilitate performance.

As reviewed in previous Chapters, the basal ganglia has been proposed to act as an attentional filter — a gatekeeper or 'bouncer' — that simultaneously selects relevant information and prevents distractors from entering WM (Awh & Vogel, 2008; McNab & Klingberg, 2008). Several computational models support this hypothesis. For instance, Hazy, Frank, and O'Reilly (2006) posit a model in which the basal ganglia serve as a gating mechanism for the maintenance of information stored in WM by the PFC. They argue that because the basal ganglia are connected to PFC through a series of parallel loops, they are well situated to control when information can be updated in WM. In effect, the basal ganglia act by disinhibiting or inhibiting the prefrontal cortex through the indirect "NoGo" and direct "Go" pathways that are well-documented in motor coordination. In order to understand the various ways that damage to the basal ganglia can lead to apparent deficits in temporal orienting, it will be interesting to consider the roles the basal ganglia may play in inhibiting distractors and gating relevant items to guide decisions (e.g. Braunlich & Seger, 2012; Frank, Loughry & O'Reilly, 2001; Schneider, 1984; McKnab & Klinberg, 2008; Murty, et al., 2011), and to test for whether these can interact with processes related to temporal orienting or timing more generally.

Given the preceding, it remains possible, therefore, that the perceptual discrimination requirement and the additional task demands in the RSVP task — such as having to overcome and inhibit extensive distraction — may have been too difficult to reveal significant effects of temporal orienting. In order to determine the role of the basal ganglia in temporal orienting at the perceptual level, it will be important for future researchers to isolate these effects using a perceptual task that does not involve inhibiting distracting information. Perhaps a simpler task design, analogous to the one used in the RT task, but requiring a fine perceptual judgement under masking conditions (see Rohenkohl et al., 2014) would have revealed modulation of perceptual sensitivity by temporal expectations in the basal ganglia group. This warrants further investigation.

The absence of significant foreperiod effects in the perceptual discrimination task also calls into question the role of the basal ganglia in temporal orienting more generally. Other task designs, such as those put forward by Coull et al. (2016), will prove useful in pulling apart the effects of foreperiod versus temporal orienting, and thus help probe the putative causal involvement of the basal ganglia in various forms of implicit temporal processes.

5.5 Conclusions

By studying the effects of temporal orienting in separate clinical populations, we can begin to develop a more complete understanding of the mechanisms that support temporal expectations. While neuroimaging research can help us understand the functional anatomy of temporal orienting, these studies cannot determine whether regions like the basal ganglia are *necessary* for temporal expectation. By examining the effects of temporal orienting in a group of participants with focal lesions, this Chapter provides new evidence concerning the debate about the influence of the basal ganglia on temporal orienting and represents the first time that temporal orienting for perceptual performance has been examined in this patient group. While it was found that temporal orienting for motor preparation was not impaired, participants with basal ganglia lesions were found to be unable to use temporal information to selectively enhance processes related to perceptual sensitivity.

In sum, these results suggest that temporal orienting, especially for motor responses, may not be dependent on the basal ganglia. Instead, other regions such as the IPS and prefrontal cortex might be more relevant for performance. Further research should be conducted to extend these findings with larger sample sizes that better control for relevant differences between groups, such as educational level.

The finding that temporal expectations are unable to enhance perceptual discrimination in participants with basal ganglia damage provokes a number of important questions: how much do deficits in temporal orienting depend on the task context and domain in which temporal expectations operate? Are the mechanisms that support temporal expectations for different purposes dissociable? How essential is the basal ganglia and its related circuitry in the mediation of timing effects, and for temporal orienting in particular? It is to these questions, *inter alia,* that we now turn to in the next chapter.

6 General Discussion

Chapter Abstract

In the final chapter of this thesis, I will assess what the experimental data (taken together) can tell us about temporal orienting for speeded action and perception more generally, and explore how we can improve the design of future experiments to investigate the supporting neural systems and mechanisms. Secondly, I will argue that the experiments of the preceding chapters provide converging support for the preservation of temporal expectations in ageing. Finally, I will provide some hypotheses for the neural mechanisms supporting temporal orienting based on the results of the studies on neurological populations. In conclusion, I will end by providing some direction for future work.

6.1 Temporal orienting in healthy ageing

6.1.1 On (spatio-)temporal orienting in elderly adults

One previous study in the literature had indicated that ageing is accompanied by significant deficits in the ability to use temporally predictive cues to enhance target detection or discrimination (Zanto et al., 2011). In Chapter 2, I revisited this question by combining temporal cues with spatial cues, which, in younger adults, have been shown to potentiate the effects of temporal orienting (Rohenkohl et al., 2014). It was hypothesized that by using these spatio-temporal cues, and guaranteeing spatial certainty, it might be possible to unmask a residual ability of older adults to benefit from temporal predictions.

In this first experiment, the colour of the cue was designed to manipulate temporal uncertainty of the target item, whereas the direction of the arrow cue predicted its location (left or right of the fixation point). The results provided some indication that older adults can use visual cues to improve their behavioural performance. However, the performance benefits were not very strong, and largely isolated to sequential effects (see Section 2.3.3, Figure 1.4). Though the results were not compared with younger participants, previous experiments in the lab have shown strong effects on similar tasks in younger adults (see Rohenkohl et al., 2014).

In hindsight, the experiment in Chapter 2 may have been suboptimal for isolating effects associated with temporal expectations. The task was taxing and contained multiple demands: sessions were long, and may have contributed to some participants feeling fatigued. Cues were complex and demanded a detailed set of instructions, which necessitated an extended training session and a practice session. The cues also required participants to shift between cue information on a trial-by-trial basis and required multiple endogenous shifts to spatial and temporal information concomitantly. Cue assignment to temporal information (through colour) was also arbitrary and not necessarily intuitive. Taken together, these nuisance factors likely contributed to an increased demand on executive functions and may have led to a dilution of temporal orienting effects.

While it is common for additional task demands to interfere or interact with the construct one is attempting to measure, this can be particularly problematic when working with older participants (and clinical populations), who may experience a general weakening of top-down control of attention (Deiber, et al., 2013; Pesce, Guidetti, Baldari, Tessitore, & Capranica, 2005). Indeed, this concern is similar to that of the one put forward by Pincham and colleagues (2012), who interpreted the lack of effects observed in Zanto et al. (2011) as evidence supporting the neural framework of diminished top-down control in ageing (e.g. Fabiani, 2012). Given the moderate effects that were found in Chapter 2, Pincham et al.'s (2012) interpretation is tempting to employ here too. However, the behavioural gains of temporal orienting (albeit only slight) admonish against this interpretation.

Given the fact that the spatio-temporal orienting task required the success of complex processing demands at multiple sub-stages of information processing — including visual perception, extraction of cue meaning, and preparation for response — even if top-down control of attention was to blame for the marginal behavioural gains, it would be difficult to know precisely which sub-stage of processing a participant is having difficulties. Indeed, reviews of attention in ageing have argued for impairments associated with ageing at each of these levels of processing (e.g. see Kramer & Kray, 2006). It is also worth noting that, at the level of visual processing, the decline of selective attention in ageing has partly been attributed to a degradation of bottom-up processing too (Fabiani, 2012; Madden, 2007). As summarized in Zanto & Gazzaley (2014), age-related declines in sensory and perceptual processes can contribute to slower and less accurate visual search (Schneider & Pichora-Fuller, 2000; Salthouse, 1985; 1996; Madden, 2007). As such, it is possible that as we age, we become more reliant on top-down mechanisms to make up for these deficiencies in bottom-up processes, leading to an increase on the demands of compensatory mechanisms required to process bottom-up information (Zanto & Gazzaley, 2014). Alternatively, it is just as plausible for older adults to experience difficulty at a slightly later processing stage. For instance, it may have been the case that the older adults experienced some difficulty extracting task-related information from the cue and shifting their attentional focus, resulting in deficient response preparation (see Hämmerer, Müller & Lindenberger, 2010).

Despite the difficulties of interpreting the null effects observed in Zanto et al.'s (2011) study, the modest, but significant, positive findings in Chapter 2 provided an incentive for probing further the question of the possible preservation of temporal orienting in healthy ageing.

6.1.2 Timing for motor and perceptual enhancement

In a subsequent set of experiments in Chapter 3, I returned to the drawing board with the lessons gathered from the first experiment and designed shorter and simpler experiments with which to test for temporal orienting in the absence of spatial cues in older and younger adults. Whereas in Chapter 2 temporal orienting was always accompanied by direction to a location, Chapter 3's experiments focused exclusively on orienting attention in time to enhance motor and perceptual performance using two paradigms.

In order to reveal any putative differences in the consequences of temporal orienting on speed of responses and perceptual analysis of visual stimuli, two tasks were used based on recent work from Davranche and colleagues (2011). In a simple speeded target detection task, motor responses were modulated by directing participants to respond to a target item (i.e. a green dot). A separate perceptually demanding discrimination task was used to measure perceptual effects. In the RSVP task, target stimuli were embedded in a stream of rapidly presented distractor letters, which stressed modulation of visual analysis. In order to enhance the chances of revealing effects of temporal expectations, intuitive auditory cues were used to help participants predict when the target items should be expected to appear.

Participants were first tested in a blocked design study, which has previously been shown to elicit strong temporal orienting effects (for review, see Nobre, 2010). In two separate groups of participants, results were again tested in a second experiment using a trial-by-trial design and again in a third experiment with neutral cues. Across these three experiments, both younger and older participants revealed strong behavioural advantages for orienting attention in time. These effects were shown to be largely attributable to the validity of the cue, and less the result of invalidity effects (e.g. *Experiment 3*). Overall, the experiments of Chapter 3, taken together with the findings of Chapter 2, demonstrated the robust preservation of temporal orienting in ageing for both speeded action and perception.

The stronger temporal orienting effects observed in Chapter 3 encourage reflection on both the limits of temporal orienting in ageing and the importance of task design in being able to elicit their effects. In addition to the speeded RT and RSVP tasks (likely) presenting fewer additional demands, the results of these studies provoke questions about the effectiveness of different types of cues to act as an aid for motor and perceptual enhancement. There are a number of reasons why auditory cues may be preferred to visual stimuli for guiding temporal expectations: for instance, encoding of auditory information may be more straightforward, or more efficient at guiding temporal predictions. In addition, audition may be inherently better suited to picking up rhythms, which has been shown to benefit participants with known timing deficits (e.g. Baker, et al., 2007; Rochester, et a., 2007; Rochester, et al., 2010; Rubinstein, et al., 2002; Lim et al., 2005; te Woerd, et al., 2015; Warlop, et al, 2015; Nombela, et al., 2013). For these reasons, while visual cues can be used to modulate and optimize behavioural performance on temporal orienting tasks — leading to improved reaction times and sensitivity to perceptual stimuli — it may not always represent the best way to guide an observer's attention in time and optimize behavioural outcomes.

In future research, when it comes to thinking about how to facilitate motor and perceptual performance, it may be helpful for the researcher to consider how easy it is for participants to form associations with the attentional cues provided.

6.1.3 Conflation of different types of temporal expectations

As mentioned in the discussion sections of Chapters 2 and 3, the results could be interpreted as providing partial evidence for non-coextensive mechanisms supporting the different types of temporal expectations (reviewed in section 1.2.3). For example, in Chapter 2, sequential effects were shown to lead to more perspicuous behavioural effects than endogenous temporal orienting. This finding suggests that some types of temporal expectations, for example those associated with more automatic processing (see Vallesi et al., 2009), may be more readily preserved in ageing than those that are dependent on voluntary, controlled sources of temporal predictions. This is in line with more recent studies that have shown a clear dissociation between the effects of foreperiod and temporal orienting (Capizzi et al., 2012; Triviño et al., 2010; Triviño, et al., 2011; Vallesi, et al., 2009). Dissociation between these effects has also been observed in children (ages 6-16), suggesting that the automatic mechanisms connected to foreperiod effects develops earlier than the voluntary orienting associating with endogenous temporal cueing (Johnson, Burrowes, & Coull, 2015).

Though it may be challenging to measure the various temporal expectation biases in isolation, some researchers have begun to design tasks to disentangle these effects. Recently, Coull and colleagues (2016) designed a task that uniquely manipulated both forms of temporal prediction within a single paradigm, which allowed them to expose distinct brain regions activated differentially by these separate types of temporal expectations. Additional research along these lines could be helpful.

In addition to the distinction between foreperiod effects and effects of temporal orienting, it may also be the case that temporal orienting for action and perception rely on non-coextensive neural mechanisms. While the designs of the experiments in Chapter 3 were not sufficiently parallel and similar to address the question in a healthy ageing sample without adding other confounding factors into play, future investigations should look to pull apart these effects, and determine the degree to which they may be interacting.

6.2 The preservation of temporal expectation in ageing

Previous research has indicated that spatial orienting is preserved in old age (Zanto & Gazzaley, 2014), however temporal expectation deficits were known to exist in older populations prior to the studies undertaken in this thesis (see Zanto & Gazzaley, 2011). Though the experiments herein only sought to look for residual abilities in temporal orienting in older adults, and were not necessarily designed to show that it remained completely unimpaired, direct statistical comparisons revealed no sign of degradation of temporal orienting compared to younger adults. These findings therefore invite further reflection on the conditions under which temporal orienting in ageing is preserved.

As overviewed in Kramer & Kray (2006), cognitive decline in ageing does not happen uniformly. Temporal expectation biases should not be expected to decline uniformly either. Rather, varying degrees of preservation of temporal expectations should be expected to occur between different groups of older adults — and this is likely to vary both for different types of temporal biases and across different domains. Future experiments should therefore look to map out what types of temporal expectations are most likely to be preserved in ageing, and under what conditions. For instance, it may be the case that more automatic processes, such as temporal expectations associated with foreperiod effects are more readily preserved than the more controlled process of temporal orienting (see Vallesi, et al., 2009). More ambitiously, researchers should also look to map out the developmental trajectory of these different types of temporal expectations, and determine how the presentation of these processes early on in development (e.g. Johnson, et al., 2015) may anticipate (or relate to) their likely preservation in later years.

Finding out when deficits in temporal expectations become exposed in ageing — and discovering which attentional processes are most likely to weaken as a result — will be vital to determining the point at which cognitive intervention may be helpful. In order to probe this question further, researchers should look to manipulate task demands within experiments over time to better understand the boundary conditions for temporal expectations. Previous studies have shown generally, as task difficulty increases, age-related declines in attention become more prominent (for review, see Zanto & Gazzaley, 2014).

Similarly, as task demands increase over time on temporal orienting tasks, older adults are likely to expose behavioural deficits. It will be important to clarify the point at which these impairments become evident, and ascertain whether these impairments present challenges for older adults trying to navigate their day-to-day surroundings.

In sum, this thesis demonstrates that temporal orienting can be preserved in ageing; however, it does not provide evidence of the neural mechanisms supporting the behaviour in healthy older adults. In a review article by Turgeon and colleagues (2016), it was concluded that there are fundamental age-related changes in the functioning of the cortico-thalamic-basal ganglia circuits in ageing, which are responsible for implementing timing at the interval range. In addition, we also know that many bottom-up sensory processes decline in ageing due to reduced neural specialization (Park, et al., 2004; Park & Reuter-Lorenz, 2009), and this can lead to deficits in many cognitive domains (Baltes & Lindenberger, 1997). While compensatory mechanisms have been proposed to help retain certain performance abilities in ageing, it is presently unknown whether temporal orienting is simply preserved in ageing or if successful temporal orienting in older adults relies on the neural recruitment of brain regions not typically utilized by younger participants. Additional research will therefore be required to fully understand the nature of the preservation of temporal orienting in ageing, and whether weaker effects in some participant groups (e.g. Chapter 2; Zanto et al., 2011) can be partially explained by differences in function of these cortico-thalamic-basal ganglia circuits and the recruitment of compensatory mechanisms.

6.3 Temporal orienting and basal ganglia dysfunction

In addition to investigating the effects of ageing on temporal orienting, a second aim of this thesis was to develop a better understanding of the basal ganglia's involvement (see section 1.3.3). In Chapters 4 and 5, I therefore examined temporal orienting in participants with PD and stroke damage to the basal ganglia. The temporal orienting tasks in Chapter 3 designed to measure motor responses and perceptual ability were found to be tolerable and intuitive for older participants. As such, they provided a good basis for interrogating the involvement of brain systems in temporal orienting in individuals with neurological deficits. It was hypothesized that using these separate tasks in participant groups with basal ganglia dysfunction could provide evidence for common involvement of temporal orienting in modulating perceptual and motor functions, or could reveal dissociations in the systems involved in modulating motor and perceptual functions by temporal expectations.

Using shorter, blocked versions of the experimental tasks employed in Chapter 3 (i.e. *Experiment 1*), the findings in Chapter 4 and 5 replicated the ability of the older control groups to benefit from temporal cues to facilitate both motor responding and perception. Perhaps surprisingly, even though the basal ganglia is implicated in explicit timing (Coull et al., 2013), the control of (spatial) attention (Nobre & Mesulam, 2014), and in action circuits (Griffin, et al., 2002; Nobre, 2001), there were no significant deficits in temporal orienting on individuals with basal ganglia damage on the speeded reaction time task. Rather, there were noticeable deficits in temporal orienting on the RSVP task, which emphasized perceptual functions. While it is difficult to isolate the effect of the basal ganglia on temporal orienting using participants with PD — for instance, since dopamine reduction can be widespread, it is difficult to separate the effects of basal ganglia dysfunction from dysfunction in other regions, such as the cerebellum, which is similarly affected — the comparable pattern of effects in participants with lesions to the basal ganglia in Chapter 5 provides some support for the basal ganglia's plausible involvement in temporal orienting for perceptual performance. However, given the small number of participants with basal ganglia lesions tested, this effect will require replication and extension.

Although these findings in the perceptual domain are no doubt intriguing, the pattern of results may not be so straightforwardly interpreted. As reviewed in the discussion sections (see sections 4.4 and 5.4), the RSVP task introduces many extraneous factors in addition to temporal orienting that make it difficult to feel confident interpreting these results as a deficit in temporal orienting for perception *per se*. Notably, the perceptual task required participants to inhibit distractor items and select the target item hidden amongst them. Alas, the basal ganglia are also strongly implicated in these functions (Awh & Vogel, 2008; Braunlich & Seger, 2012; Frank, Loughry & O'Reilly, 2001; Schneider, 1984; McKnab & Klinberg, 2008; Murty, et al., 2011). As such, these effects may have interacted with effects related to temporal predictions, making it difficult to know whether basal ganglia damage has any consequence on temporal orienting.

Just as in Chapter 2, it becomes clear in the experiments from Chapters 4 and 5 how important it is to consider all aspects of a task before jumping to conclusions. In general, it seems that deficits in temporal orienting are more likely to appear when task complexity is high — e.g. in older participants (e.g. Chapter 2), stroke survivors and participants with PD, where there is known cognitive deficits. These results therefore may not necessarily be evidence of temporal expectation deficits, but instead an interaction between temporal expectations and other task demands. Future researchers ought to think carefully about the choice of stimulus parameters, the executive demands, the inclusion of distraction, and the response requirements in order to isolate effects of temporal expectations. While this is especially important for ageing and neurological populations, simple task designs when implemented in younger adults can still generate key insights by limiting interaction effects associated with more complex task designs. Given temporal expectations are known to interact with other task factors (see Griffin & Nobre, 2005; Nobre, Rohenkohl, & Stokes, 2012), future studies ought to attempt to tease apart whether the deficit in the RSVP task observed in participants with basal ganglia dysfunction is a deficit of temporal expectation modulating perceptual analysis or a deficit in overcoming distraction and selecting the relevant target stimulus for performance.

One of the defining features of attention is the ability to focus on relevant information and exclude information that is task irrelevant. In hindsight, the RSVP task in particular may have been ineffective at distinguishing effects of temporal orienting from other competing demands, since the task involves many other functions. In the case of participants with basal ganglia dysfunction, low performance on the RSVP task might just as readily be interpreted as a deficit in inhibiting distracting information and selection as a deficit associated with temporal expectations. In future studies, it will be important for researchers to design tasks that are able to isolate the effects of temporal orienting from these competing theories.

In order to better isolate temporal orienting effects on perception, experimenters should look to design challenging perceptual discrimination tasks that omit competing demands as much as possible, such as distracting information. For instance, a modification on the experiment in Chapter 2, which uses Gabor patches as target stimuli, could be conducted. Such an experiment could eliminate the spatial element of the task entirely by presenting the target items foveally. By combining visual cues with audio cues (or forgoing the former in place of the latter) the experiment may elicit stronger behavioural effects by allowing participants to take advantage of more intuitive cues.

6.4 Conclusions & Future Directions

Temporal expectations have been shown to facilitate various cognitive processes, from preparing and executing motor responses to aiding perceptual discrimination. In addition to examining how temporal information can be used to bias behaviour, this thesis sought to explore the boundary conditions for temporal expectation deficits related to ageing and neurological disorders. In contrast to previous findings (Zanto et al., 2011), temporal expectations coded implicitly can be preserved in healthy ageing across different task domains (Chapters 2 & 3) and can act as an aid to speed motor responses in those with basal ganglia dysfunction (Chapter 4 & 5). Taken together, these experiments represent a foundation for future neuropsychological research in temporal orienting.

While this thesis contributes to the discussion concerning the role of the basal ganglia in temporal orienting, the study of the neural mechanisms behind temporal expectation still represent fertile ground for further study. Further, whether there exist dissociable mechanisms responsible for tuning motor-related processes and those used for enhancing perception remains unresolved. By taking advantage of brain-imaging and brain-disruption techniques, future research should explore the extent to which these regions might provide support for timing estimates used to guide temporal expectations in temporal orienting tasks.

So far, recent studies have shown that when TMS is applied to the cerebellum, sub-second duration timing can be impaired (Fierro, et al., 2007; Koch, et al., 2007; Lee, et al., 2007), conversely when TMS is applied to the right prefrontal cortex only supra-, but not sub-second durations timing is impaired (Jones, et al., 2004; Koch, et al., 2007). While temporally specific disruption with TMS would be ideal to explore the relevance of the basal ganglia in supporting temporal expectation — as has been fruitful with investigating the causal role of other networks in rapid attentional control (Zanto et al. 2011) — subcortical stimulation poses a challenge. There are, however, some methods using ultra-sound being considered (Tufail, et al., 2010). Unlike TMS, which cannot be focussed on subcortical structures without simultaneously disrupting cortical structures, ultrasound techniques can be focused using multiple transducer arrays as used in magnetic resonance guided focused ultrasound (MRgFUS) lesioning (e.g. Hynymen, et al., 2006). Further research needs to be conducted in order to determine whether these techniques represent viable alternatives that can be safely utilized in experiments on humans (Hamada & Rothwell, 2015). Of course, such methods do not obviate the need for experimenting with patient populations. By continuing to explore temporal orienting effects in lesioned populations, by studying patient populations with basal ganglia dysfunction (e.g. PD, Huntington's disease, and Schizophrenia), and using MEG to detect specific temporal changes in subcortical activity, researchers can complement brain-imaging and brain-disruption techniques to help clarify the extent to which timing systems might support temporal orienting.

As part of the endeavour to clarify the brain mechanisms responsible for temporal orienting, researchers should also continue to explore age differences in temporal expectations. One central question will be: what accounts for age-specific timing errors and what are the boundaries and limitations on this behaviour? For example, to further explore this question researchers could experiment with titrating responses to individual perceptual thresholds (e.g. Rohenkohl, et al., 2014). This would serve to qualify the conclusion by Zanto and colleagues (2011) that elderly participants experience some degree of expectation deficit by determining the conditions under which these deficits are likely to appear. In the long term, a second aim should be to develop a neurologically and developmentally plausible model of the fundamental processes involved in human temporal cognition and the role these processes might play in our ability to navigate the world. By coming to better understand how, for example, specific temporal biases are instantiated in the brain, and how/when they might break down, we will be better able to design treatment strategies and offer targeted cognitive rehabilitation.

While in old age, or after suffering a neurological disorder, we may never fully recover the strength of our younger selves (see section 2.1), some researchers are beginning to develop ways to treat deficits in attention through cognitive rehabilitation (for review, see Robertson & O'Connell, 2014). As we age, there is an increased reliance on environmental support (Lindenberger & Mayr, 2014). By learning more about when and under what conditions this shift from internal-to-external processing occurs in ageing, researchers can look to develop age-appropriate cognitive interventions that take advantage of external kinds of support. Attention-training programs have already been successfully developed for people who have suffered from a stroke (Barker-Collo, et al., 2009), and external sensory cues have been used to support behaviour in patients with neurological damage using external arousing or temporal cues (George, Mercer, Walker, & Manly, 2008; Robertson, Mattingly, Rorden & Driver, 1998; Robertson, Tegner, Tham, Lo & Nimmo-Smith, 1995). While approaches for cognitive rehabilitation are still in their infancy, the research seems to suggest that substantial attentional gains in ageing and after a neurological disorder is possible — however, whether or not such gains are generalizable to real contexts is yet to be determined (Lincoln, et al., 2008).

As ever, further research is needed.

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7 Appendix

7.1 Methods for Supplementary Outcome Variables

In addition to the primary outcome variables in Chapter 3, the response times in the speeded reaction time (RT) task and the perceptual discrimination values (*d'*) in the rapid serial visual presentation (RSVP) task, the proportion of anticipatory responses in the speeded RT task and the response times in the RSVP task were analyzed. Anticipatory responses were defined as either responses occurring before the onset of the target or responses with a RT less than 100 ms. RTs in the non-speeded RSVP task were adjusted according to the participant's accuracy using the inverse efficiency measure (Chambers, Stokes, & Mattingley, 2004; Romei, Driver, Schyns, & Thut, 2011; Townsend & Ashby, 1983). The inverse efficiency score (IES) was calculated by dividing the mean reaction time by the proportion of correct responses.

For each supplementary measure, participants who scored more than three standard deviations away from the mean value in at least one condition were excluded from the analysis. To examine how sensitivity to temporal information changed with age, a 3-way mixed-design analysis-of-variance (ANOVA) with foreperiod (short, long) and cue validity (Experiments 1 and 2: valid, invalid; Experiment 3: valid, invalid, neutral) as within-subjects factor, and age group (young, old) as a between-subjects factor for each task was conducted. When sphericity could not be assumed (Mauchly's sphericity test: $p < .05$), p-values were adjusted using the Greenhouse-Geisser correction (G-G correction).

Supplementary Analysis: Blocked versus Trial-by-Trial Design. In order to explore whether differences in performance depended on whether the auditory cues were blocked, a 4-way analysis of variance with study ('blocked design', 'trial-by-trial design') as between-subjects factor was conducted. Only older participants who participated in both studies were included in the analysis ($n = 13$).

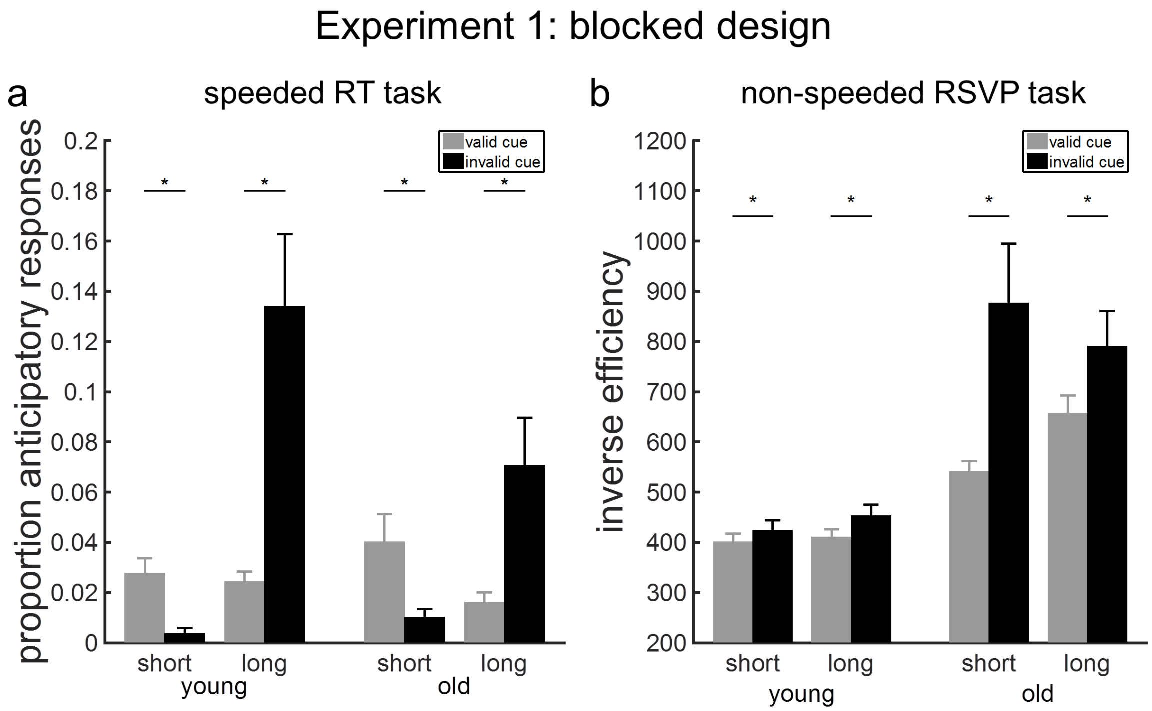
7.2 Supplementary Results

7.2.1 Experiment 1: Temporal Orienting in a Blocked Design

Anticipatory responses in the speeded RT task. Two participants (one young, one old) were excluded from the analysis on the proportion of anticipatory responses. This was because the proportion of their anticipatory responses was more than 3 standard deviations (SD) higher than the average proportion of anticipatory responses across all the other participants.

Both groups of participants committed a significantly larger number of anticipatory responses when they were cued to expect the target at the short foreperiod. Main effects of foreperiod ($F(1,32) = 29.55, p < .001$) and cue validity ($F(1,32) = 20.15, p < .001$), and a foreperiod-by-validity interaction ($F(1,32) = 27.62, p < .001$) on the proportion of anticipatory responses (Supplementary Figure 7.1a) were observed. Post-hoc *t*-tests were conducted to inform the foreperiod-by-validity interaction. Anticipatory responses on late targets were more frequent when participants expected a short foreperiod (invalid cue) compared to when they expected a long foreperiod (valid cue) ($t(33) = -5.02, p < .001$). The validity of the cue had an opposite effect on the proportion of anticipatory responses when the foreperiod was short: participants made more anticipatory responses when a short (valid cue) compared to a long foreperiod (invalid cue) was expected ($t(33) = 4.40$, $p < .001$) (Supplementary Figure 7.1).

In addition, there was an age-by-foreperiod ($F(1,32) = 9.06$, $p = .005$) and an age-by-validity interaction ($F(1,32) = 6.16$, $p = .02$), but no three-way interaction ($F(1,32) = 1.38$, $p = .25$). The age-by-foreperiod interaction was further examined by running separate ANOVAs for the early versus late foreperiod. When the target appeared late, younger individuals tended to make more anticipatory responses than older individuals (main effect of age: $F(1,32) = 3.55$, $p = .07$), whereas no such trend was observed for short foreperiods (main effect of age: $F(1,32) = 1.77$, $p = .19$). The age-by-validity interaction was further explored by running separate ANOVAs for valid versus invalid auditory cues. Younger individuals tended to make more anticipatory responses than older individuals when the cues were invalid ($F(1,32) = 2.61$, $p = .12$), but no such trend was present for valid cues ($F(1,32) = .07$, $p = .80$) (Supplementary Figure 7.1a).



Supplementary Figure 7.1 Temporal orienting effects in Experiment 1 (blocked design). (a) Effects of temporal expectations on the proportion of anticipatory responses in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

Response times in the RSVP task. One older participant was excluded from the analysis because of high RTs.

Since the omnibus ANOVA revealed a three-way interaction between foreperiod, validity, and age (*F*(1,33) = 8.28, *p* = .04), separate ANOVAs for short versus long foreperiods were conducted. When the target appeared early, the main effects of age (*F*(1,33) = 19.94, *p* < .001) and validity (*F*(1,33) = 10.76, *p* = .002), as well as the two-way interaction (*F*(1,33) = 8.26, *p* = .007) were significant. Post-hoc independent sample *t*-tests revealed that older individuals responded more slowly compared to younger adults independent of the cue type, but the magnitude of the effect was larger for invalid compared to valid cues (invalid cue: *t*(33) = 4.97, *p* < .001, Cohen's *d* = 1.67*;* valid cue: *t*(33) = 3.82, *p* = .001, Cohen's *d* = 1.26*)* (Supplementary Figure 7.1b). When the foreperiod was long, main effects of validity (*F*(1,33) =8.27, *p* = .007) and age (*F*(1,33) = 35.77, *p* < .001) were observed, but no significant age-by-validity interaction (*F*(1,33) = 2.11, *p* = .16).

7.2.2 Experiment 2: Temporal Orienting in a Trial-by-Trial Design

Anticipatory responses in the speeded RT task. One older participant was excluded because of a high proportion of anticipatory responses.

Younger and older participants showed a similar pattern of anticipatory responses when predictive cues were fully intermixed. As in Experiment 1, anticipatory responses were accentuated when cues predicted the target to appear after the short foreperiod. The three-way ANOVA revealed a main effect of foreperiod (*F*(1,34) = 28.29, *p* < .001) and a foreperiod-by-validity interaction (*F*(1,34) = 13.96, *p* = .001). No other effect was significant (main effect of age: $F(1,34) = .34$, $p = .57$; age-by-foreperiod interaction: $F(1,34) = 2.24$, $p = .14$; main effect of validity: $F(1,34) = 3.62$, $p = .07$; age-by-validity interaction: $F(1,34) = .49$, $p = .49$; age-by-foreperiod-by-validity interaction: $F(1,34) = .004$, $p = .95$). Post-hoc paired-sample *t*-tests showed that when the target appeared late, the proportion of anticipatory responses was higher when the cue was invalid rather than valid ($t(35) = -3.14$, $p = .003$). In contrast, when the target appeared early, the proportion of anticipatory responses was higher when the cue contained valid, instead of invalid temporal information ($t(35) = 4.03$, $p < .001$). (Supplementary Figure 7.2a).

Response times in the RSVP task. Two participants (one old, one young) were excluded because of high response times. All participants were included in the analysis. Analysis of RTs using the inverse efficiency measure showed main effects of foreperiod ($F(1,34) = 17.34$, $p < .001$) and cue validity ($F(1,34) = 7.59$, $p = .009$), as well as a foreperiod-by-validity interaction ($F(1,34) =12.83$, $p = .001$). We also observed a main effect of age ($F(1,34) = 6.32$, $p = .02$) and an age-by-foreperiod interaction ($F(1,34) = 17.41$, $p < .001$), but no age-by-validity interaction ($F(1,34) = .16$, $p = .69$) and no age-by-foreperiod-by-validity interaction ($F(1,34) = .42$, $p = .52$). RTs were shorter when the auditory cue contained valid compared to invalid temporal information. The foreperiod-by-validity interaction indicated that the magnitude of this effect was larger for short ($t(35) = -3.11$, $p = .004$) compared to long foreperiods ($t(35) = -2.26$, $p = .02$) (Supplementary Figure 7.2b).

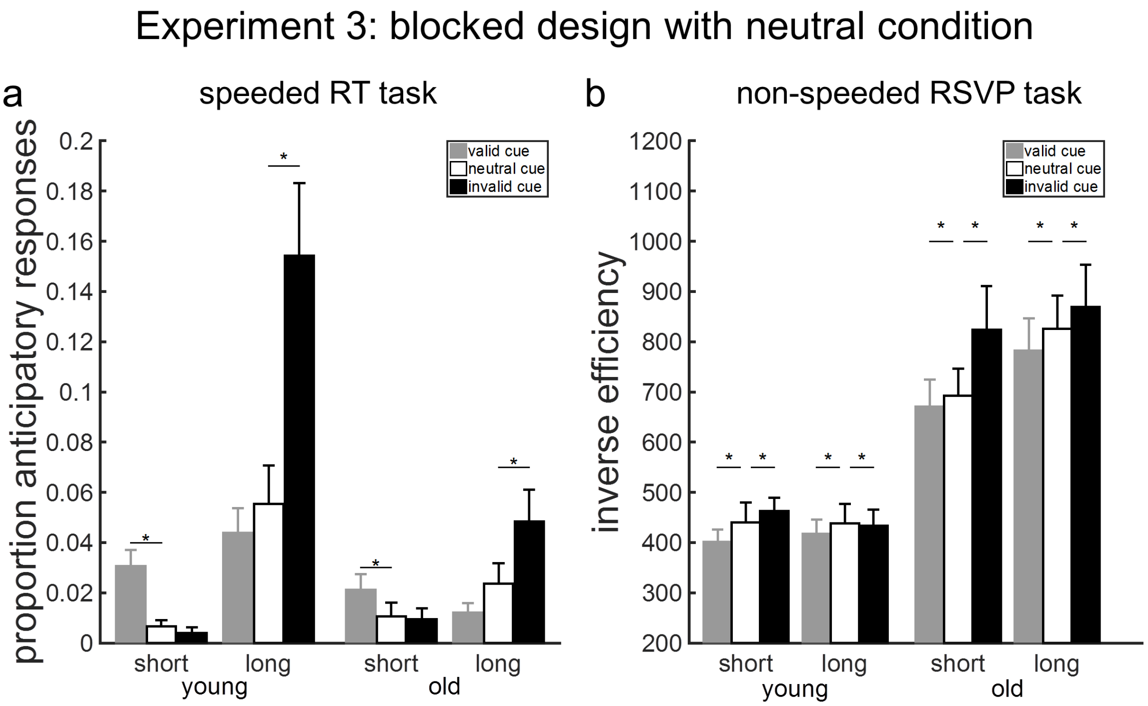
To test the age-by-foreperiod interaction, separate ANOVAs for short and long foreperiods were conducted. When the target appeared after a long interval, older participants responded more slowly compared to young adults ($F(1,34) = 10.90$, $p = 0.002$), but age did not modulate response times when the target appeared after a short interval, or did so only marginally ($F(1,34) = 2.87$, $p = .10$).

Supplementary Figure 7.2 Temporal orienting effects in Experiment 2 (trial-by-trial design). (a) Effects of temporal expectations on the proportion of anticipatory responses in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

7.2.3 Experiment 3: Benefits and Costs of Temporal Cues

Anticipatory responses in the speeded RT task. Three participants (two young, one old) were excluded from the analysis on the proportion of anticipatory responses.

There was a three-way interaction between age, validity and foreperiod ($F(1.38, 41.30) = 7.06$, G-G adj. $p = .006$). To understand this interaction, separate two-way ANOVAs for short and long foreperiods were conducted. For short foreperiods, a significant main effect of validity ($F(1.62, 48.62) = 19.89$, G-G adj. $p < .001$) was observed, but no main effect of age ($F(1,30) = .00$, $p = .99$) and no age-by-validity interaction ($F(1.62,48.62) = 3.04$, G-G adj. $p = 0.07$). Post-hoc *t*-tests showed that anticipatory responses were more frequent for valid versus neutral audio cues ($t(31) = 4.80$, $p < .001$), whereas there was no significant difference in anticipatory responses for invalid versus neutral cues ($t(31) = -0.76$, $p = 0.45$).



Supplementary Figure 7.3. Temporal orienting effects in Experiment 3. (a) Effects of temporal expectations on the proportion of anticipatory responses in the speeded RT task. (b) Effects of temporal expectations on sensitivity scores (*d'*) to the target items in the RSVP task. Error bars represent SEM.

A two-way ANOVA limited to the long foreperiod showed main effects of age (*F*(1,30) = 10.66, *p* = .003) and validity (*F*(1.55, 46.45) = 24.30, *p* < .001) as well as an age-by-validity interaction (*F*(1.55, 46.45) = 7.15, *p* = .004). Post-hoc independent sample *t*-tests demonstrated that younger adults had a higher proportion of anticipatory responses when the cue was valid (*t*(30) = 2.98, *p* = .006) or invalid (*t*(30) = 3.36, *p* =.002), but not when the cue was neutral (*t*(30) = 1.83, *p* = .08).

Response times in the RSVP task. Two old participants were excluded because of high response times. Main effects of age (*F*(1,33) = 25.63, *p* < .001), foreperiod (*F*(1,33) = 10.81, *p* = .002) and validity (*F*(1.56,51.38) = 8.81, G-G adj. *p* = .001) were observed. An age-by-foreperiod interaction (*F*(1,33) = 13.40, *p* = .001) was also observed, but no age-by-validity interaction (*F*(1.56,51.38) = 2.96, G-G adj. *p* = .08), no foreperiod-by-validity interaction (F(1.37,45.24) = 2.38, G-G adj. *p* = .12), and no three-way interaction between age, foreperiod and validity (F(1.37,45.24 = .53, G-G adj. *p* = .53).

Post-hoc *t*-tests to separate the patterns of validity benefits and invalidity costs showed that participants were faster when the audio cue preceding the target was valid compared to neutral (*t*(34) = -2.43, *p* = .02), but slower when the cue was invalid relative to neutral (*t*(34) = 3.13, *p* = .04). The interaction between age and foreperiod was further investigated by running separate ANOVAs for each foreperiod. Younger participants were significantly faster than older participants for both foreperiods, but the effect was larger for the long compared to the short foreperiod (short foreperiod: *F*(1,33) = 20.22, *p* < .001; long foreperiod: *F*(1,33) = 29.03, *p* < .001).

7.2.4 Blocked versus Trial-by-Trial Design

Speeded RT task. This analysis was limited to the thirteen older participants who took part in Experiments 1 and 2.

A within-subjects ANOVA with design ('blocked', 'trial-by-trial'), foreperiod, and cue validity as factors and the mean RT as outcome variable (Supplementary Figure 7.1a versus Supplementary Figure 7.2a) revealed a significant main effect of design ($F(1,12) = 7.59$, $p = .02$), as well as a significant three-way interaction ($F(1,12) = 14.95$, $p = .002$) (see Supplementary Table 7.1). This result suggests that RTs were longer, and the asymmetric cueing benefit stronger, in the blocked compared to the trial-by-trial version of the task. This is in line with the additional sources of temporal predictions in the blocked vs. trial-by-trial design. Only in the blocked design is there additional information related to tonic differences in the conditional probability for targets to appear at short versus long foreperiods.

RSVP task. Perceptual sensitivity in the RSVP task was not dependent on whether the temporal cues were blocked, nor did the design interact with any other factor (Supplementary Table 7.1).

Supplementary Table 7.1

Analysis of variance (ANOVA) to compare the blocked design (Experiment 1) to the trial-by-trial design (Experiment 2).

Effect	df1	df2	*F*	*p*	η^2
RTs in the Speeded RT task					
Experimental design*	1	12	7.59	.02	.39
Foreperiod*	1	12	35.06	<.001	.75
Validity*	1	12	37.23	<.001	.76
Experimental design x Foreperiod	1	12	2.48	.14	
Experimental design x Validity*	1	12	5.77	.03	.33
Foreperiod x Validity*	1	12	104.73	<.001	.90
Experimental design x Foreperiod x Age*	1	12	14.95	.002	.56
***d'* in the RSVP task**					
Experimental design	1	12	.69	.42	
Foreperiod*	1	12	8.20	.01	.41
Validity*	1	12	19.82	.001	.62
Experimental design x Foreperiod	1	12	.09	.77	
Experimental design x Validity	1	12	.28	.61	
Foreperiod x Validity*	1	12	6.10	.03	.34
Experimental design x Foreperiod x Age	1	12	.48	.50	

Note. * = significant effects.