Modulation of Working Memory

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I, Nahidsadat Zokaei, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Visual working memory, a limited temporary storage system for relevant information, is a critical contributor to many essential cognitive functions. In this thesis, I aimed to investigate some of the mechanisms underlying working memory in healthy humans and neurological patients, as well as its modulation by processes attributed to attention and the neurotransmitter dopamine.

There currently is an important controversy regarding models of working memory. I investigated whether a resource model of memory (which argues for a limited resource distributed amongst to-be-remembered items) might be extended to the domain of visual motion. The results suggest that this is indeed be the case, supporting the utility of this model as a general conceptual framework for understanding working memory across a range of visual features and modes of presentation (Chapter 2).

A comprehensive model of working memory should consider its relationship with attention. My findings point to an intimate yet highly specific relationship between these two processes, demonstrating that attention is essential for maintenance of *integrated features* within working memory (Chapters 2 and 4). Further, evidence for a causal role of early visual areas in maintenance of items in focus of attention, compared to the full content of working memory, is provided using transcranial magnetic stimulation (Chapter 3).

Finally, I investigated neuromodulation of working memory processes by dopamine in patients with dopamine dysfunction (Parkinson's disease) and using the dopamine agonist, Cabergoline, in healthy controls. The results demonstrate that dopamine can modulate working memory precision (Chapter 5 and 6). Furthermore, deficits in working memory were also observed in individuals with glucocerebrosidase mutations who have a significantly raised risk of developing Parkinson's disease (Chapter 7). I discuss the possibility that specific deficits in working memory might provide a cognitive marker of risk for neurodegeneration and development of Parkinson's disease.

Acknowledgments

I am indebted to many people for completing my PhD, only some of whom it is possible to give particular mention here. Firstly; I would like to thank my supervisor, Prof. Masud Husain, for his guidance, patience, motivation and immense knowledge. His high scientific standard, hard work and approach to research are just few qualities I hope to match someday. I could not have hoped for a better supervisor/mentor, not just for my PhD but for years to come.

I especially like to thank my parents and my sister Zoha. They have given me unparalleled support throughout my education. The mere expression of thanks does not suffice. I am also sincerely grateful to Ofogh for his support and consideration and Omid, Ali, Sholeh and Saleh for keeping me sane throughout these rather crazy years.

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Special thanks go to patients and their families, for their patience and kindness, without them the work done in chapters 5 and 7 would not be possible. Work presented in these two chapters were done in collaboration with my colleagues in UCL; Prof. Anthony Schapira and Atul Mehta, Drs. Paul Jarman, Christos Proukakis, Prasad Korlipara, Alisdair McNeill and Derralyn Hughes and the findings have been submitted to Brain.

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Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

List of Tables

Chapter 2

Chapter 4

Chapter 5

Chapter 7

Chapter 1

General Introduction

"Life is all memory, except for the one present moment that goes by you so quickly you hardly catch it going."

Tennessee Williams

1. 1 Introduction

Memory is a crucial cognitive process without which we would not be able to function in our daily lives. From driving a car to reading a book, or chatting with friends, we rely on memory to guide our behaviour. An individual's identity and definition of self relies on these processes; from memory of our actions, thoughts and beliefs to memory for

those said and executed by others. Therefore it is of no surprise that a vast amount of research has been conducted on understanding memory.

Memory refers to the processes that are used to acquire, maintain and retrieve information, in time scales ranging from milliseconds to years. There are several memory systems that fit such a description but are both behaviourally and anatomically dissociable from one another. In fact they are characterized by differences in their storage capacity, timing, conscious access and active maintenance. The concept of different types of memory systems is based on neuropsychological evidence from patients with focal cerebral lesions (Shallice and Warrington, 1970; Scoville and Milner, 2000; Milner, 2005) followed by behavioural, neuropharmacological, electrophysiological and imaging studies (e.g., Moscovitch et al., 1995; Rugg et al., 1998; Wiggs et al., 1999; Cabeza et al., 2002).

One storage mechanism has been considered to be dedicated to brief maintenance of information. This system was first formally identified by William James (James, 1890), who labeled it as primary memory. More commonly known as working memory; this mechanism provides a temporary storage system for maintenance and storage of information in order to support cognitive processes by providing an interface between various functions including perception, action and long-term memory (Baddeley, 2003). We all have experienced situations where we drive down a road only to realize that we have left our coffee cup on the roof of our car, or frantically search for our glasses only to find them on our head. These are just a few examples of failures in updating our working memory. Working memory is a critical contributor to many essential cognitive functions such as reasoning, language comprehension, learning, planning and general fluid intelligence (e.g., Baddeley, 1987; Engle et al., 1999; Conway et al., 2003).

The most influential model of working memory, proposed by Baddeley and Hitch (1974), argues for a multi-component working memory system. According to the latest version of this model (Baddeley, 2000), working memory consists of 4 major components (Fig. 1.1). In this scheme, there is a central executive system, which controls and coordinates activities within slave storage systems. The phonological loop, one of the slave systems, maintains speech-based information for a short period of time as well as transforming visual information into speech-based codes, while the visuospatial sketchpad, the other slave system, maintains visual and spatial information.

The episodic buffer acts as an interface between sub-systems of working memory and long term memory. It has a limited capacity and is considered to be necessary to bring together information to form integrated episodes.

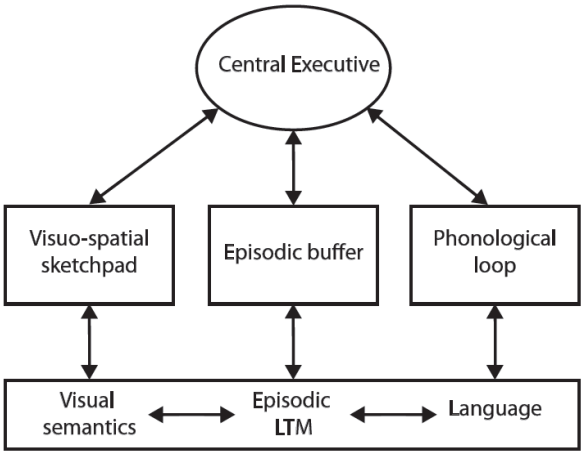

Figure 1. 1: A schematic representation of the multi-component model of working memory.
The model comprises of a control system (central executive) and two storage systems (visuo-spatial sketchpad and phonological loop). Episodic buffer is an interface between the working memory systems and the counterparts of these systems in the long term memory.

The visuospatial sketchpad, also referred to as visual working memory, provides a limited, temporary storage system for relevant visual information (Baddeley, 2003). Understanding the limits and mechanisms underlying visual working memory has become fundamental to understanding perception (Simons and Rensink, 2005; Brady et al., 2011), attention (Awh and Jonides, 2001; de Fockert et al., 2001; Wheeler and Treisman, 2002a; Lepsien and Nobre, 2007; Lepsien et al., 2011) and action (e.g., Woodman and Luck, 2004). Visual working memory has been extensively studied. However, there still remains a great deal of controversy regarding its characteristics, limits and nature. Below I will briefly review the theoretical and empirical background that stimulated the questions addressed in this thesis.

1. 2 Models of visual working memory

One of the fundamental features of working memory is its limited capacity (Miller, 1956; Cowan, 2001, 2005). There are currently two main theoretical frameworks, which differ in their description of how this capacity is defined.

Consideration of models of working memory also provides an insight into the functional role of attention in memory processes. Working memory and attention are intimately connected constructs in psychology. It has been suggested that attention, that is our ability to focus cognitive resources on task-relevant information, plays an important role in different stages of working memory. Influences of attention have been reported for the preparatory period before a memory task (Schmidt et al., 2002; Bollinger et al., 2011), selection and encoding (Vogel and Machizawa, 2004; Vogel et al., 2005), maintenance of information (Awh et al., 1998; Postle and D'Esposito, 1999; Jha, 2002) as well as retrieval (Theeuwes et al., 2011).

I next, provide a comprehensive description of current models of working memory, the role of attention in these models and experimental evidence supporting each model.

1. 2. 1 Object-based models

It is commonly believed that working memory capacity is limited by the number of to-be-remembered objects. More specifically, as viewed by many models of memory, the capacity is estimated to be about four "chunks" of information (Cowan, 1988, 2001), defined in terms of the number of integrated objects in the visual domain (Luck and Vogel, 1997). In line with this framework, an item-limit model of working memory has been developed which argues for a limited number of object "slots", each storing information regarding an individual object with equal precision/resolution.

According to these models, no further objects can be stored in working memory once the object limit is reached. Figure 1.2 is a schematic of object-based models. As illustrated, for memory arrays with fewer objects than the object limit of memory (here 4 items) each item occupies a memory "slot" and is maintained in working memory. However, beyond an individual's "slot" limit, only a limited number of objects (corresponding to individual's number of slots) is stored and no information regarding the remaining objects is maintained (see the two objects which are not occupying slots when N=6 in the memory array, Fig. 1.2).

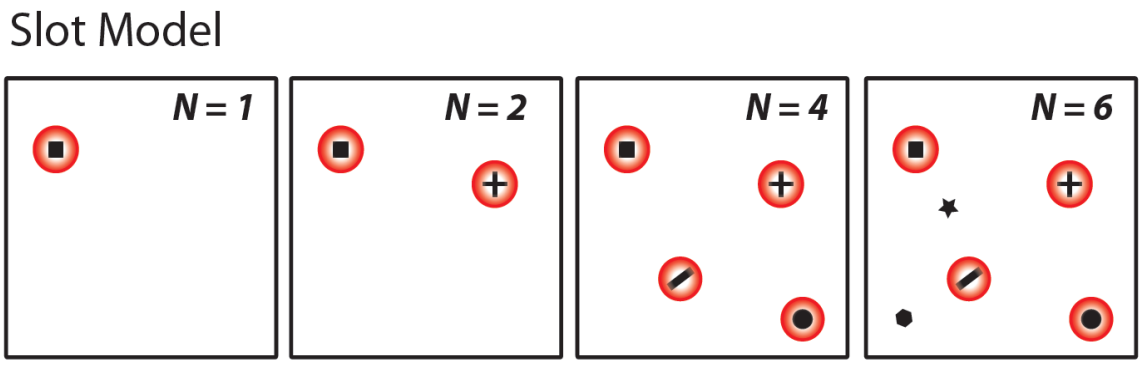

Figure 1. 2: Schematic representation of object-limit model of memory capacity.
There are a limited number of memory "slots", each storing one object. No information is stored about items beyond this limit (here 4).

In order to provide an estimate of an individual's capacity limit, visual working memory has been examined using the change-detection paradigm. In such tasks, participants are asked to detect the presence of suprathreshold changes among an array of items, after a short retention period, by making a binary (same/different) response (Vogel et al., 2001a; Wilken and Ma, 2004a; Awh et al., 2007). A schematic of a sample trial is presented in Figure 1.3A. Using this methodology one can measure the capacity of visual working memory by computing the maximum number of items in a memory array that results in higher than chance accuracy in change-detection.

An alternative to change-detection tasks relies on remembering a visual feature and reproducing the exact qualities of the stored feature after a retention period, using a method of adjustment (Wilken and Ma, 2004; Zhang and Luck, 2008; Bays et al., 2009b; Fougnie et al., 2010) (Fig. 1.3B). For example, in the example presented in Figure 1.3B, participants are asked to remember the colour of each square at different spatial locations. Following a retention interval, participants are probed by a location cue to reproduce the exact colour of the probed square by choosing the appropriate value from the colour wheel. Using this methodology, one can measure the precision/fidelity with which an item is stored in working memory by calculating the distribution of errors in relation to the true value of the target (Zhang and Luck, 2008; Bays et al., 2009; Gorgoraptis et al., 2011). Both change-detection and adjustment methodologies have been employed extensively to study the nature of visual working memory.

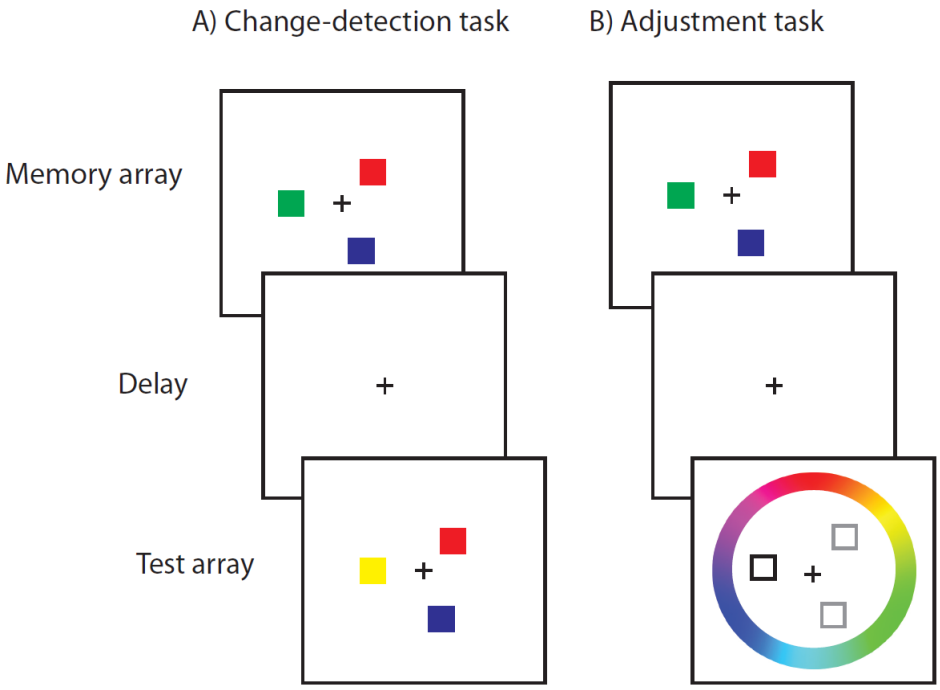

Figure 1. 3: Different methods for measuring visual working memory.
A) Change detection tasks where participants are asked to keep in mind a memory array. Following a retention period, participants have to indicate whether the test array is identical to the memory array or whether an item has changed (here a colour change). B) Adjustment task, where participants are asked to keep in mind a memory array. Following a delay period, participants have to reproduce the exact qualities of a cued item (bold outline square) in memory.

Results from studies using change-detection methodology have been interpreted to show that the number of memory slots is approximately 3-4 objects (Luck and Vogel, 1997; Anderson et al., 2011; Luria and Vogel, 2011), with some variation across individuals (Vogel et al., 2005). Importantly, in a landmark series of experiments, Luck and Vogel (1997) demonstrated that working memory performance was unaffected by the number of features within the objects. Participants performed change-detection tasks for objects comprising either individual features or conjunction of multiple features (within or across feature dimensions). They were just as accurate for objects comprising single features as those consisting of multiple features. These findings have since been replicated (Vogel et al., 2001; Luria and Vogel, 2011). According to object-based models of working memory, although initial feature-binding relies on attention, maintenance of stored items can be achieved in the absence of attention resources.

Electrophysiological studies have also provided evidence that reflects the encoding and maintenance of a limited number of items stored in working memory (Vogel and

Machizawa, 2004; Vogel McCollough et al., 2005; Carlisle et al., 2011). Vogel and Machizawa (2004) recorded event-related potentials (EPRs) from normal human participants while they performed a change-detection visual working memory task. In order to compare changes in EPRs in memory maintenance and retrieval to baseline performance, participants were cued to attend to one side of space and perform the change-detection memory task on items presented on that side.

A large negative-going voltage was recorded over the contralateral hemisphere to the memorized hemifield approximately 200 msec after the onset of the memory array. This negativity remained throughout the duration of the retention interval and, most importantly, reflected the number of items maintained in working memory (Fig. 1.4). In trials where the memory array exceeded individual's limited capacity, no further change in the amplitude of the activity was observed. However, below this capacity, increasing the items in the memory array resulted in an increase in the amplitude of the reported activity (Fig. 1.4). It was therefore argued that this contralateral delay activity (CDA) reflects the number of items maintained in working memory and provides electrophysiological evidence for the item-limit of working memory.

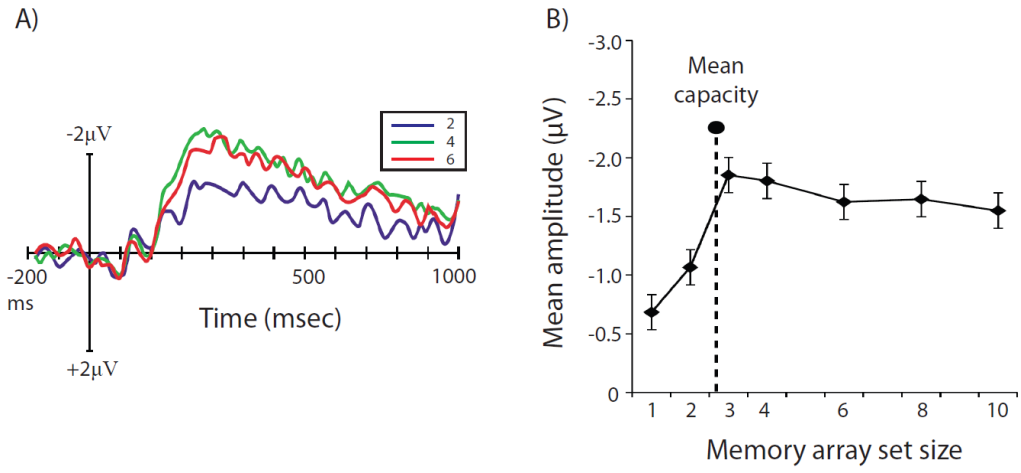

Figure 1. 4 : Modulations in ERP amplitude for different memory set sizes.
A) ERP difference waves at lateral occipital and posterior parietal electrodes sites. There is an increase in the amplitude of negativity from memory set sizes 2 to 4. However, there is no change in amplitude from memory sizes 4 and 6. B) Mean amplitude of delay activity plateaus beyond mean capacity of participants, and for set sizes beyond 3-4 items, i.e., number of slots proposed by slot models of memory (from Vogel and Machizawa, 2004).

In line with the integrated object account, it has been shown that the CDA amplitude reflects the number of objects maintained in working memory regardless of the number of features within these objects (Luria and Vogel, 2011). Moreover, in another study it was demonstrated that orienting attention to a subset of internal representations of items during working memory maintenance reduced the magnitude of CDA to reflect the number of items "relevant" to the task in hand after the presentation of the retro cue (Kuo et al., 2012). In this investigation, attention was manipulated using a spatial retro cue- a cue prioritizing a specific location long after the visual array had been extinguished.

The studies reported above have used change-detection methodology to investigate the limits of visual working memory. Recently however, Zhang and Luck (2008) examined working memory precision using an adjustment task (Fig. 1.3B). They aimed to decompose possible sources of error in memory performance. It was argued that random errors (guessing) can arise at set sizes above individuals' working memory capacity as a result of failure in encoding. In line with the object-limited model of memory, the results showed a dramatic increase at random responses in set sizes above memory capacity. Below capacity (i.e., 3-4 items), however, there was a decrease in precision of memory as set size increased. In other words, participants performed more accurately when 1 object was maintained compared to 3 objects. A similar pattern of findings has since been reported (Zhang and Luck, 2008, 2009; Anderson et al., 2011), showing that working memory resolution exhibits a monotonic decline as set sizes increase until it reaches an individual's item limit, after which resolution achieves a clear asymptote.

These results challenged the classical "slot"/object-limit model of working memory since this model is not able to account for variable precision of memory *below* the item-limit of memory. To account for this, Zhang and Luck (2008) proposed a revised version of the slot model: the "slot+averaging" model. According to this model, a memory resource is divided into a few fixed-resolution slots (<3). Below the limit of slots, objects can be stored in *more than one slot* and averaged to provide a high-resolution memory representation. So if there are two objects to remember and three slots, one object can be maintained in two slots at a higher resolution than the other item held in only one slot. Beyond the slot limit, similar to classical item-limit model however, no information is stored, resulting in an increase in random responses. Importantly, this model has maintained the critical feature of item-limit models arguing

for a limit of 3-4 objects, a finding that has been challenged in the literature (See section 1.2.2 below).

Together these findings point to a visual working memory system that is firstly limited by the number of objects it can store and secondly, a limit that is independent of the number of features within each item. The item-limits of working memory is also represented in the amplitude of CDA, highlighting CDA as an electrophysiological marker of working memory capacity. Although the studies reported here, and many more, provide a strong case for item-limit models of working memory, this concept has more recently been challenged specifically by models that favor a resource-like nature of working memory processes.

1. 2. 2 Resource models

Recent progress in visual working memory research has resulted in an emphasis on measuring the fidelity or precision of memory representations (Wilken and Ma, 2004; Bays et al., 2009; Fougnie et al., 2010). Change-detection tasks with a fixed magnitude of change might not be sensitive to small differences in memory resolution. Typically, the magnitude of the change to be detected in such experiments is constant and arbitrarily large with observers asked to make a binary (same/different) response. Just because a participant makes an error on such a task, it does not mean they had no memory for it at all. Conversely, a correct response does not tell us how well they remembered an item either. Therefore, working memory capacity estimated using change-detection might not provide a sensitive measure of memory performance.

Considering these limitations, recent studies have investigated the resolution with which visual features are stored in working memory using discrimination (Palmer, 1990; Lakha and Wright, 2004; Bays and Husain, 2008), change-detection with varied change magnitude (Alvarez and Cavanagh, 2004) and the method of adjustment (Wilken and Ma, 2004; Bays et al., 2009; Fougnie et al., 2010). Based on such studies examining the fidelity of memory, resource models of memory have been developed. According to these models, the resolution with which an item is stored in memory is proportional to the *fraction of memory resource* dedicated to that item. Working memory resource allocated to each item is affected by both number of items, i.e., set size (Bays and

Husain, 2008; Bays et al., 2009), and complexity or information load within each object (Alvarez and Cavanagh, 2004). The important feature of these models is that working memory is not limited by the number of objects it can store, but rather the precision of memory for an object depends purely on the available working memory resources.

Although studies using change-detection have classically provided evidence for the item-limit model of working memory, change-detection tasks using varied magnitude of information load have provided evidence for a resource model. In a study by Alvarez and Cavanagh (2004) participants performed a change detection task on objects consisting of either small amount of information (i.e., objects defined by categorically different colours) or high amount of information (i.e., perceptually similar 3D cubes). The results showed that successful change detection relied on the amount of information load of the maintained objects. Furthermore, there was a trade-off between the complexity of the objects and the total number of items successfully maintained in working memory. The authors argued that when presented with more complex objects, more resource is allocated to these items and hence the total number of items maintained in memory is reduced. Importantly, impairment in performance for more complex items was not due to lack of discrimination between these objects, but instead resulted from a lower resolution of the represented objects in memory. Similar capacity-resolution tradeoff has also been reported in infants (Zosh and Feigenson, 2009). Taking these findings into account, some researchers have argued for a resource model of working memory that is influenced by the complexity of each object. According to such a model, more simple objects can be stored in memory compared to fewer complex items, as each complex object requires more resource to be successfully maintained (Alvarez and Cavanagh, 2004; Brady et al., 2011).

Some investigators have recently used an alternative to change-detection tasks, i.e., method of adjustment, which relies on remembering and reproducing a feature dimension from stored items (Wilken and Ma, 2004; Bays et al., 2009; Fougnie et al., 2010) (Fig. 1.3A). The results from studies using this methodology have revealed that the precision with which visual features are stored depends on the number of items simultaneously held in memory (Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009, 2011; Brady et al., 2011). There is a graded decrease in the precision of memory as the number of items increase, even from one to two items, well below the classical item limit of slot models (Bays and Husain, 2008; Bays et al., 2009;

Gorgoraptis et al., 2011). Importantly, the object limit proposed by slot models has not been observed as performance is above chance even for set sizes of up to 5 or 6 items (Bays and Husain, 2008; Gorgoraptis et al., 2011) (Fig. 1.5).

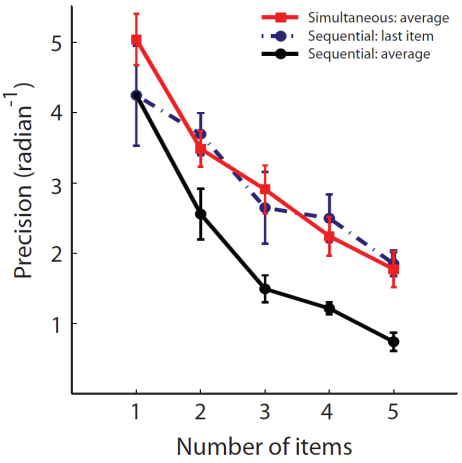

Figure 1. 5: Effect of the number of items on memory in both sequential and simultaneous presentation of oriented bars.

Average precision decreased with increasing number of items presented in a sequence (black line) or simultaneously (red line). This was also true for the last item in the sequence (dashed blue line) (from Gorgoraptis et al., 2011).

Based on these findings, resource models have been proposed which argue for a limited working memory resource that is divided amongst all to-be-remembered items (Bays and Husain, 2008; Bays Catalao et al., 2009; Bays et al., 2011, 2011; Gorgoraptis et al., 2011). The fraction of memory resource allocated to each item is proportional to memory set size and hence with larger set sizes each item in memory receives a smaller proportion of the limited resource. As an analogy, one can conceptualize memory resource as a bottle of juice. When dividing the juice between 2 people, each person receives half of the juice. However, dividing the juice between 5 people results in each individual receiving a lower proportion. The same applies to working memory resource; when dividing the resource between many objects, each object will receive a lower portion of the resource and hence will be maintained with lower precision compared to when fewer items are to be maintained. A schematic representation of the resource model of working memory is presented in Figure 1.6.

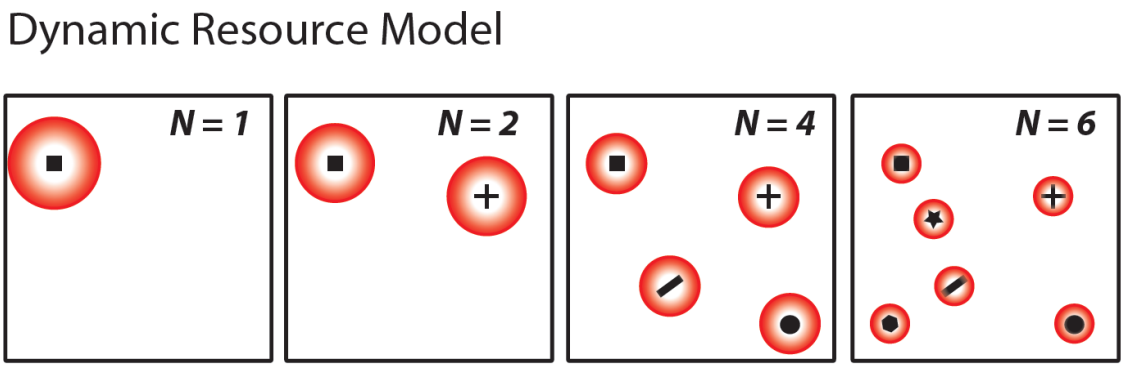

Figure 1. 6: Allocation of working visual working memory according to a resource model of memory.
The allocation of memory resources to multiple visual items is illustrated by the size of the red circles: larger circles indicate greater resources dedicated to representing an item in memory and hence greater precision on recall. The resource model of memory proposes that limited memory resource must be shared out between all to-be-remembered items and hence for larger set sizes (e.g., N=6), less resource is dedicated to each item.

Since the proposal of resource models of working memory, studies using precision as an index of working memory have so far examined recall for orientation, spatial location and colours presented simultaneously (Bays and Husain, 2008; Bays et al., 2009; Brady et al., 2011) and more recently for sequences of orientations (Gorgoraptis et al., 2011). Importantly, this resource has been shown to be flexibly shared between objects, with allocation of resource biased by both attention and toward objects of upcoming eye movements (Bays and Husain, 2008). Furthermore, allocation of attention to internal representations maintained in working memory (using retro cues long after the visual array has been extinguished) has been shown to improve precision of memory for those items (Pertzov et al., in press, *JEP:HPP*).

Investigations on non-human primates have also provided evidence supporting the resource model of memory. A study comparing visual working memory performance in human participants and macaque monkeys demonstrated a similar pattern of behaviour in both species; decrease in precision of memory with larger memory set sizes (Elmore et al., 2011). Similar findings have been reported in another study using macaque monkeys, showing a dramatic decrease in fidelity of memory representations and an increase in reaction times as the number of items in memory increases (Lara and Wallis, 2012). These findings are in line with human psychophysics (Bays and Husain, 2008; Bays Catalao et al., 2009; Bays et al., 2011, 2011; Gorgoraptis et al., 2011), providing evidence for the resource model of working memory across different species.

It has also been shown that macaques and humans exhibit the same ERP signature of working memory maintenance that predicts the resolution of memory performance (Reinhart et al., 2012). In this study, both monkeys and humans performed a memory-guided saccade task while surface ERPs were recorded. The results demonstrated that non-human primates have a homologous electrophysiological signature of visuospatial working memory to those of humans, with the CDA amplitude correlating negatively with precision of performance (i.e., magnitude of error). The monkey CDA satisfied different criteria for establishing homology between CDA in monkeys and human, including the timing of CDA and its relationship with behaviour, spatial distribution across the skull as well as scaling with the demands of the task (i.e., the length the delay interval).

This study is one of the first to show that the neural marker of working memory is modulated by the *precision* of maintained information. In line with these findings, similar results have been reported in a change-detection task showing that precision of memory influenced CDA amplitude in human participants only in trials where the number of maintained items was low, i.e., 2 items (Machizawa et al., 2012). Therefore, one can argue that CDA amplitude is influenced by both the *number* of retained items as well as *precision* of memory for these maintained items. Taken together, this body of research suggests that in cases where more sensitive measures of working memory are employed, there is evidence for a resource model.

In order to explain the plateau in memory fidelity beyond 3-4 items (Zhang and Luck, 2008, 2009), an additional source of error in working memory has been proposed (Bays et al., 2009). It has been argued that the object-limit reported previously might be due to an artefact of an increase in "misbinding" errors- errors resulting from incorrect conjunction of features of objects stored in memory.

According to this scheme, three sources of error can arise in memory. Similar to that proposed by Zhang and Luck (2008), errors can arise as a result of both variability in memory for the *target* feature and *guessing*. In addition, the model proposed by Bays et al. (2009) argues for an extra source of error: how well participants remember the correct *conjunction* of features. Items in memory, other than the one (target) that is probed, can systematically bias recall if a feature associated with them is misattributed

to the target instead (Fig. 1.7). Thus features belonging to non-targets might corrupt accurate recall of the target.

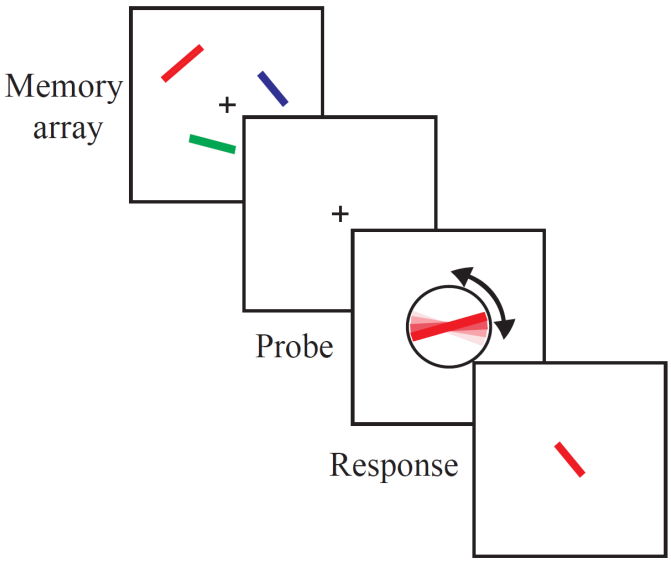

Figure 1. 7: A schematic representation of misbinding error at response.
Participants are presented with a memory array. After a retention period, they are asked to reproduce the orientation of the bar with the same colour as that of the probe. In trials where participants misbind information, they report the orientation of a bar in memory that is different to the one that is probed. In the example here, the orientation of the red bar (target) is being probed but the participant's response matches that of the blue bar (non-target).

The two models of error in memory vary in one critical assumption. According to Zhang and Luck (2008), because of the limited item capacity of memory, as the number of to-be-remembered items increases beyond the capacity limit, the proportion of random responses also increases. However, as proposed by Bays et al. (2009), the proportion of random responses should not be affected by the number of to-be-remembered items as even in larger set sizes, objects receive a proportion of memory resource and hence are stored in memory, although with lower precision. According to this model, larger set sizes can result in an increase in misbinding errors, i.e., misbinding features within maintained objects so the wrong features are attributed to an item that is probed (Fig. 1.7).

For "misbinding" errors to fit within the theoretical framework of a resource model, it might be easiest to involve a stage of independent storage of object features. Contrary to this assumption, "automatic" maintenance of bound information in each memory "slot"

is a critical feature of slot models of working memory. Thus slot models predict that errors in recalling features of an object will be correlated, as all features belonging to an object are stored in a single memory "slot". The resource model does not make such an assumption. Detailed examination of participants' ability to reproduce two features (colour and orientation) of a single object from memory has revealed a strong independence of errors between feature dimensions (Bays et al., 2011). Thus, errors in colour recall were not correlated with errors in orientation recall, in line with the predictions of the resource model pointing to independent storage of features within objects.

The extent to which "binding" errors can provide a better understanding of errors in working memory and modulation of this error by memory load is currently under intense investigation. Studies have started to examine modulation in proportion of misbinding errors for simultaneous or sequential presentation of colour and orientation and spatial location and colour conjunctions for different sizes of memory arrays (Bays et al., 2009; Gorgoraptis et al., 2011). Consistent with predictions made by the resource model, misbinding errors increase with larger memory set sizes. Furthermore, one study has also demonstrated misbinding errors in recalling the identity and location of real-life objects, pointing to "swap errors" that arise between objects in a visual environment (Pertzov et al., 2012). In other words, participants remembered the correct objects that were presented as well as locations but misplaced objects at locations of other objects in the visual world.

Within the framework of resource model it has been suggested that a further mechanism might be necessary to maintain the bound information of independently-stored features (Bays et al., 2011). Attentional processes have been nominated as a possible mechanism. In fact cueing an item prior to presentation of memory array decreased the proportion of "misbinding errors" that occurred for the cued items compared to invalidly cued items (Gorgoraptis et al., 2011). In that study, participants were presented with a colour cue at the beginning of each trial (62.5% valid) prioritizing one of four items later presented in the memory array. Validly cued items were indeed protected by any systematic interference from other items in memory compared to both baseline and invalidly cued items. Interestingly, prioritizing an item during working memory maintenance long after the memory array had been extinguished (i.e., retro cueing) resulted in similar findings (Pertzov et al., in press, *JEP:HPP*); participants made less

"misbinding" errors for validly cued items compared to baseline and invalid cueing conditions. These studies provide evidence for a role of resources traditionally associated with visual attention on maintenance of bound objects in working memory. Of course, there is a long history of attention processes being required to bind features for visual perception (Treisman and Gelade, 1980; Treisman, 1998). These new studies suggest that similar processes might also extend to maintaining feature binding in working memory, although the nature of such effects need to be scrutinized more closely.

The studies reviewed so far demonstrate the controversy of how capacity is defined by different models of working memory. These differences further extend to computational models and the nature of sources of error in memory. Furthermore, within each theoretical framework there might be different roles of attention (see also 1.3.4). In order to establish one model, researchers firstly need to extend its predictions across a variety of visual features and different modes of presentation (e.g., sequential vs. simultaneous). Furthermore, a head-to-head comparison between the two conceptual frameworks of working memory is essential to establish the model that explains behaviour best.

1. 3 Neural correlates of visual working memory

Providing a comprehensive understanding of visual working memory relies not only on studying behaviour but also investigating the neural correlates of this cognitive process. Psychophysical, non-human electrophysiological and human neuroimaging studies have shown various regions of the brain important in different aspects of working memory processes (e.g., Fuster and Alexander, 1971; Fuster, 1973, 1990; Watanabe, 1981; Funahashi et al., 1993; Pasternak and Greenlee, 2005). Highlighted by many studies is the involvement of sensory cortices in maintenance of information for short periods of time. Sensory areas involved in visual perception have been extensively studied (e.g., Mather and Moulden, 1980; Shadlen and Newsome, 1996; Mather, 2011), presenting a great opportunity to investigate the causal role of these regions in *maintenance* of different visual features. Below I will review evidence pointing to the involvement of early visual areas in working memory maintenance.

1. 3. 1 Psychophysical studies

Simple visual features within objects (e.g., orientation, size or motion direction) are encoded separately in the human visual cortex. Direct sources of evidence for the involvement of these areas in *maintenance* of features, comes from studies using interference tasks, some of these present a "mask" during the delay interval and examine the special properties of the mask that interferes with maintained information. Manipulating the properties of the mask can provide an insight into the nature of maintained information by investigating the behavioural consequences of the mask on memory performance. Retention of speed of motion was impaired when an intervening mask with different speed of motion was presented during the retention period (Magnussen and Greenlee, 1992; Blake et al., 1997) indicating that motion information is maintained in working memory at high resolution.

Further, it has been shown that the information maintained in visual working memory is localized in space (Zaksas et al., 2001). In that study, monkeys compared the direction of two moving random-dot stimuli, sample and test, separated by a temporal delay and were asked to make a same/different judgment on the direction of motion of the two

stimuli. A mask was introduced in the delay either at the location of the sample or the test stimuli (Fig. 1.8). Performance was affected only when the mask was presented in the location of the upcoming test stimuli. This selective masking effect suggests that the information maintained is spatially localized (Fig. 1.8). Furthermore, the local speed of the dots in each stimulus (sample, mask and test) were varied in a manner that the local speed of dots in the mask was either similar to that of sample or the test stimuli. The mask decreased performance when its local speed matched the speed of the sample array (Fig. 1.8). This is critical since the speed of the dots was orthogonal to the task at hand. Therefore, both the location and the properties of the mask influence memory performance for motion direction. Together, these findings point to the conclusion that mechanisms involved in maintenance of basic features are both finely tuned and spatially localized, in line with organization of early visual areas.

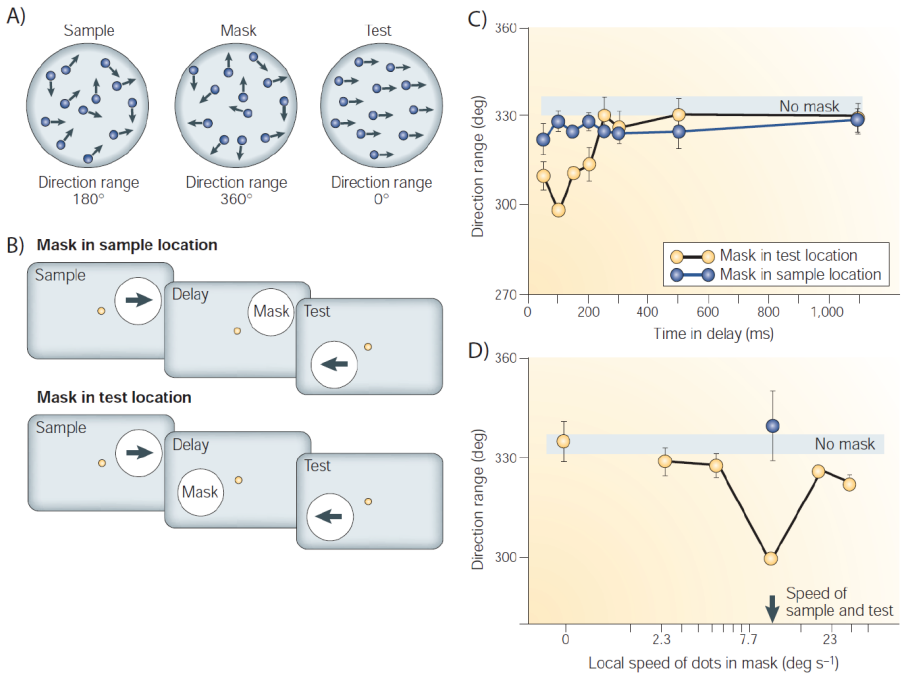

Figure 1. 8: Visual working memory for motion direction.
A) Stimuli used to measure retention of motion direction; B) Monkeys perform a same/different judgment on two temporally separated motion directions. On half the trials, the mask stimulus is presented at the same location as the sample (top) and in other at the test stimuli (bottom). C) Temporal and spatial specificity of the remembered stimulus. Direction range threshold are plotted as a function of the mask onset and location. The mask interfered with performance only when presented early in the delay at the location of the upcoming test. D) Stimulus specificity of the remembered sample. The local speed of dots in the mask was varied. The mask decreased performance only when its local speed matched the speed of the remembered sample even though the speed was orthogonal to the task. Information about speed is preserved along with information about stimulus direction (from Pasternak and Greenlee, 2005).

1. 3. 2 Physiological studies

Non-human physiological studies have also tested the involvement of visual areas in working memory maintenance. In one study, activity of neurons in area MT/V5 was recorded during a delay interval in a motion discrimination task where a motion direction had to be maintained and later compared to a sample motion (Bisley et al., 2004a). MT/V5 neurons showed bursts of activity early in the delay period followed by a subsequent suppression of firing rate and reactivation prior to the presentation of the sample motion direction. Consistent with this finding, it has been shown that in a similar task, miscrostimulation of direction-selective cortical columns in area MT/V5 of monkeys during working memory maintenance impaired performance to chance level (Bisley et al., 2001).

Further evidence was reported in a study (Super et al., 2001) where trained monkeys performed a delay-response task on the location of a figure defined by motion or orientation, after it had been removed. Activity of neurons in area V1, with receptive fields (RF) that covered the figures, was recorded. Contextual modulation (CM) for each neuron was calculated by subtracting an individual neuron's activity when noisy representations were presented compared to when figures were presented in its RF. CM related to the presented figure was strong for both behaviourally correct and incorrect trials earlier in the delay interval. Later in the delay, however, CM related to the figure was stronger for behaviourally correct trials. These results highlight the central role of early visual areas in working memory maintenance, demonstrating the presence of delay activity in these areas corresponding to information maintained in working memory.

1. 3. 3 Neuroimaging studies

Neuroimaging techniques have also been employed to study the neural correlates and the role of visual areas in visual working memory (e.g. Smith and Jonides, 1998; Owen et al., 2005; Linden, 2007; Linden et al., 2012). Although many investigations have been performed, some of the most interesting involve memory for faces or places. The fusiform face area (FFA) is a brain region involved in perception of faces (Kanwisher and Yovel, 2006) while the parahipocampal place area (PPA) plays a significant role in perception of places (i.e., scenes and buildings) (Epstein et al., 1999). In a study by

Ranganath, DeGutis and D'Esposito (2004), activity in FFA and PPA was greater during encoding and maintenance in conditions where the favored stimuli (i.e., faces for FFA) was relevant to the working memory task (Ranganath et al., 2004). Similarly, Postle and colleagues (2003) demonstrated target specific activity in area FFA in a working memory task for serial presentation of faces (Postle et al., 2003).

In a landmark study by Harrison and Tong (2009), fMRI and pattern classification analysis was employed to demonstrate that information held in working memory can be decoded from activity patterns in early visual areas V1-V4 of humans. Participants were presented with a sequence of two oriented gratings followed by a cue indicating the grating to be remembered. Following an 11 second delay interval, a test grating was presented and participants were asked to report whether the test grating was rotated clockwise or anticlockwise relative to the cued grating (Fig. 1.9A). It was found that activity patterns in the studied visual areas were predictive of the cued grating, i.e., the grating held in memory. Such orientation-selective activity pattern sustained throughout the delay interval (Fig. 1.9B) highlights the involvement of these early visual areas in working memory maintenance in the absence of other physical stimuli.

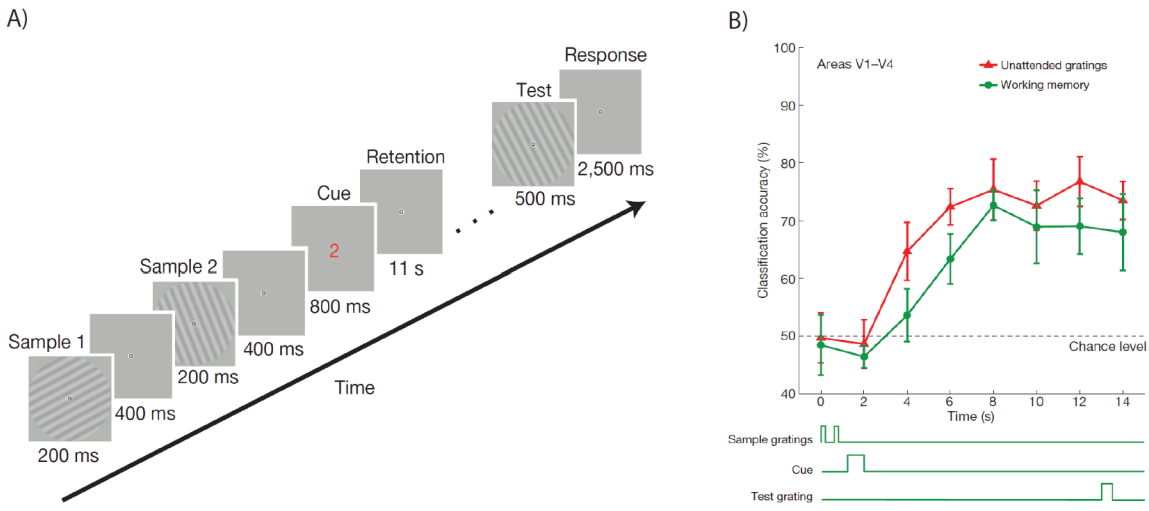

Figure 1. 9: Working memory task and time course of fMRI activity
A) A sequence of gratings were presented followed by a cue indicating which grating to remember. After a retention period (11s) a test grating was presented and participants reported whether it was rotated clockwise or anti-clockwise relative to the cued grating. B) Orientation decoding of unattended stimulus gratings (ref triangles) and remembered grating during working memory (green circles), for activity obtained from areas V1-V4. Note that the information persists throughout the delay period during working memory task (from Harrison and Tong, 2009).

Similarly, Serences and colleagues (2009) used multivoxel pattern classification analysis and have reported sustained pattern of activation in V1 specific to the intentionally stored features (colour or orientation) from a multifeature object. The pattern of activity during the delay activity was similar to that observed during discrimination of the stimuli, pointing to the conclusion that representations maintained in working memory are similar to those evoked during perception. In a more recent study (Munneke et al., 2010) maintenance of spatial locations in working memory resulted in an increase in blood-oxygen-level dependent (BOLD) signal (compared to a control ipsilateral location) in early visual areas V1-V3 illustrating a direct increase in activity in visual cortex during the working memory task.

Together these studies point to the conclusion that at least some aspects of working memory retention of information might be accomplished through active maintenance of the neural activity employed in sensory processing.

1. 3. 4 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is currently being used as an investigative tool to study various cognitive processes including perception (e.g., Hotson and Anand, 1999; Zangaladze et al., 1999), attention (e.g., Ashbridge et al., 1997; Walsh et al., 1999) and memory (Oliveri et al., 2001; Campana et al., 2006; Romero et al., 2006; Silvanto and Cattaneo, 2010). This technique can produce focal, transient and importantly, reversible disruption of cortical network function (Walsh and Rushworth, 1999; Pascual-Leone et al., 2000; Walsh and Cowey, 2000). Using this approach, one can induce "virtual lesions" during performance of cognitive tasks in normal, healthy humans to establish the causal role of different brain regions for a given behaviour.

The neural correlates of motion perception have been extensively studies (e.g., Shadlen and Newsome, 1996; Andersen, 1997; Mather, 2011). Thus, TMS has been used to examine the contribution of these cortical areas, that process sensory information, in working memory in humans. TMS applied to human V5/MT+, eliminated motion priming- an implicit form of sensory memory (Campana et al., 2002). This effect was

specific to visual motion and area V5/MT+ and therefore, it was concluded that priming of basic stimulus features depends on sensory cortical areas.

Further, TMS has been used to show that activity in V5/MT+ reflects motion qualities of items maintained in working memory (Silvanto and Cattaneo, 2010). In that study, participants were asked to maintain a motion stimulus and a phosphene was induced during the retention period. Phosphenes are artificial percepts that can be induced by applying TMS over human visual cortex and have been used to investigate the neural impact of various processes including attention (Bestmann et al., 2007; Cattaneo et al., 2009), visual imagery (Sparing et al., 2002) and auditory-visual interactions (Romei et al., 2007, 2009). The rationale behind the study by Silvanto and Cattaneo (2010) was that if neurons of area V5/MT+ are engaged in working memory, the TMS-induced phosphenes, from this region, during maintenance should reflect the properties of the retained item. The results confirmed that the qualities of the subjectively reported phosphenes matched the properties of item in memory (Silvanto and Cattaneo, 2010).

In summary, the evidence reviewed in above sections illustrates the role of early visual areas in maintenance of information in working memory.

1. 3. 5 Working memory content or focus of attention?

Recently, researchers have started to question the extent to which activity in early visual areas reflects the full contents of working memory. The reason why this might be the case is firstly because sustained activity during working memory delay intervals does not necessarily mean that objects are being remembered as some regions (e.g., FFA) can show above-baseline activity during cognitive states other than memory maintenance (Gauthier et al., 2000). Secondly, many studies on working memory retention have confounded the findings with attention: task relevant items are those maintained in working memory. Therefore it has been argued that sustained activity might be correlate of attention rather than working memory content.

It has been proposed that items in working memory can adopt different states depending on their relevancy to the task in hand (Olivers et al., 2011). According to this view, although multiple items can be maintained in working memory, the number of items in the “focus of attention”/active state is limited to only one item (Fig. 1.10). This

privileged item has full access to sensory inputs through feedback connections to lower visual areas of the brain. Previous studies have mainly examined memory representations in early visual areas for items that were most relevant to the task at hand and hence in an active state of representation. For example, in the study by Harrison and Tong (2009), after the presentation of the memory array (consisting of 2 items), the target item was cued prior to presentation of test stimuli. The delay between the cue and the test stimuli was used to decode the presentation of maintained information in early visual areas. Therefore, in each trial only one item was relevant to the task at hand and hence inside the focus of attention.

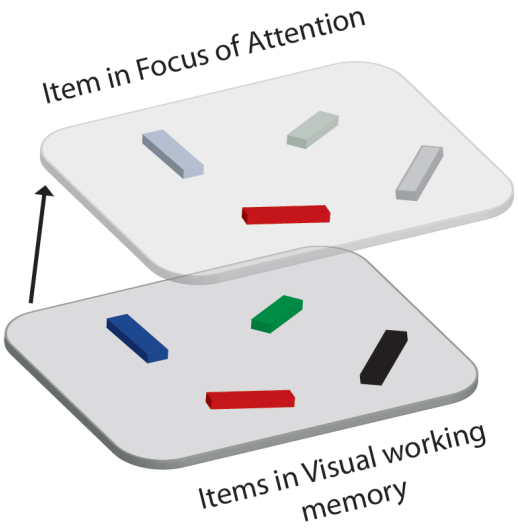

Figure 1. 10: A schematic representation of items maintained in visual working memory at different states.
Various items can be maintained in visual working memory. However, the items in the focus of attention (active state) is limited to one item (here the red bar) (from Olivers et al., 2011).

In a recent study, Lewis-Peacock et al. (2011) aimed to provide an understanding of the relationship between sustained activity and working memory maintenance. The results demonstrated that memory representations can be preserved across delay intervals *despite the loss of sustained neural trace*. In this experiment, participants performed a task, which at any given time, one of the two items being retained in working memory were cued as relevant. These cues were used to direct the internal focus of attention, so that items in memory could either be in or out of the focus of attention. Using multivariate pattern analysis, it was found that delay period activity reflected the item in the focus of attention rather than the full content of working memory. Importantly and remarkably, refocusing attention to an unattended object could restore the neural signature of that item long after the visual array had been extinguished (Fig. 1.11).

Modulations in the neural trace, however, did not affect performance of participants behaviourally. These findings challenge previous studies arguing that the sustained activity reported previously reflects sustained attention to a particular item in memory rather than contents of working memory.

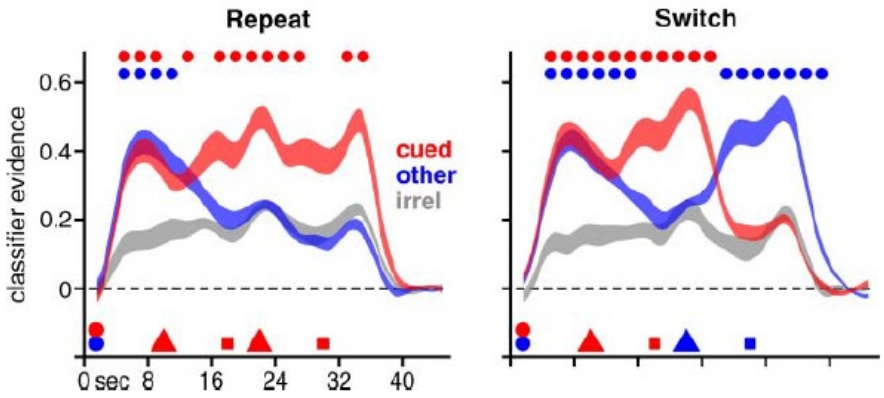

Figure 1. 11: Reorienting attention in memory.
Classifier decoding for trials where the cued item was maintained during the delay interval (Repeat) and those trials were the cued item was switched to the other item in memory (Switch). Classifier values were divided into three categories of cued (red), other (other) and irrelevant (gray). The coloured shapes along the horizontal axis indicate the onset of the targets (red and blue circles), the first cue (red triangle), first probe (red square), the second cue (red/blue triangle-depending on trial type) and final recognition probe (red/blue square). Data for each category are shown as ribbons whose thickness indicates ± SEM across participants (from Lewis-Peacock et al., 2012).

It is important to note that although these new findings and theoretical frameworks put forward an alternative on the role of early visual areas in working memory processes, there are many studies, ranging from monkey electrophysiology to human studies, demonstrating sustained activity in early visual area in working memory maintenance. Future research should aim to address the limitations mentioned in this section and specifically investigate the *causal role* of early visual areas on visual working memory maintenance.

1. 4 Neuromodulation of working memory

Fronto-parietal regions of the brain have been implicated in working memory processes (Fuster and Alexander, 1971; Fuster, 1973, 1990; Watanabe, 1981; Miller and Cohen, 2001). For example, parietal and prefrontal cortex (PFC) neurons show delay-related activity on saccadic working memory tasks, encoding the remembered location of the visual stimulus (Funahashi et al., 1993).

In humans and patients, the dopaminergic system originates in the ventral tegmental area (VTA) of the midbrain and projects to the PFC, anterior cingulate cortex, anterior temporal structures (such as amygdala, hippocampus and entorhinal cortex) and the basal forebrain (Bannon and Roth, 1983) (Fig. 1.12). Furthermore, PFC contains large numbers of dopamine receptors (Goldman-Rakic, 1992, 1995; Goldman-Rakic et al., 1992). Therefore the anatomical distribution of the dopaminergic system might suggest a role for this neurotransmitter in working memory processes.

It is important to gain an understanding on the role of dopamine in working memory processes for two important reasons. Firstly, one should consider the important role of dopamine in a wide variety of neurological diseases such as Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder and deficits in working memory are considered to be an important aspect of these disorders (Mehta et al., 2000a; Owen, 2004a; Haenschel et al., 2009; Cools and D'Esposito, 2011; Haenschel and Linden, 2011). A better understanding of dopamine function would potentially improve both our understanding of the abnormal brain and aid development of possible treatments. Furthermore, the questions raised are theoretically important, helping us understand fundamental issues in the field of neuroscience, bridging cognitive processes and neurotransmitter activity in the brain.

Although several other neurotransmitter systems have also long been implicated in working memory processes, including the serotoninergic system (Arnsten and Goldman-Rakic, 1984; Arnsten et al., 1988; Luciana et al., 1998), for the purposes of this thesis, I will focus on the dopaminergic system and its role on working memory.

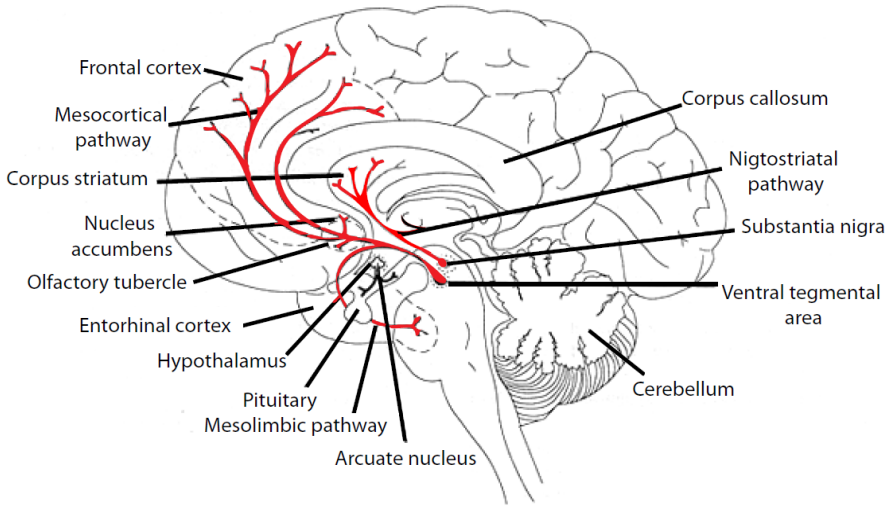

Figure 1. 12: Dopaminergic pathway that connects the frontal cortex to basal ganglia.
The system originates from the ventral tegmental area and projects to prefrontal cortex, basal forebrain and the anterior temporal structures.

1. 4. 1 Animal studies

A landmark study by Brozoski et al. (1979), revealed one of the first direct pieces of evidence for the role of dopamine on working memory performance. Dopamine depletion in PFC of monkeys resulted in severe deficits on a delayed response task. Working memory impairment was comparable to that observed in monkeys with complete ablations of the PFC. However it was not observed in monkeys in which other neurotransmitters, such as serotonin, were depleted. Importantly, administration of dopamine receptor agonists administered to monkeys with dopamine depletion in PFC reversed working memory impairment (Brozoski et al., 1979). Further, iontophoresis of D1 agonists in PFC alters memory-related activity (Williams and Goldman-Rakic, 1995a).

Since these influential observations, many studies have further supported the role of dopamine in PFC on working memory (for reviews see Goldman-Rakic et al., 1992, 1990; Goldman-Rakic, 1995; Cools and D'Esposito, 2011). However, behavioural and electrophysiological investigations have shown that the relationship between working memory performance and dopaminergic mechanisms of PFC is complex. For example, administration of low dose of dopamine agonists can improve working memory in monkeys (Williams and Goldman-Rakic, 1995a), especially impairments that are associated with factors such as aging (Arnsten et al., 1994; Cai and Arnsten, 1997;

Castner et al., 2000). Furthermore, Arnsten et al. (1994) illustrated that a dopamine antagonist impaired working memory performance of young monkeys (with good baseline performance) but did not affect performance of aged monkeys with dopamine depletion. Conversely, a dopamine agonist improved performance in aged monkeys but did not affect performance in young monkeys highlighting the importance of baseline performance on the effects of dopamine on working memory function.

Similar findings have been reported in other species. In a study on rats, it has been shown that poor performance on a difficult working memory task (with a long delay between sample and test) was accompanied by low levels of dopamine in PFC, while good performance on a simple task (with a shorter delay) was accompanied by high dopamine levels in PFC (Phillips et al., 2004). Importantly, administration of dopamine agonists resulted in *impaired* performance in the easy task and *improved* performance in the difficult task. These findings have been replicated since, showing that both too much (Sahakian et al., 1985; Murphy et al., 1996a; Zahrt et al., 1997) or too little (Sawaguchi et al., 1990; Seamans et al., 1998) dopamine activity in PFC can impair working memory performance.

The effects of dopaminergic drugs seem rather paradoxical as they result in both improvements as well as impairments in working memory performance. These findings have been explained by considering an "inverted U-shaped" relationship between cognitive performance and dopamine (Fig. 1.13). According to this scheme, there may be an optimal level of dopamine which is necessary for ideal working memory performance with both dopamine depletion and over-dosing the system with hyper dopaminergic states leading to impairments in memory (Cools and D'Esposito, 2011). Hence, in those with optimal levels of dopamine, further administration of dopamine agonists may impair working memory performance On the contrary; working memory in those with reduced dopamine function in PFC can be improved by administration of dopamine agonist. A schematic representation of the relationship between working memory performance and dopamine is illustrated in Figure 1.13.

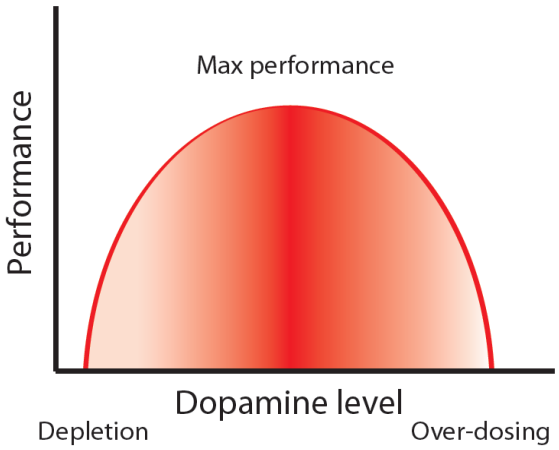

Figure 1. 13: Relationship between cognitive performance and dopamine levels follows an "Inverted U-shaped" function.

Both too little and too much dopamine impairs performance. Note that the likelihood of that the drug causes beneficial or detrimental effects depends partly on baseline dopamine levels. Adapted from Cools & D'Esposito (2011).

1. 4. 2 Human pharmacological studies

Effect of D1 agonists on working memory

Dopamine receptors are categorized into two distinctive groups based on their different properties and effects. Non-human primate studies have mainly focused on the role of D1 receptors playing a role in working memory (Williams and Goldman-Rakic, 1995a; Castner et al., 2000). Unfortunately, however, there currently are no selective D1 agonists for use in humans. Several studies have therefore employed the pharmacological subtraction design. The rationale behind this is that any changes in performance on a drug that is a combined D1/D2 receptor agonist compared to a D2 agonist alone can be explained purely in terms of the effect of D1 agonist. Müller et al. (1998) compared working memory performance in a visuospatial delayed match to sample task under pergolide (D1/D2 agonist) and bromocriptine (D2 agonist) in healthy participants. In each trial, participants were asked to memorize the location of a randomly generated seven-point pattern and compare to a second pattern after varied delay intervals. The results showed that pergolide alone resulted in an improvement in working memory performance (Müller et al., 1998) highlighting the potential role of D1 agonist in visuospatial working memory. It was later shown in another study that pergolide improved both spatial and object delayed match-to-sample performance (Kimberg and D'Esposito, 2003). Replicating such findings however remains challenging as some studies have failed to demonstrate any effect of pergolide on working memory performance (e.g., Bartholomeusz et al., 2003).

Effect of D2 agonists on working memory

Pharmacological studies have also examined the role of D2 receptors in human working memory. These have demonstrated improved performance in spatial delayed match-to-sample tasks on bromocriptine when administered in a lower does (1.25mg) compared to higher doses (2.5 mg) (Luciana et al., 1992, 1998; Luciana and Collins, 1997; Mehta et al., 2000b). It is important to note that lack of any effects at higher doses may be caused by an increase in sedation or nausea by this drug. Similar to animal studies, investigations in human point to the conclusion that the extent to which individuals benefit from dopamine might depend on baseline levels of working memory performance. Kimberg and colleagues (1997) reported that bromocriptine improved performance only in individuals with lower working memory span (measured by reading span task) (Kimberg et al., 1997). However, these results have been hard to replicate as a subsequent study from same group reported completely opposite findings, with no effect on the N-back working memory task despite using the same drug and dosage (Kimberg et al., 2001). Another D2 agonist commonly used in pharmacological studies is cabergoline. Recently, Frank and colleagues (2006) showed impaired performance in working memory on cabergoline in normal individuals with high baseline working memory span, evidence that baseline working memory performance modulates responsivity to D2 drugs.

Effect of amphetamine and methylphenidate on working memory

A number of studies using non-selective agents such as amphetamine and methylphenidate have also shown beneficial effect of these agents on working memory performance. Amphetamine is a non-selective dopamine agonist; it works by increasing the release of dopamine and blocking its re-uptake. Individuals' reaction times on a spatial delayed match to sample task is faster on amphetamine compared to placebo (Barch and Carter, 2005). Performance on a 2-back working memory task has been reported to improve in healthy participants after administration of amphetamine (Mintzer and Griffiths, 2003). In line with these findings, studies have reported enhancement in performance in individuals on amphetamine with deficits in working memory caused by sleep deprivation (Pigeau et al., 1995; Magill et al., 2003). In a landmark study by Mattay et al. (2000), amphetamine was reported to improve

performance on an N-back working memory task only in those with poor baseline performance. Contrary to this, individuals with good baseline performance were impaired on amphetamine. Importantly, they found that the degree of improvement in this task on amphetamine was inversely correlated with task-related enhancement of PFC activity. Therefore increase in PFC activity on amphetamine was associated with a large improvement in performance accuracy (Mattay et al., 2000).

Another source of evidence highlighting baseline dependency of dopaminergic effects in humans comes from studies investigating drug effects that take into account genetic differences between individuals. Catechol-O-methyltransferase (COMT) gene is an enzyme that breaks down dopamine released in the synaptic gap between two neurons and it is thought to have a greater influence on dopamine levels in PFC compared to striatum (Gogos et al., 1998; Tunbridge et al., 2004). Lower COMT activity implies more dopamine in the synapse while higher COMT activity results in less dopamine. There are two types of variants of genes that determine levels of COMTs in an individual. Individuals with Val-allele have high COMT activity and hence low baseline dopamine levels. Conversely, individuals with Met-allele have low COMT activity and hence high dopamine levels. Studies examining at dopaminergic effects of performance in these two group of individuals have shown that those with Mel-allele genotype, i.e., those who have high dopamine levels, perform significantly better on working memory tasks compared to those with Val-allele genotype (Egan et al., 2001; Malhotra et al., 2002; Diamond et al., 2004; Meyer-Lindenberg et al., 2005).

There are also dissociable effects of dopaminergic medication on these two variants of the COMT gene (Fig. 1.14). Mattay et al., (2003) showed that on amphetamine, those with Val-allele genotype had faster reaction time (with no loss in accuracy) on an N-back working memory task which was associated with lower PFC activity compared to placebo. Individuals with Met-allele genotype had worse performance on amphetamine accompanied by an increased PFC activity (Mattay et al., 2003).

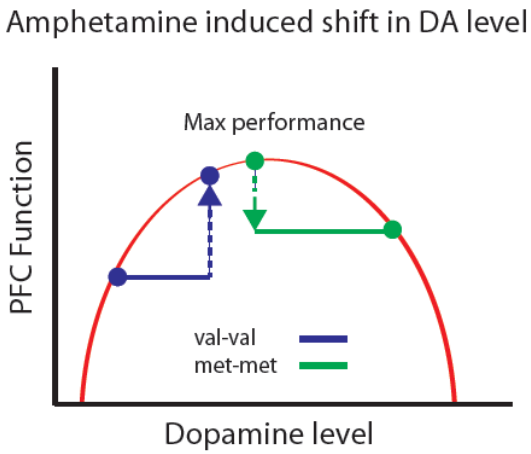

Figure 1. 14: Theoretical inverted-U model describing the effects of amphetamine and COMT genotypes on PFC DA signaling.
On amphetamine, individuals with Val-allele genotype show improved PFC function as DA signaling is shifted towards an optimal value, while those with Met-allele genotype shift Da levels onto the down slope of the slope which has no or deleterious effect on PFC function. (from Mattay et al., 2003).

Methylphenidate is also a non-selective dopamine agent which also has noradrenergic effects. It primarily increases the synaptic concentration of dopamine by blocking the dopamine transporter (Seeman and Madras, 1998). Studies on the effect of Methylphenidate on working memory performance are rather complex. Mehta and colleagues (2000) found improvement in spatial self-ordered pointing in healthy individuals accompanied by a reduction in task-related activity in PFC on Methylphenidate (Mehta et al., 2000). This task can be considered to be a test of executive working memory requiring the ability to generate and monitor a sequence of responses or spatial locations. Contradictory to these findings, later studies have shown no change in performance on Methylphenidate either in spatial span or spatial self-ordered pointing task (Turner et al., 2003).

Together, the results reported in this section highlight the importance of the dopaminergic system in working memory performance. In line with animal studies, the extent of any effect on working memory in humans appear to depend highly on baseline levels of dopamine in a way that dopaminergic drugs improve working memory performance in individuals who have lower levels of dopamine. Impaired performance on dopaminergic drugs is reported in those with high levels of baseline dopamine. One must however consider a wide range of contradictory findings as these observations

have not always replicated. Further studies are required to shed light on the exact role of dopamine in working memory processes.

1. 4. 3 Human imaging studies

Pharmacological studies use indirect measures, manipulating the amount of dopamine in the brain to investigate its effects on working memory performance. However, direct measurement of dopamine transmission in humans can be made using neurochemical positron emission tomography (PET). PET is an imaging technique. The system detects gamma rays emitted indirectly by positron-emitting radionuclide (tracer), which has been introduced into the body to build an image of functional processes in body. Although it is important to note that the application of this method is limited to striatal dopamine and not optimized for detecting dopamine levels in PFC. In a recent study this technique was applied to quantify individual differences in the degree to which dopamine is synthesizes in the terminals of midbrain dopamine neurons (Cools et al., 2008). Subjects with low working memory capacity had significantly lower dopamine synthesis capacity in the striatum than those with high working memory capacity (Cools et al., 2008) (Fig. 1.15). Similar findings have been reported in older individuals, demonstrating that variability in striatal dopamine function is related to working memory capacity. Interestingly, the striatal dopamine synthesis capacity predicted both working memory capacity as well as PFC activity during working memory performance (Landau et al., 2009). These data provide direct evidence for the support of baseline-dependency hypothesis of dopaminergic system and working memory performance.

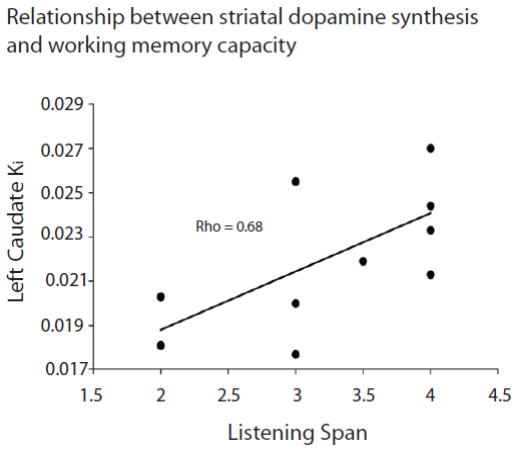

Figure 1. 15: Correlation between working memory capacity (measure by listening span) and dopamine synthesis capacity in the striatum (from Cools et al., 2008).

PET studies raise an alternative hypothesis, specifically on baseline-dependent effects of dopamine on PFC function. It can be argued that these effects reflect modulation of frontostriatal connectivity, which varies as a function of dopamine levels in the striatum rather than in PFC. In order to test this hypothesis, the effect of bromocriptine administration to healthy individuals on functional interactions between the PFC and striatum has been investigated (Wallace et al., 2011). During working memory retrieval, bromocriptine increased frontostriatal connectivity in those with low working memory capacity while those with high working memory capacity exhibited a decrease in frontostriatal connectivity. However, evidence pointing to the role of dopamine in striatum compared to PFC should be considered with caution. The PET method available to study dopamine transmission in humans is optimized for detecting signals in the striatum rather than PFC. Also worth noting is the lack of D1 selective drugs for human research, as noted previously. D2 receptors are more abundant in the striatum and hence may bias the findings into highlighting the role of striatum compared to PFC (Cortés et al., 1989; Lidow et al., 1991; Goldman-Rakic et al., 1992). Furthermore, compared to animal studies, the tasks used in human studies employ a wide range of cognitive functions, i.e., flexible updating of the goal in hand or shifting amongst tasks. Hence the degree to which dopamine levels in either PFC or striatum are predictive of drug effects may depend on the cognitive demand of the task in hand.

1. 4. 4 Neurological patients

Working memory impairments in PD patients

Additional evidence for the role of dopamine in working memory comes from studies that have examined individuals with neurological disorders associated with an impaired dopaminergic system. Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by a loss of dopaminergic neurons in midbrain and a further depletion of dopamine in basal ganglia. There are extensive connections between basal ganglia and prefrontal cortex and it has now been known for many years that the classic motor symptoms of PD are accompanied by deficits in various cognitive functions including deficits in working memory (Verbaan et al., 2007; Savica et al., 2010; Schapira and Tolosa, 2010). In fact it has been suggested that working memory impairments in PD are detectable prior to motor symptoms/signs of PD (for a review, see Schapira and Tolosa, 2010).

Evidence from many studies has shown that the degeneration of motor functions that characterize PD is accompanied by deterioration of executive processes; deficits that resemble those observed in patients with PFC lesions (Gotham et al., 1988; Lange et al., 1992; Owen et al., 1992; Cooper et al., 1992; Cools et al., 2001, 2001). Cognitive impairments in PD patients vary widely, with 22%-50% of PD patients exhibiting some sort of cognitive impairments (Verbaan et al., 2007). Non-medicated, newly diagnosed patients with mild clinical symptoms have been repeatedly shown to be impaired on tests of spatial/visual working memory (Morris et al., 1988; Owen et al., 1992).

For example, in a population-based sample of 239 newly diagnosed PD patients, 36% of the group demonstrated cognitive impairment specifically on a pattern recognition memory task (Foltynie et al., 2004a). In another study, 115 newly diagnosed PD patients with a mean disease duration of 19 months were tested on a variety of neuropsychological tests (Muslimović et al., 2005). PD patients performed significantly worse on a subset of tests including those investigating executive functions and working memory. Bradley and colleagues (1989) found that patients with mild PD were impaired on tests of visuospatial working memory but unaffected in verbal working memory (Bradley et al., 1989). Similarly, both Postle et al. (Postle et al., 1997a) and Owen et al. (Owen et al., 1997a) have shown that medicated patients with mild PD were impaired on spatial working memory but performance was preserved in working memory for visual shapes. Impaired spatial span has been reported in both mild and severe PD in a more complex spatial task (Owen et al., 1992, 1993). Compared to controls, medicated patients with both mild and severe PD were impaired. Interestingly, there was a trend

towards impairment even in non-medicated patients with extremely mild PD (Owen et al., 1992, 1993).

A growing body of evidence also suggests that the administration of levodopa to those with PD improves working memory. Levodopa is a precursor for many neurotransmitters collectively known as catecholamines which also include dopamine. This drug is commonly used in the clinical treatment of PD. Levodopa improved both accuracy and reaction times on both spatial and object delayed match-to-sample tasks in patients with PD (Costa et al., 2003). In a neuroimaging experiment, Mattay et al. (2002) examined the effect of levodopa on an N-back working memory task in PD patients. Patients on medication had a tendency to perform better and had less activity in PFC regions compared to patients off medication (Mattay et al., 2002). Similarly, Swanison and colleagues (2000) have reported impairments in spatial recognition memory task in non-medicated PD patients compared to medicated patients (Swainson et al., 2000).

Attentional impairments in PD patients

One possible cause for impaired working memory performance in PD patients may be deficits in the ability to filter out irrelevant information as it has been suggested that basal ganglia are involved in filtering irrelevant information (e.g., McNab and Klingberg, 2008; Lee et al., 2010). This idea is supported by an fMRI study where a pre-cue informed participants to attend or ignore non-standard items (separated by colour) within a memory array (McNab and Klingberg, 2008). Greater activation in the left and right-middle frontal gyri and the left basal ganglia was observed when participants were cued to ignore the non-standard item compared to when asked to maintain these items. This preparatory activity was robust in participants with larger working memory capacity. Furthermore, activity in the left basal ganglia in response to the cue indicating "ignore" was inversely correlated with subsequent parietal lobe activation. The parietal lobe has been associated with maintenance of information in working memory (Todd and Marois, 2004). It might therefore be argued that the left basal ganglia are involved in filtering distractors to assist in representing any task-relevant items in working memory.

Lee et al. (2010) tested whether working memory deficits in PD patients is caused by impairment in filtering ability or reduced working memory capacity. Medicated PD patients were tested on a visuospatial memory task while electroencephalograms were recorded. In each trial, participants (controls and PD patients) were presented with a cue followed by a memory array. Participants had to remember information regarding the orientation of the red-coloured bars on the cued side of the screen. Following a retention interval, a test array was presented and participants had to make a same/different response in relation to the maintained items (Fig. 1.16). Three types of conditions were employed. In the 2-red or 4-red conditions, all items presented were relevant to the task at hand and participants had to keep in mind either 2 or 4 items in memory respectively. In the 2-red, 2-green condition however, 2 relevant (i.e., red bars) and 2 task-irrelevant (i.e., green bars) items were presented on both cued and un-cued sides of the screen. Successful performance required ignoring the task-irrelevant items while maintaining the 2 task-relevant items in working memory.

Memory capacity (K) and CDA amplitude during retention interval were measured. Working memory capacity was significantly lower in PD patients compared to controls (Fig. 1.16). CDA amplitude, which is known to reflect the amount of information maintained in memory (irrespective of their task-relevance) (Vogel and Machizawa, 2004) was also lower in PD patients. Importantly, CDA mean amplitude in the 2-red,2-green condition was similar to that observed in 4-red condition in PD patients highlighting the fact that these patients had difficulty ignoring task-irrelevant items since in both conditions, the same number of items were maintained in working memory (Fig. 1.16).

In light of these findings, it was suggested that working memory impairments previously reported in PD patients is caused by *both* a lower working memory capacity and inability to filter distractors (Lee et al., 2010). However, in this study the working memory task and the attentional abilities were integrated since change-detection was performed on half of items presented on one side of the screen and hence in all trials (both with distractors and without), half of the presented items were irrelevant to the task. Hence one can argue that it is not possible to distinguish the exact deficits – attentional and/ or mnemonic- in PD patients using this paradigm.

Although there is a large body of evidence pointing to working memory impairment and limited evidence of impairment in filtering abilities in patients with PD, some studies have failed to document any deficit in working memory in this group (Cooper et al., 1991a; Dalrymple-Alford et al., 1994). Thus the exact nature of impairments in PD and the role of dopamine in these impairments remain unclear.

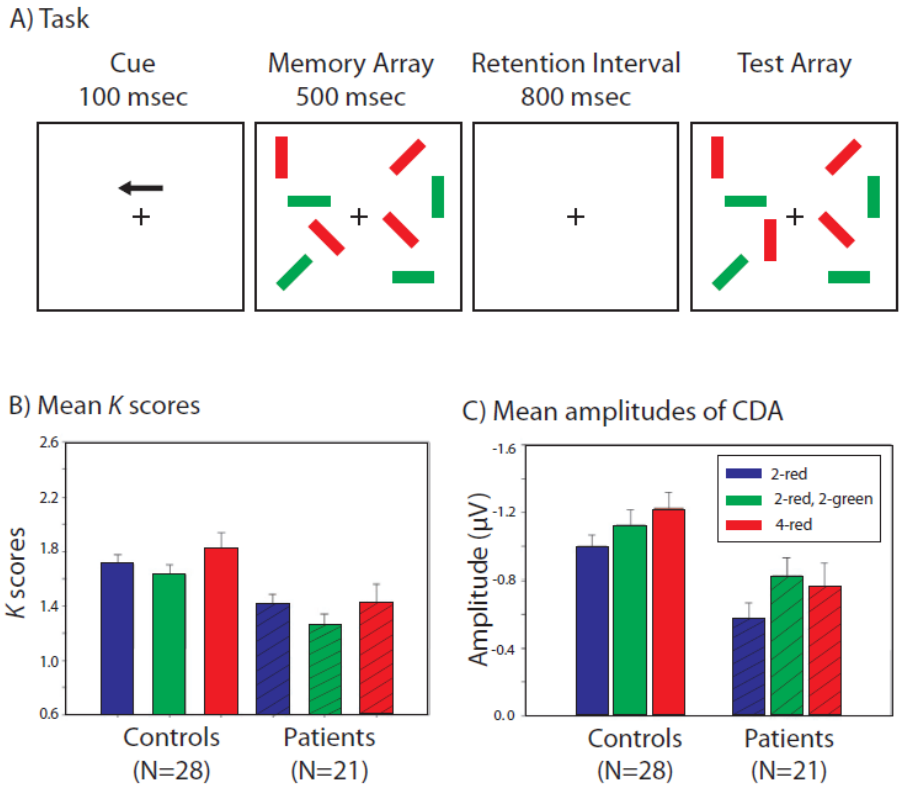

Figure 1. 16: The task and results of PD patients on and off medication.
A) An example of a 2-red, 2-green condition in which the left hemifield was task relevant. Participants were asked to perform a change-detection task on the red items presented on the left side of the screen only. B) Mean K scores of both control and PD pateints as a function of trial type. K was signficiantly lower in PD patients compared to controls. C) Mean amplitude of CDA during the retention interval. Amplitude of CDA was lower in PD patients compared to Controls (from Lee et al., 2010).

Working memory/attentional impairments as marker for early neurodegeneration?

Although there remains a great deal of controversy on the exact characteristics of cognitive impairments, specially working memory impairments in PD, these deficits are indeed detectable prior to motor signs of PD (Schapira and Tolosa, 2010). One of the key priorities in PD research is to detect this disease at its earliest states so that neuroprotective or other therapies might be used before there is widespread neurodegeneration (Schapira and Tolosa, 2010). Cognitive impairments observed in early PD may potentially provide a means of early detection. However, it would be an enormous undertaking to screen for them on a population-wide basis in the hope of finding people who might subsequently develop PD. An alternative strategy would be to target individuals who are at particularly high risk of developing PD.

Over the last few decades, different genes have been associated with PD including those that affect the lysosomal enzyme glucocerebrosidase (GBA) (Klein and Westenberger, 2012). Indeed, GBA mutations represent the highest known genetic risk factor for developing PD (Clark et al., 2009; Neumann et al., 2009). Classically, GBA mutations have been associated with Gaucher's disease (GD), a condition that results from homozygosity or compound heterozygosity for mutations in the GBA gene (Pastores and Hughes, 2011). GD has been subdivided into different types based on absence (Type I) or presence (Type II and III) of neuropathology, but recent studies have shown clinical and pathological findings that point to involvement of the central nervous system in patients classified as Type I (Sidransky, 2004; Capablo et al., 2008). In fact, several studies have now identified Type I GD as a risk factor for Parkinson's disease (PD) (Sidransky et al., 2009a; Bultron et al., 2010; Rosenbloom et al., 2011) and dementia with Lewy bodies, a dementia associated with PD pathology (Clark et al., 2009). High penetrance of PD has also been reported in heterozygous carriers of the GBA mutation (Goker-Alpan et al., 2004), pointing to GBA as a PD causal dominant gene (Anheim et al., 2012a).

Individuals with GBA mutations are therefore a potentially important group of people to screen for impairments that might be the earliest signs of PD. Recently cognitive dysfunction has been identified in individuals with GBA mutation. In fact, cognitive impairments in those PD patients with GD appear to be more frequent and severe compared to sporadic PD patients without GD, as measured by the Montreal Cognitive assessment (MoCA) (Brockmann et al., 2011). Visual working memory performance has also been reported to be impaired in GBA mutation carriers with PD (Alcalay et al.,

2012). In that study both GBA mutation carriers with early-onset PD and non-carrier PD patients were tested on a variety of verbal and visual neuropsychological memory tests. Carrier PD patients were severely and prominently impaired in visual memory tests compared to non-carrier PD patients, highlighting some differences that may exist between the two patient groups. Based on these findings, the authors suggested that GBA mutation might be an independent risk factor for cognitive impairments in PD patients.

Although studies have started to examine the relationship between cognitive deficits in PD patients and GD patients, a great deal remains un-elucidated. In fact, understanding the cognitive profile of patients with GBA mutation serves several important purposes. If this mutation results in specific memory impairments, assessment of working memory may be a useful tool in diagnostic work-up of individual patients. Moreover, the pattern of memory deficits can contribute to our knowledge on the relationship between genetics, brain function and critical cognitive processes. Finally one should also consider the influence of these findings on effective treatment of cognitive impairments in these patients.

In summary, evidence reviewed in this section demonstrates the role of dopamine in working memory processes, from animal studies to human neuroimaging and psychopharmacological investigations. It should be clear from my review that the result of these studies often presents controversial and sometimes paradoxical findings on the exact role of dopamine in working memory and the nature of deficits in patients with impaired dopamine function, e.g., PD patients. Further studies are required to establish the exact role of this neurotransmitter in visual working memory and elucidate which working memory deficits can be used as cognitive biomarkers for determining individuals who are at risk of developing neurodegenerative disorders such as PD.

1. 5 Overview of thesis

In this thesis, I aim to investigate the mechanisms underlying visual working memory and modulation of its mechanisms by attentional manipulations and the neurotransmitter dopamine. My research is mainly divided into two sections.

Firstly, I investigate visual working mechanisms in healthy individuals. Recent advances in models of working memory (See Sections 1.2) leads to formulation of unique predictions that can be extended to a variety of visual features. Motion is a fundamentally important source of information in the visual scene and is crucial for survival in an ever-changing visual environment. Surprisingly, however, compared to other visual features, far less is known about the mechanisms underlying working memory for motion. Importantly, given that the neural correlates and brain regions involved in motion perception are relatively well-studied (Shadlen and Newsome, 1996; Andersen, 1997; Mather, 2011), a great opportunity arises to investigate the involvement of sensory cortices in maintenance of this feature in working memory. Therefore in the first part of this thesis, I aimed to investigate the nature of working memory for motion, the role of attention in these processes and establish the causal role of early visual areas involved in motion processing in maintenance of motion information in working memory by using TMS.

The second part of this thesis focuses on the neuromodulation of working memory by dopamine. I investigated the role of dopamine in visual working memory both in a psychopharmacology study on healthy individuals and in patients with PD. Furthermore, as highlighted previously, one of the aims of PD research is to detect individuals who are at early stages of neurodegeneration. We know that individuals with GBA mutation are at a higher risk for developing Parkinson's disease and are shown to have parkinsonian motor signs (Aharon-Peretz et al., 2004; Sidransky et al., 2009; Anheim et al., 2012; McNeill et al., 2012). Therefore, I investigated whether patients and carriers of the mutated gene might have deficits in working memory, even without overt signs of Parkinsonism, to establish whether working memory impairments might be a risk factor for individuals at risk of developing PD.

Chapter 2

Working memory precision for motion directions

2. 1 Introduction

Motion is a fundamentally important source of information in the visual scene. From tracking the movements of a predator in the wild to computing the direction of moving cars when crossing a road, segregating objects using motion cues is critical to survival. However, compared to other visual features, e.g., colour, orientation or spatial location,

we know far less about the nature of working memory for motion, particularly for sequences of moving stimuli over time.

Previous studies have shown that different features of visual motion, including direction of motion can be maintained in memory for several seconds (Magnussen and Greenlee, 1992b; Blake et al., 1997), the information stored is spatially localized (Zaksas et al., 2001) and that the neural activity during delay period reveals that motion direction is represented in MT neurons (Bisley et al., 2004). However, less is known about the *limits* of working memory for visual motion.

Kawasaki and colleagues (2008) conducted a change detection study to investigate the capacity limit for different features including direction of motion (Kawasaki et al., 2008). In this study, participants were asked to retain information regarding a specific feature, (either colour, orientation, motion direction or conjunction of features) in a sample display of one to eight items. After a retention interval, a test display containing one probe item was presented and participants determined whether there was a change in the attended feature between the probe and the maintained item presented in the same location. The capacity of visual working memory for motion direction was significantly lower than colour and shape and was estimated to be 2 items.

However, change detection tasks with a fixed magnitude of change, might not be sensitive to changes in the *fidelity* of memory. However, as highlighted by recent studies (e.g., Wilken and Ma, 2004; Bays et al., 2009), more sensitive measures of memory representations are more informative regarding the nature of maintained information. Here we applied a more sensitive measure of working memory to measure *precision* of memory for motion directions; the method of adjustment which relies on observers remembering a visual feature and reproducing the exact qualities of the stored feature after a retention period (Fig. 1.3B).

Studies using precision as an index of working memory have so far examined recall for orientation, spatial location and colour presented simultaneously (Bays and Husain, 2008; Bays, Catalao and Husain, 2009; Bays et al., 2011), and more recently for sequences of orientations (Gorgoraptis, Catalao, Bays and Husain, 2011). To the best of our knowledge there has been no systematic investigation of the precision of memory for visual motion stimuli. In Experiment 2.1 we examined the nature of memory

distribution for motion direction presented in sequences, investigating the effects of set size and serial position of target (i.e., where it appeared in a sequence) on precision of memory.

The method we use provides a sensitive measure of memory precision and allows us to test the predictions made by both object-based and resource models of memory for sequences of items. According to the object-based models of working memory, below the object limit of each individual, items will be maintained in working memory with equal precision. Upon reaching the object-limit though, no information regarding any "extra" objects will be maintained. Resource model of memory however, predicts a gradual decrease in the fidelity of memory as the number of items maintained in working memory increases. In Experiment 2.1, we used sequences of up to 4 motion directions. For set sizes below 4, the object-limit models would predict no change in precision of memory representations while the resource model predicts a graded decrease in precision even when memory set size is increased from 1 to 2.

Furthermore, in Experiment 2.1, for the first time, we also directly test the two computational models distinguishing errors in memory at recall (Zhang and Luck, 2008a; Bays, Catalao and Husain, 2009a). Zhang and Luck (2008) proposed a revised version of the object-based model, slots+ averaging model, where a memory resource is divided into a few fixed-resolution slots (<3). Below the limit of slots, bound items can be stored in more than one slot and averaged to provide a high resolution memory. However, beyond the object limit no information is stored for the added objects which results in an increase in proportion of *random responses*. Therefore this model predicts that error in memory at recall arise as a result of either variable memory of the target object or guessing.

Alternatively, Bays et al. (2009) proposed a model that also takes into account the misbinding errors in recall: errors resulting from incorrect conjunction of features that arise because non-targets can systematically corrupt memory by biasing recall. According to this scheme, larger set sizes not only result in a decrease in precision but also cause an increase in misbinding errors. In Experiment 2.1 we tested whether taking into account errors corresponding to misbinding would improve models of working memory.

One question that follows is how memory is distributed between two different motion directions presented simultaneously, rather than sequentially, at the same location. Such motion transparency, involving two overlapping directions of motion occurs naturally in the visual environment: from rain streaming down a window of a moving car to when an animal is moving behind foliage on a windy day. In Experiment 2.2 we investigate the distribution of memory resource and precision of memory for items that are not temporally or spatially distinguishable, i.e., transparent motion sheets. This paradigm allows us to examine the nature of memory representations in situations where temporal and spatial information are shared amongst to-be-remembered items. Further, we investigate the sources of error that are affected by this type of information presentation.

2. 2 Experiment 2.1

2. 2. 1 Method

2. 2. 1. 1 Participants

Eleven healthy individuals (4 male) with an average age of 22 years (range: 18 -28) participated in this study. All participants had normal or corrected to normal vision and reported normal colour vision. Participants provided written consent to the procedure of the experiment, which was approved by the local ethics committee.

2. 2. 1. 2 Stimuli

Stimuli were generated by Cogent toolbox (www.vislab.ucl.ac.uk/Cogent/) for MATLAB and were displayed on a 14.1" flat panel display (resolution: 800 × 600 pixels, refresh rate: 60 Hz). Participants were seated approximately 60cm from the monitor in a dimly illuminated room.

In each trial, a sequence of Random Dot Kinematograms (RDKs) was presented at the centre of the screen on a black background (Fig. 2.1). RDKs consisted of 25 dots, each covering 0.1º of visual angle. Dots were displayed within an invisible circular aperture

of 150 pixels in diameter (5.7 º of visual angle). Dot lifetime was 500 msec and dots reaching the edge of the circular aperture were re-positioned randomly on the other side of the aperture; therefore dot density was kept constant throughout the presentation.

Motion was 100% coherent (constant speed of 4.5 degrees/sec for all dots). Direction of motion for each RDK within a sequence was set at a random value between 0-360º while maintaining a minimum angular separation of 60º between different motion directions. RDKs were presented in a randomly selected colour from a selection of 5 different colours (red, green, blue, white and yellow), with no repetition of colour in each sequence.

2. 2. 1. 3 Procedure

Each trial started with a fixation cross (500 msec) followed by a sequence of RDKs. Sequences varied in length from 1 to 4 RDKs. Observers did not know beforehand how many RDKs would be displayed in each trial. Within a sequence, each RDK was presented for 500 msec and was followed by a 500 msec blank interval before the presentation of the next RDK. Participants were asked to remember the direction of motion of all RDKs. The last item in the sequence was followed by a 500 msec blank interval before the probe display was presented.

The probe stimulus consisted of a circle (5.7 º of visual angle in diameter) presented at the centre of the screen with an arrow positioned at a random orientation – drawn from the uniform distribution [0-360˚] – within the circle. This probe stimulus was presented in the same colour as one of the RDKs in the sequence. Participants were asked to adjust the orientation of the coloured arrow, using a trackball, to match the direction of motion of the RDK presented in the same colour in the sequence.

The probability of probing any of the RDKs within the sequence was kept constant for all items in the sequence. Probe display was presented until response. Participants were told to respond as accurately as possible, with no time pressure. A schematic presentation of a sample sequence is presented in Figure 2.1.

Each participant completed 330 trials, 6 blocks of 55 trials. Each possible combination of sequence length and target position in the sequence (10 possible combinations) was presented for 30 trials throughout the whole experiment.

Control delay condition: 30 additional trials consisted of the condition where a single RDK was presented followed by a long retention period (3500 msec). The duration of the retention period in this condition is equal to the duration of the presentation of 3 RDKs. Therefore the duration between presentation of RDK and probe stimuli in this condition is equal to the duration between presentation of the first RDK in sequence of 4 items and the probe stimulus. Thus this condition served as a control to examine the effects of temporal decay on memory precision when one motion direction had to be remembered for the same duration as the first item in sequences of 4.

Different conditions were randomly intermixed within each block. Participants were familiarized with the experimental apparatus and completed a practice block of 30 intermixed trials prior to experiment.

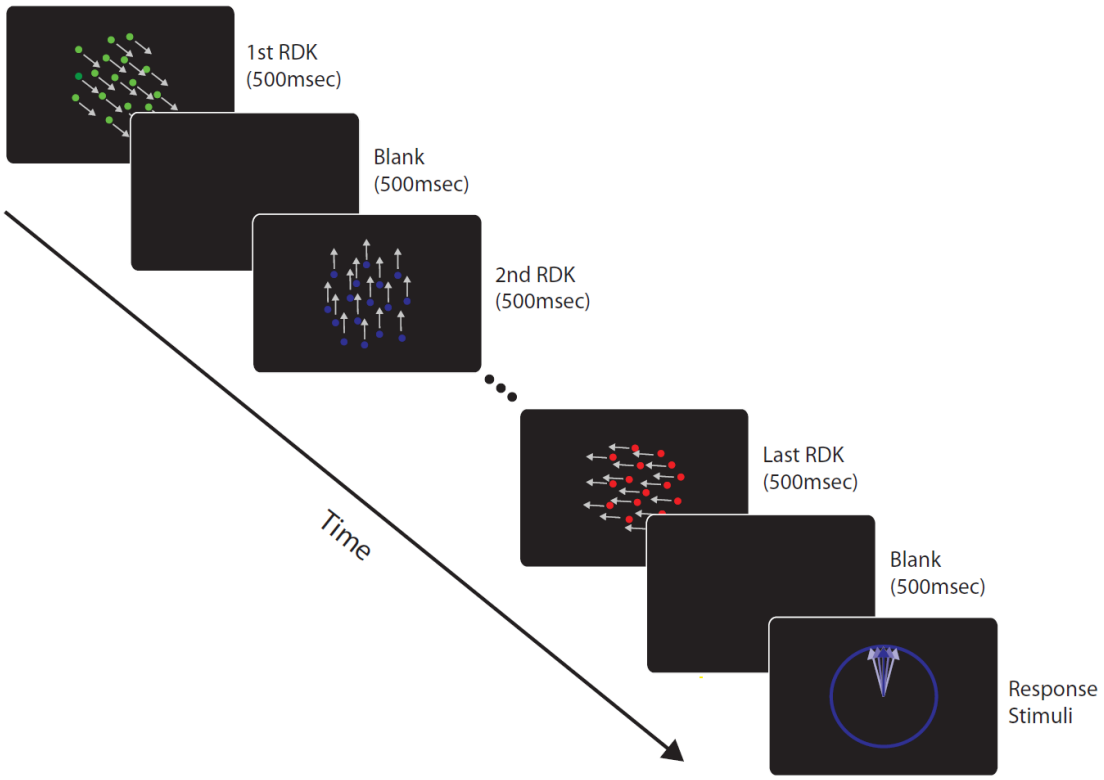

Figure 2. 1: An example of a sample trial.
Sequences of 1-4 RDKs, moving coherently in different directions of motion were presented. Any of the RDKs could be probed by colour of the response stimuli and participants were asked to adjust the orientation of the response stimuli to the direction of the motion of the RDK with similar colour.

2. 2. 2 Analysis

***Behavioural Analysis**:* In each trial, error was calculated as the deviation of the response value (i.e., the reported motion direction of the target) from the target value (i.e., the real value of the target motion direction).

Following previous work (Bays and Husain, 2008; Bays, Catalao and Husain, 2009) we defined precision as the reciprocal of the standard deviation of error measured using the method described by Fisher (1993) for calculating standard deviation in a circular parameter space (Fisher, 1993). This is a measure of variability of response; less variability in response corresponds to more precise memory. Using this definition, we calculated the precision of working memory for different sequence lengths and serial positions of the target for each. Chance precision, that is the expected precision value if a participant responded at random in all trials, was calculated and subtracted from the precision values obtained for each condition. Precision was calculated for each serial position of the target within each sequence length and averaged for overall precision per sequence length.

***Model Estimates**:* In order to distinguish different sources of error in memory for tasks similar to the one we used (adjustment tasks), two probabilistic models have recently been proposed. According to Zhang and Luck's (2008) model, there are two possible sources of error on each trial:

1. A Von Mises (circular Gaussian) distribution in memory centred on the target direction (Fig. 2.2A).

2. A uniform distribution of error corresponding to random responses (Fig. 2.2B).

The model is described by the following equation:

Equation (2.1): $$p\left(\widehat{\theta}\right) = (1-\gamma)\,\phi_{\kappa}\left(\widehat{\theta}-\theta\right) + \gamma\frac{1}{2\pi}$$

where θ is the target motion direction and $\widehat{\theta}$ is the response direction. ϕ_κ is the Von Mises distribution with mean of zero and concentration parameter κ . The concentration parameter κ corresponds to the variability of recall of the target, where greater κ corresponds to lower variability in the distribution. γ corresponds to the proportion of trials where participants were guessing, i.e., responding at random.

Recently, an additional source of error has been identified by Bays et al. (2009) (see also http://www.sobell.ion.ucl.ac.uk/pbays/code/JV10/). According to this model, a proportion of errors in these tasks correspond to the probability of incorrectly responding with the motion direction of one of the other, *non-target* RDKs. These responses can be captured by Von Mises distributions centred on each of the non-target motion directions in a sequence (Fig. 2.2C).

The model is described by the following equation:

Equation (2.2): $$p\left(\widehat{\theta}\right)=\alpha\phi_\kappa\left(\widehat{\theta}-\theta\right)+\beta\frac{1}{m}\sum_{i}^{m}\phi_\kappa\left(\widehat{\theta}-\varphi_i\right)+\gamma\frac{1}{2\pi}$$

Probability of responding with the target direction is given by α, and β corresponds to the probability of *misbinding* errors, i.e., trials on which a participant responds with a non-target direction as a result of incorrect conjunction of features (here colour and motion direction) in memory. {φ1,φ2, … φm} correspond to motion directions of the *m* non-target items. Probability of responding at random (γ) is calculated as 1-α-β.

Maximum likelihood estimates of parameters α, β, γ and κ were obtained using Expectation Maximization (Myung, 2003) for each participant and each experimental condition.

It's important to note that neither of the two models described here include noise in sensory and motor systems that may affect performance at recall. However, one would assume that such noise remains constant across different sequence lengths and serial

positions and hence any effects observed on modelling parameters can be reliably attributed to noise in memory rather than sensory or motor systems.

Model Comparison*:* To determine which of the two models provides a better fit of the data, we used likelihood ratio tests used to compare two models in cases where one is a special case of the other (i.e., "nested" models). Here, the model proposed by Zhang and Luck (2008) (the null model) is a special case of the model proposed by Bays et al. (2009) (the alternative model), in which the β parameter (*probability of non-target responses*) is fixed at zero. The likelihood ratio test statistic (D) was calculated separately for each sequence length and serial position, collapsing data across subjects, and statistical significance tested by comparison to the χ^2 distribution with 1 d.f.

D can be calculated by the following equation:

Equation (2.2):

D= -2[ln (likelihood for null model)-ln (likelihood for alternative model)]

The model with more parameters, specifically in nested models, will always fit the data at least as well as the null model. However, this test determines whether this difference is significantly better or not. The two models were separately fitted to the data and the log-likelihood of each was calculated and D (i.e. test statistics) was defined as twice the difference in these log-likelihood values. The probability distribution of the test statistics for nested models approximates a χ^2 distribution with degrees of freedom equal to df(alternative model) – df(null model) where df represent the number of free parameters in each model.

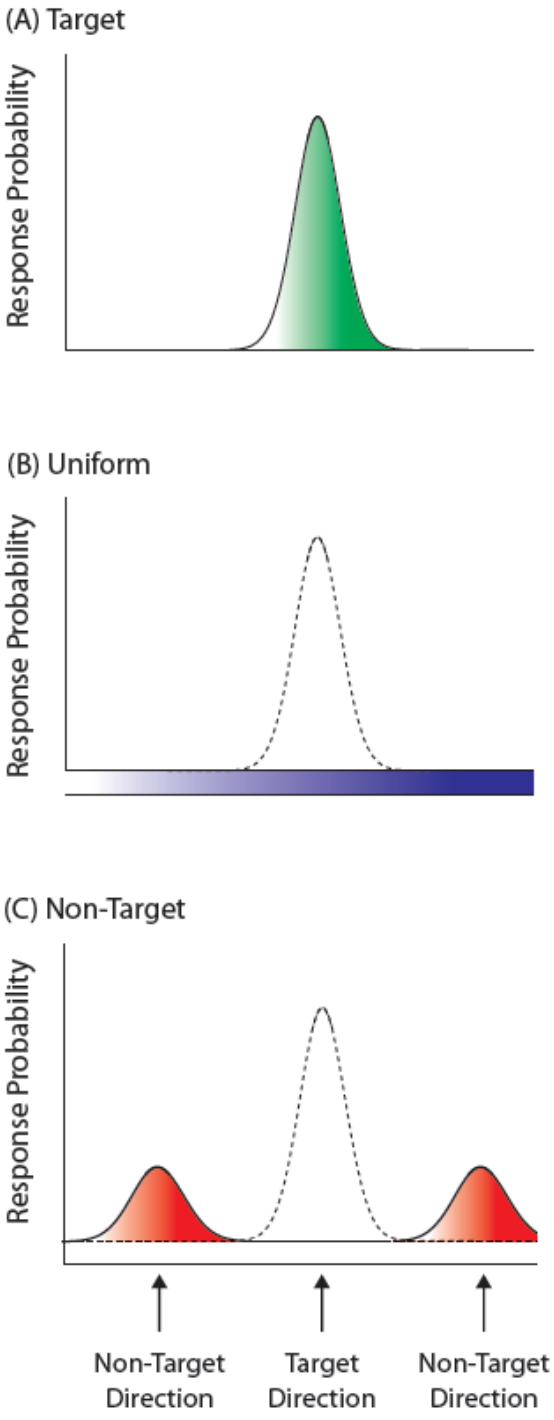

Figure 2. 2: Three sources of error in memory used for modelling performance.
A) A Von Mises (circular Gaussian) distribution with concentration parameter κ, centred on the *target direction* of motion, capturing variability in memory for target direction of motion, with the area under the distribution (shaded) being proportional to the probability of responding to the *target* motion direction; B) A uniform distribution of error corresponding to *random error*, with the area under this distribution corresponding to the proportion of random responses and C) Von Mises distributions with concentration parameter κ, centred on one of the *non-target directions* of motion, resulting from errors in identifying which motion direction belonged with the target colour (*misbinding*). The area under the distribution corresponds to the proportion of *non-target* responses.

2. 2. 3 Results

2. 2. 3. 1 Effect of sequence length and serial position of target on working memory precision

We first examined the distribution of errors in relation to the target direction for different sequence lengths. As illustrated in Figure 2.3, in longer sequences the proportion of responses falling close to the target direction decreased; observed as a reduction in the responses made around the target as sequence length increases. Furthermore, the longer tails of the distribution in longer sequences provide evidence for additional sources of error (either guessing or misbinding errors) that may occur in longer sequences (Fig. 2.3).

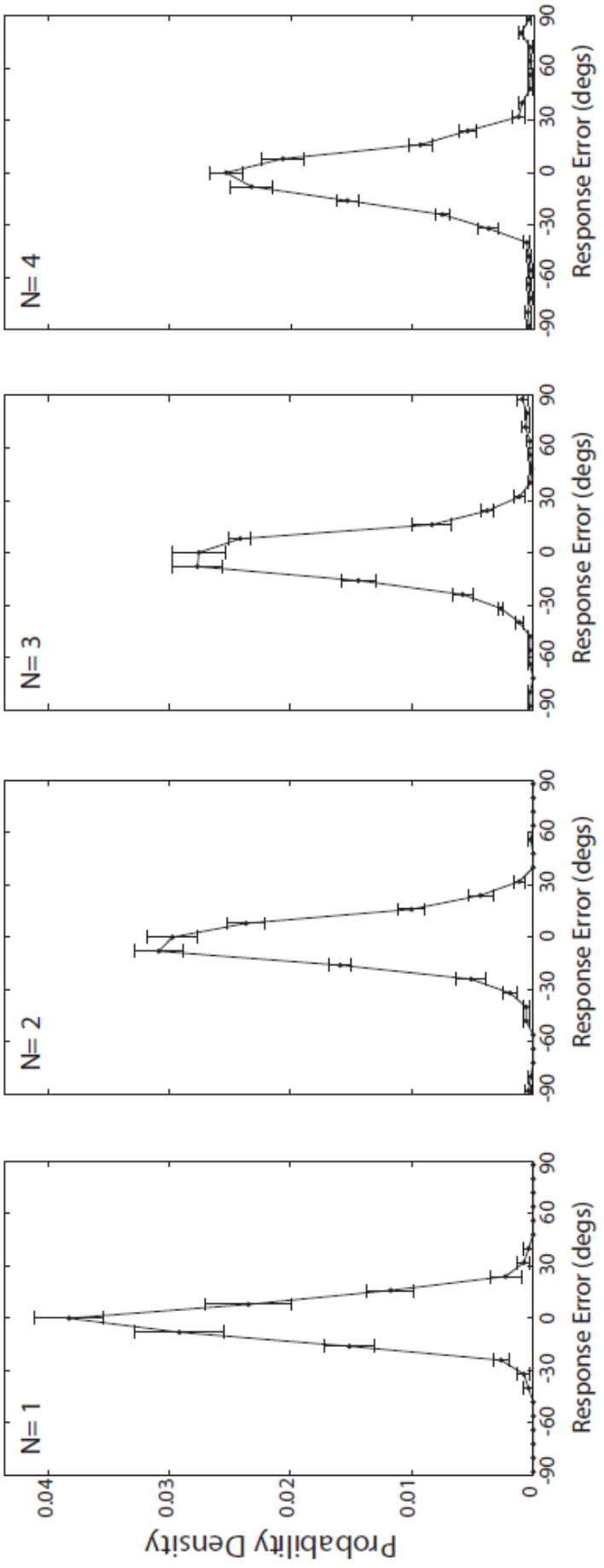

Figure 2. 3: Distribution of errors relative to the target direction for different sequence lengths.
Response probability is plotted as a function of the difference between response and target direction, for different sequence lengths (1-4 items). As sequence length increases, the variability in recall of the target direction (width of the distribution) increases.

We then investigated whether precision of memory for motion direction was affected by the number of items in a sequence. Mean precision for each sequence length (collapsing across all serial positions) was calculated. Precision decreased significantly as the number of items in the sequence increased; one-way ANOVA: $F(3, 106)= 21.406$, $P<0.001$ (Fig. 2.4A). More importantly, overall precision decreased significantly when sequence length was increased from only 1 to 2 RDKs ($t(10)= 4.881$, $p= 0.001$), contrary to what would be predicted by object-based models of memory.

A similar pattern of results was observed for comparisons between other sequence lengths; two vs. three ($t(10)= 6.238$, $p<0.001$) and three vs. four ($t(10)= 2.39$, $p= 0.038$, n.s. after Bonferroni correction). Performance was significantly better than chance for all sequence lengths (e.g., sequence length 4: $t(10) = -15.13$; $p<0.001$) and in all participants.

We also examined how precision of recall is affected by the serial position of a target stimulus, i.e., *when* the target was presented in the sequence. There was a significant effect of serial position on precision of recall (Fig. 2.4B; two-way ANOVA, main effect of serial position, $F(3, 100)= 10.47$, $p< 0.001$). Precision was best for the last item regardless of sequence length, demonstrating a strong recency effect. Interestingly, when the data from the last item in each sequence was excluded, all other items in the sequence were remembered with similar precision regardless of serial position (two-way ANOVA, main effect of serial position, $F(2,50)= 0.65$, $p=0.53$).

The precision of recall for the last item in a sequence was further influenced by sequence length. This item was remembered with higher precision when presented in shorter sequences (Fig. 2.4B, last items; one-way ANOVA of the last item; $F(3, 40)= 4.05$, $p= 0.01$). Note that although several studies of visual working memory using sequences have also demonstrated recency effects (Phillips and Christie, 1977; Wright et al., 1985; Neath, 1993; Hay et al., 2007; Botvinick et al., 2009; Blalock and Clegg, 2010), using precision as an index of recall allowed us to observe that the *magnitude* of the recency effect was modulated by sequence length.

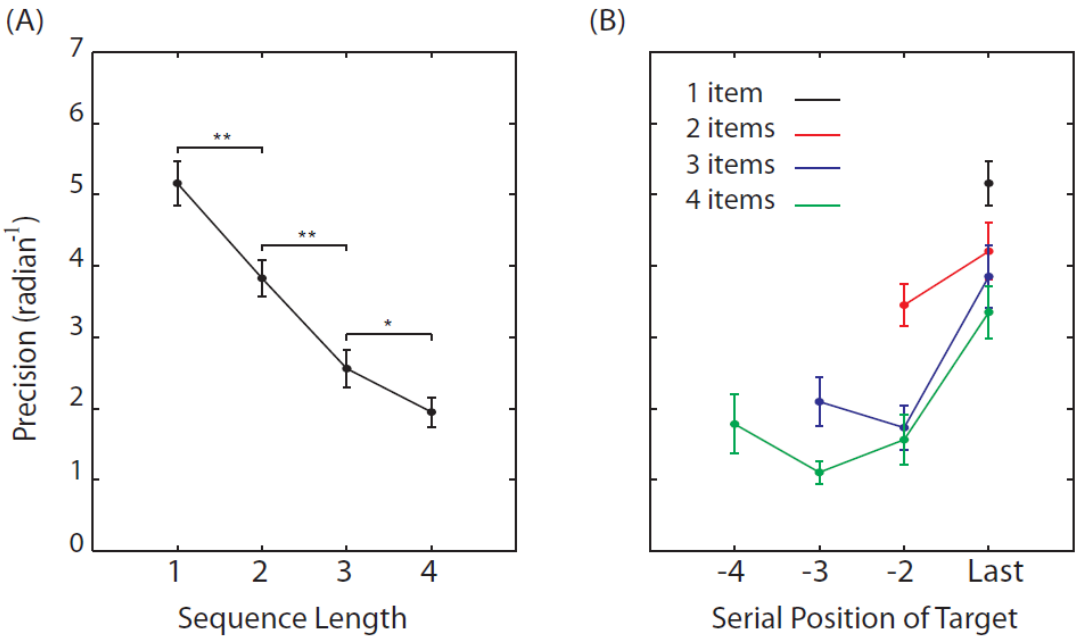

Figure 2. 4: Precision of memory for different sequence lengths.
A) Average precision for each sequence length: precision decreased with increasing number of items in a sequence (* p< 0.05, ** p< 0.01); B) Within each sequence, the last item was always remembered best (recency effect) and precision decreased as sequence length increased at any of the serial positions within a sequence. Zero precision indicates chance performance, error bars demonstrate SEM across participants (N= 11).

A similar effect was observed at other serial positions of the target. Precision of memory for items presented 2nd to last in the sequence was significantly lower when part of a longer sequence (Fig. 2.4B; one-way ANOVA; $F(2, 30)= 10.77$, $p<0.001$). t-test analysis on the 3rd to last items for sequence lengths three and four illustrated that precision for the 3rd to last item was significantly higher for items presented in a sequence of three compared to those presented in a sequence of four; $t(24)= 3.106$, $p= 0.011$ (Fig. 2.4B). Thus, regardless of the serial position of the target, memory for motion direction was determined by the fraction of memory resource allocated to that item, which in turn was determined by the overall number of items in the sequence.

2. 2. 3. 2 Is loss of precision for earlier items in a sequence explained by temporal decay of information?

Loss in precision for earlier items in the sequence might be caused by either temporal decay of memory or interference from other items in the sequence (Hole, 1996; Berman

et al., 2009; Lewandowsky et al., 2009; Zhang and Luck, 2009). To test these alternative hypotheses, we compared precision of memory for one item followed by either a short or a long (equal to presentation duration of 3 items) retention period, our control condition (See Methods section, 2.2.1.3 Procedure).

Precision of memory was not affected by increasing the retention interval ($t(10)= 1.658$, $p=0.128$, Fig. 2.5). However, precision decreased significantly when three items were presented in the retention interval, i.e., trials where the target RDK was the 1st item presented in a sequence of 4 (Fig. 2.5; $t(10)= -8.132$, $p<0.001$). Therefore the loss of precision observed for earlier items in the sequence cannot be attributed to temporal decay of memory but rather the interference of items that follow the earlier items.

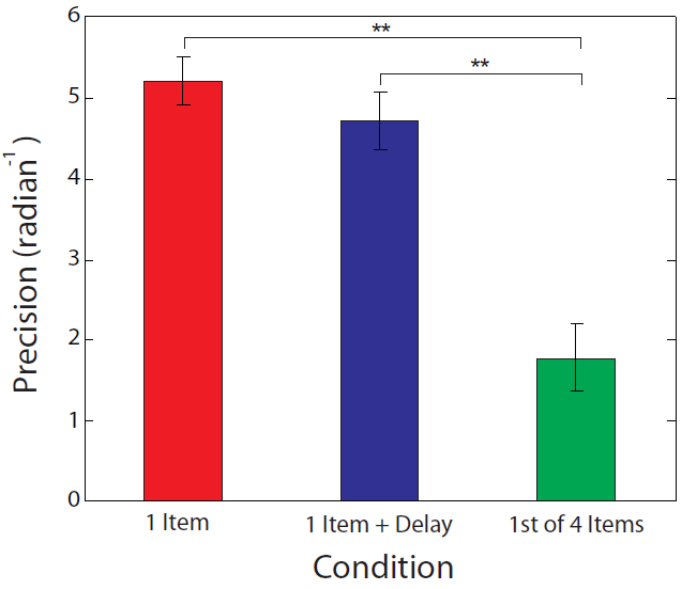

Figure 2. 5: Effect of temporal decay versus interference.
No loss of precision in memory with increasing retention interval (left and middle bar), but precision decreased significantly when 3 items were presented in the retention interval (right bar) (** p< 0.01). Error bars indicate SEM across participants (N = 11).

2. 2. 3. 3 Model Comparison

We applied the two alternative models, i.e., models proposed by Zhang and Luck (2008) and Bays et al. (2009) to the data (see Analysis and Bays et al., (2009) for details).

Maximum likelihood estimates of the probability of responding at random and variability in recall of the target direction under both models were estimated. The probability of responding with a non-target motion direction was estimated using Bays et al.'s (2009) model (see also www.sobell.ion.ucl.ac.uk/pbays/code/JV10/).

The concentration parameter (κ) which captures variability in memory for target direction, did not differ significantly between the two models for all different sequence lengths (Fig. 2.6A, two-way ANOVA, main effect of model type; $F(1,80)= 0.15$, $p=0.7$). Furthermore, there was no significant difference between the proportion of target responses estimated by the two models (Fig. 2.6B, two-way ANOVA, main effect of model type; $F(1,80)= 0.99$, $p=0.32$). Thus, with respect to these two parameters, the models are reassuringly equivalent.

However, overall, the probability of *random* responses was significantly higher when estimated by the model proposed by Zhang and Luck (2008) compared to that of Bays et al. (2009); two way ANOVA, main effect of model type; $F(1,80)=33.55$, $p <0.001$(Fig. 2.6C). In particular, there was a significant increase in random responses estimated by Zhang and Luck's (2008) model, *in longer sequences* (Fig. 2.6C- dashed black line; one-way ANOVA, $F(3,40)= 18.310$, $p<0.001$), increasing to up to 11% for items presented in a sequence of 4. Comparisons between the proportion of random responses for each sequence length confirmed a significant increase in random responses estimated by Zhang and Luck's model in sequences of 3 ($t(10) = 2.99$, $p<0.02$) and 4 items ($t(10) = 6.62$, $p<0.001$).

By contrast, random responses estimated by the model proposed by Bays et al. (2009) were infrequent (<3%) and did not significantly differ for different sequence lengths (Fig. 2.6C- red line; one-way ANOVA, $F(3,40) = 1.95$, $p = 0.14$). Crucially, however, there was an increase in probability of *non-target responses*, the extra parameter proposed by Bays et al. (2008), in longer sequences (Fig. 2.6D; one-way ANOVA, $F(3,40)= 16.85$, $p<0.001$).

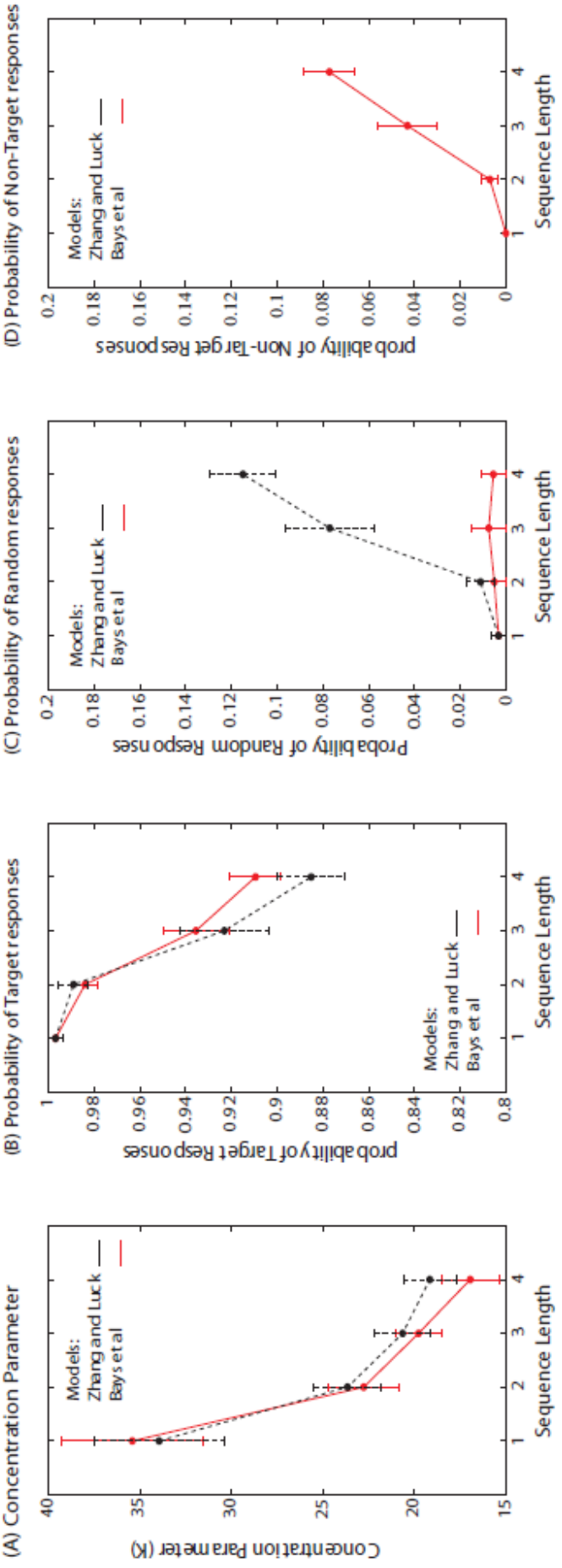

Figure 2. 6: Modelling parameters estimated by Zhang and Luck (2008) and Bays et al's (2009) models, analysed for different sequence lengths. A) Concentration parameter decreased significantly as sequence length increased therefore memory for target is more variable in longer sequences, B) Probability of responding with the target direction of motion was significantly lower in longer sequences, C) Probability of responding with a non-target motion direction increased significantly in longer sequences, D) No difference in random responses for different sequence lengths. Error bars indicate SEM across participants (N= 11).

For sequence lengths of 2 to 4 items, log likelihood values (LL) were calculated under both models to test which provided a better fit to the data. Since there are no non-target items in a sequence of 1, the log LL for this condition under both models are identical and hence will not be reported. Table 2.1 shows the LL values under each model and the probability that the null model (Zhang and Luck, 2008) provides a better fit for the data based on a likelihood ratio test. As illustrated in Table 2.1, for all sequence lengths, Bays et al.'s (2009) model provides a significantly better fit for the data compared to Zhang and Luck's model (2008).

Table 2. 1: Log likelihood (LL) values for each model and the p-values of the likelihood ratio test for different sequence lengths.

Sequence Length	Zhang and Luck (2008) LL Value	Bays et al. (2009) LL Value	p-value
2	-1209.66	-4.67	<0.001
3	-1815.60	-914.94	<0.001
4	-2425.86	-1856.32	<0.001

Furthermore, we calculated LL values for each serial position condition for all participants collapsed together. Table 2.2 provides the LL values for each serial position condition under both models and the significance of the likelihood ratio test.

For all earlier items in a sequence, the model proposed by Bays et al. (2009) provides a significantly better fit for the data compared to the model proposed by Zhang and Luck (2008) (Table 2.2). As for last items in the sequence, Bays et al.'s (2009) model is a significantly better fit for the data when presented in a sequence of 2. It is important to note that it has recently been shown that last item in a sequence is significantly less prone to misbinding errors (Gorgoraptis, Catalao, Bays and Husain, 2011b). Therefore, the reason why the model proposed by Bays et al. (2009) does not provide a better fit for last items is because the proportion of non-target responses is near zero for these items. Memory for the last item is therefore less likely to be corrupted by other items in the sequence.

Table 2. 2: Log likelihood (LL) values for each model and the p-values of the likelihood ratio test for different serial positions in each sequence lengths.

Sequence Length	Serial Position	Zhang and Luck (2008) LL Value	Bays et al (2009) LL Value	p-value
2	First	-27.56	-25.47	<0.05
2	Last	-25.27	28.92	<0.01
3	First	-126.92	-118.06	<0.001
3	Second	-151.11	-137.21	<0.001
3	Last	-2.545	-1.37	0.13
4	First	-197.07	-191.24	<0.001
4	Second	-241.70	-223.20	<0.001
4	Third	-160.17	-154.90	<0.002
4	Last	-21.17	-20.65	0.145

2. 2. 3. 1 Effect of sequence length and serial position of target on model estimates

Given that overall the model proposed by Bays et al. (2009) is a significantly better fit for the present data, we will use parameters estimated by this method to distinguish the possible sources of error in recall and investigate the effects of sequence length and serial position of target on these sources of error. Note that this model includes the target error and random errors just as in Zhang and Luck (2008) but simply extends that model to consider the possibility of non-targets also influencing errors. If we had relied on the model by Zhang and Luck (2008) for our analysis, errors systematically biased by non-targets would have simply been subsumed as 'random' errors, and we would have no index of misbinding – attributing the feature belonging to a non-target to the target.

We therefore applied the three-component model of response errors to our data (see Analysis and Bays et al., 2009 for details). Maximum likelihood estimates of the probability of responding at random, the probability of responding with a non-target motion direction and variability in recall of target direction were estimated.

There was a significant decrease in κ as sequence length increased from one to four (Fig. 6.2A, red line; one-way ANOVA, $F(3,40)= 11.66$, $p< 0.001$), demonstrating more variability in memory for the target direction in longer sequences. However it's important to highlight that the decline in κ is not proportional to 1/set size. Assuming for example that a "memory resource" is represented by a pool of neurons, storage of multiple items in memory would result in the sharing of this pool amongst the to-be-rememebred items. However, the firing rates of neurons are corrupted by noise (Bialek and Rieke, 1992), therefore an increase in the number of items in memory will result in an increase in the variability of the population estimate. Theoretical studies using maximum likelihood decoding scheme have shown that the relationship between precision and the number of items follows a power-law (Seung and Sompolinsky, 1993). Behavioural studies investigating the relationship between number of to-be-remembered items and precision have also shown a power-law relation between the number of items and precision of memory (Bays and Husain, 2008a; Bays, Catalao and Husain, 2009a), consistent with the findings of the present study showing that the number of items and precision of memory do not follow a linear relationship.

The *probability of target responses,* i.e., responses correctly centred on the target direction of motion, decreased significantly in longer sequences (Fig. 2.6B, red line; one-way ANOVA, $F(3,40)= 17.841$, $p< 0.001$). Participants were more likely to respond with the target direction when presented in shorter sequences, while the *probability of non-target responses,* i.e., responses incorrectly centred on the non-target directions of motion, increased with increasing sequence lengths (Fig. 2.6D; one-way ANOVA, $F(3,40)= 16.85$, $p<0.001$, red line). This increase in probability of responding to non-target directions can be attributed to misremembering the correct conjunctions of colours and motion directions, i.e., *misbinding* features of stimuli. *Responding at random* (i.e., guessing) was very infrequent (<3% of responses) and there was no significant difference in the probability of guessing for different sequence lengths (Fig. 2.6C, red line; one-way ANOVA, $F(3,40) = 1.95$, $p = 0.14$).

There was no effect of serial position on the concentration parameter κ ($F<2$, $p= 0.126$) (Fig. 2.7A). Therefore, there was no difference in variability in memory for targets presented at different serial positions within each sequence. However, probability of responding to *non-target directions* was significantly higher for items presented earlier

in a sequence (Fig. 2.7B; two-way ANOVA, main effect of serial position, $F(3,100)= 8.55$, $p<0.001$). This was accompanied by a decrease in probability of responding to *target direction* (Fig. 2.7C; two-way ANOVA, main effect of serial position, $F(3,100)= 8.50$, $p<0.001$). Therefore, for earlier items in a sequence, participants were more likely to misremember which colour was associated with the target motion direction. There was no significant difference in probability of responding at *random* at different serial positions of target ($F<2$, $p= 0.378$) (Fig. 2.7D). Together, these results illustrate that the loss in precision observed for earlier items in a sequence is driven by a significant increase of incorrect conjunctions of colour and direction – *misbinding* – rather than an increase in random responses or a more variable memory for the target direction.

Variability in memory for the target direction presented *last* in a sequence increased significantly in longer sequences (Fig. 2.7A; $F(3,40)= 3.62$, $p= 0.02$). However, no significant difference was observed for probability of responding to *non-target directions* or responding at *random* for last items in different sequence lengths ($F< 2$, $p= 0.126$). Therefore for items presented last in the sequence, only κ decreased significantly in longer sequences (Fig. 2.7A).

What about items earlier than the last one? There was a significant increase in probability of responding to *non-target directions* for earlier items presented in longer sequences. Probability of responding to non-target direction for the penultimate item was significantly larger when presented in longer sequences ($F(2,30)= 5.16$, $p= 0.012$) while probability of responding to target direction was significantly smaller in longer sequences ($F(2,30)= 7.81$, $p= 0.002$). A similar pattern of result was observed for 3rd to last items, with probability of responding to target being larger when presented in sequence of 4 compared to sequence of 3 ($t(10)= 2.703$, $p= 0.022$), along with a significant decrease in probability of responding to target direction in sequences of 4 ($t(10)= 2.234$, $p=0.049$) (Fig. 2.7C).

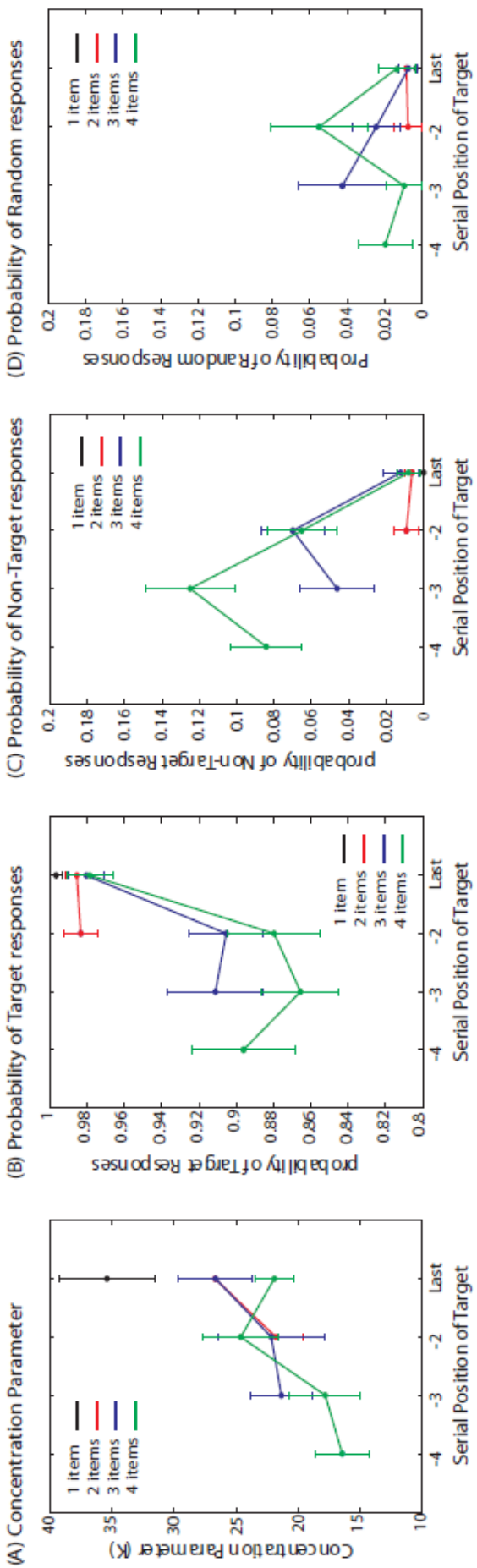

Figure 2. 7: Modelling parameters calculated for each serial position for each participant.
A) Concentration parameter for each sequence length and serial position of the target; significant decrease in concentration parameter for longer sequences for the last item only; B) Probability of responding with the target direction for all sequence lengths and serial positions of the target; C) Probability of responding with a non-target direction of motion for all sequence lengths and serial positions of the target; D) Probability of random responses; no significant difference in random responses for different sequence lengths and serial positions. Error bats indicate SEM across (N= 11).

These findings illustrate two separate sources of error in memory that result in loss of precision in longer sequences for the last item and earlier items in the sequence. For the last item, the loss in precision in longer sequences is a result of an increase in *variability in memory*, while for items earlier than the last item the loss in precision is primarily caused by an increase in misremembering the correct conjunctions of colours and motion directions – *misbinding*.

2. 2. 4 Discussion

In Experiment 2.1, we provide evidence for the resource model of memory for sequences of motion directions. Mean precision of memory for motion directions declined as sequence length increased with precision being lower for earlier items in the sequence. Using a more sensitive measure of working memory performance, we further demonstrated that the resolution with which even the last item of a sequence is maintained is dependent on set size. These findings not only provide further support for the resource model of working memory but also highlight the importance of employing precision measurements to provide a more comprehensive and detailed view of working memory.

Furthermore, we showed that a model accounting for "*misbinding errors*" in response (i.e., the model proposed by Bays et al., 2009) provides a significantly better fit for the data, revealing that decrease in memory precision for earlier items is explained by an increase in interference from other items in the sequence, rather than random responses or a temporal decay of information.

2. 3 Experiment 2.2

In Experiment 2, we aimed to extend our findings to stimuli that share both spatial and temporal properties using transparent motion in order to examine mechanisms with which working memory maintain objects in these situations. Further, we investigated

the sources of error that are affected where both spatial and temporal information attributed to to-be-remembered objects are identical.

2. 3. 1 Method

2. 3. 1. 1 Participants

Eleven healthy volunteers (5 male) with an average age of 29 years old (range: 20-70 years) participated in this experiment. They all had normal or corrected to normal vision and reported normal colour vision. They all provided written consent of the procedure of the experiment approved by the local ethical committee.

2. 3. 1. 2 Stimuli

The stimuli in this experiment were generated by Cogent toolbox for MATLAB and displayed on a 14.1" flat panel display (resolution: 800 × 600 pixels, refresh rate: 60 Hz). Participants were seated approximately 60cm from the screen in a dimly lit room. This experiment consisted of 3 experimental conditions.

In the "transparent motion" condition, a RDK consisting of 50 dots was presented. The properties of the dots were consistent with those in Experiment 2.1. Half of the dots (25 dots) were presented in a colour different than the other half and moved in a different direction (coherently). This resulted in the percept of two sheets of transparent motion. In situations where two dots of different colour had identical spatial position, one dot was chosen at random to be presented on top of the other. In the control "sequential motion" condition, a sequence of 2 RDKs were presented at fixation. The properties of the two RDKs were identical to those in Experiment 2.1.

When participants are asked to estimate the direction of motion of superimposed motion stimuli moving at an acute angle to one another, the angle between the two motion stimuli is often misperceived by few degrees. This phenomenon is called motion repulsion (Levinson and Sekuler, 1976; Marshak and Sekuler, 1979; Mather and Moulden, 1980; Hiris and Blake, 1996; Rauber and Treue, 1999). In order to minimise motion repulsion, minimum angular separation between the two motion directions was

set to be above 90 degrees, above which repulsion effect is minimized (Rauber and Treue, 1999; Braddick et al., 2002). A schematic presentation of transparent motion stimuli is presented in Figure 2.8.

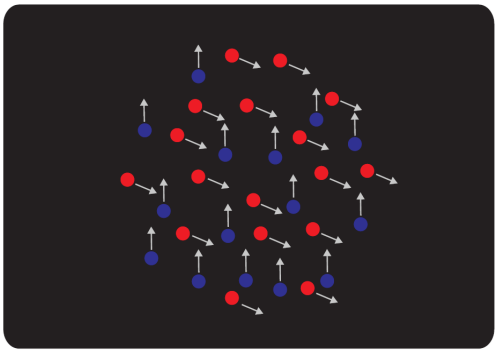

Figure 2. 8: A schematic representation of transparent motion stimuli.
Two sets of differently coloured dots moved coherently at an oblique angle to one another.

We also employed a cuing condition to examine the effects of prioritizing one motion direction prior to presentation of items on precision of working memory. Thus the "transparent motion cued" condition was identical to the "transparent motion" condition, except that at the beginning of each trial, the colour of the fixation point was used as a 100% valid cue for the colour of the target motion direction that would be probed.

2. 3. 1. 3 Procedure

Experimental procedure for the "sequential motion condition" was similar to Experiment 2.1 except for the following difference. After the display of fixation cross (500 msec), a sequence of 2 RDKs were presented, each presented for 2000 msec. The duration of presentation was increased to match the duration of presentation of the stimuli in the "transparent motion" condition. Following a 500 msec delay, the probe display was presented.

Each trial of the "transparent motion" condition started with a fixation cross (500 msec) followed by the transparent motion stimuli (4000 msec). Presentation duration was increased to ensure complete perception of the two motion directions. This was followed by a 500 msec blank interval before the probe display was presented.

Each trial of the "transparent cued" condition started with a coloured fixation cross (500 msec) that acted as a 100% valid cue for the target motion direction. Participants were asked to only attend and maintain the motion direction with similar colour to the colour of the fixation cross. Transparent motion was presented for 4000 msec and was followed by a 500 msec blank before the presentation of the probe display.

The probe display was identical to that presented in Experiment 2.1. Each motion direction had equal probability of being probed in sequential and transparent motion conditions. In the cueing condition, the probe was always presented in the same colour as the cued colour. Participants were told to respond as accurately as possible and reaction times were not measured.

Participants were familiarized with the procedure of the experiment by completing 10 trials of each experimental condition prior to the experiment. Each participant completed 60 trials per condition, divided into 2 blocks of 30 and intermixed randomly.

2. 3. 2 Results

Precision of memory (1/standard deviation of error) was calculated for each condition per participant. We first compared precision of memory for two motion direction presented either in a sequence or simultaneously (i.e., transparent condition). Precision was significantly lower for motion directions presented in the transparent motion condition compared to when presented in a sequence (Fig. 2.9A; $t(10)= 3.20$, $p= 0.01$).

In order to distinguish possible sources of error that could result in the observed modulation of precision, we applied the three-component model of error in memory describe previously (see Analysis for details; Bays et al., 2009). *Variability* of memory around the target direction was significantly greater in the transparent condition compared to the sequential condition (i.e., κ was reduced; Fig. 2.9B; $t(10)= 2.54$, $p= 0.03$). Furthermore, the probability of responding with *non-target direction*s of motion i.e., *misbinding errors* increased significantly in the transparent motion condition (Fig. 2.9C; $t(10)= 2.32$, $p= 0.04$). There was no significant effect of condition on probability of responding with the *target direction* ($t(10)= 1.72$, $p= 0.12$) or responding at *random*

($t(10)= 0.42$, $p= 0.68$). Thus the stored memory of an item was more variable and more prone to *misbinding* errors in the transparent compared to sequential condition.

Additionally, precision significantly improved when the colour of the target direction was cued prior to stimuli presentation in the transparent motion condition (Fig. 2.9A; $t(10)= 7.93$, $p <0.001$). This increase in precision in the cued condition was associated with both a significant decrease in *variability* of memory around the target direction (Fig. 2.9B; $t(10)= 2.59$, $p = 0.027$) and a significant decrease in probability of responding with *non-target directions* (Fig. 2.9C; $t(10)= 2.41$, $p = 0.037$) in the cued condition. Furthermore, this decrease in probability of responding to non-target directions was accompanied by a significant increase in probability of responding with the *target direction*; $t(10)= 2.753$, $p = 0.020$. No significant difference between the *random* responses in both condition was observed ($t(10)= 1.826$, $p = 0.098$).

2. 3. 3 Discussion

Together these results show that motion directions presented simultaneously as transparent motion are more variable and prone to *misbinding* errors. Therefore, in conditions where spatial and temporal information are identical between to-be-remembered items, firstly and foremost items in working memory are more easily corrupted by features from other items in memory and are also noisier in nature.

Moreover, prioritizing one transparent motion enhances precision, causing a decrease in both variability of memory and *misbinding* errors, highlighting the close relationship between selective attention, working memory precision and feature binding.

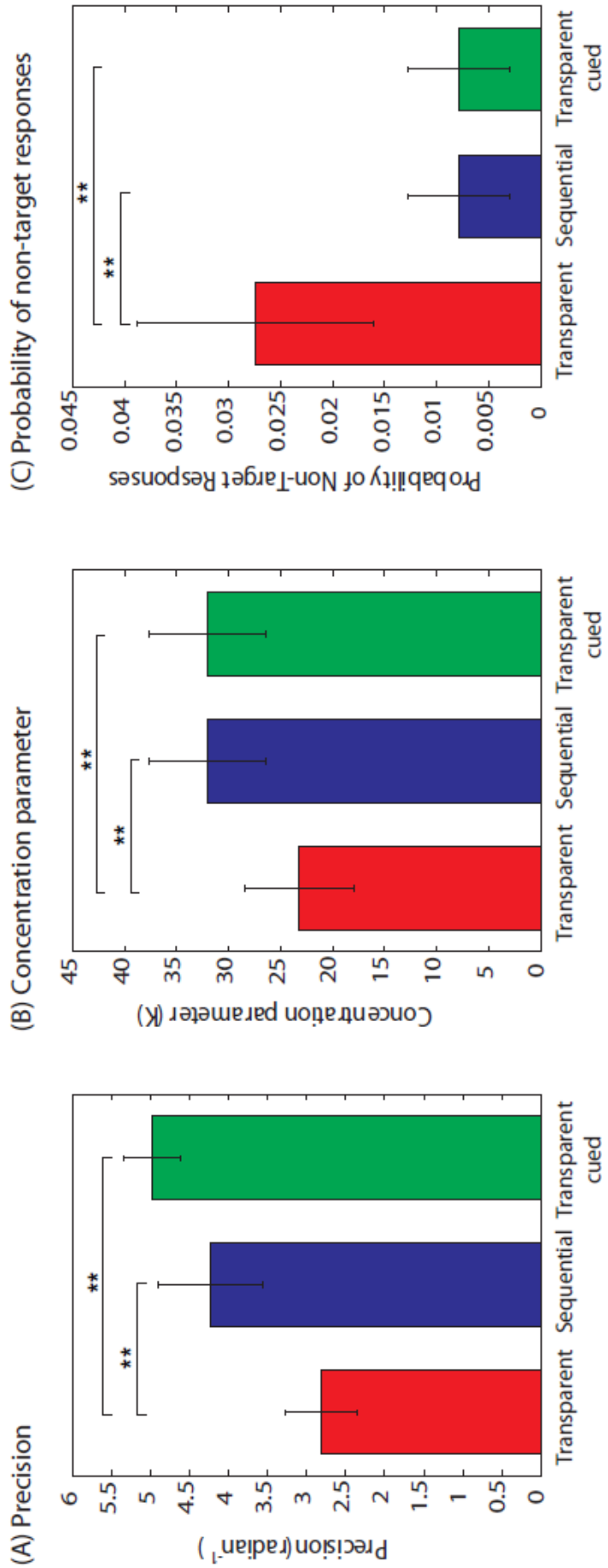

Figure 2. 9: Behavioural and modelling results for transparent, sequential and transparent cued conditions.
A) Precision was significantly higher for items presented in the sequential and cueing conditions compared to transparent condition. B) Estimated modelling concentration parameter was significantly lower in the transparent condition compared to sequential and cueing conditions. C) Probability of non-target responses was significantly higher in the transparent condition compared to sequential and cueing conditions. Error bars indicate SEM across participants (N= 11).

2. 4 General Discussion

Recent studies on precision of visual working memory for orientation, colour and location (Bays and Husain, 2008; Bays, Catalao and Husain, 2009; Bays et al., 2011; Gorgoraptis, Catalao, Bays and Husain, 2011) have provided evidence for a resource model of memory where memory resource is dynamically allocated between visual objects. Here we extend the findings to another visual feature, visual motion, by investigating the precision of memory for motion directions presented both sequentially and simultaneously as transparent motion.

Precision of memory declines in longer sequences

In Experiment 2.1, motion directions were presented in sequences of varied lengths. We demonstrated a decline in precision for motion directions presented in longer sequences (Fig. 2.4A). Importantly, a significant drop in precision was observed even when sequence length was increased from one to two items. These findings are contrary to predictions of the object-based models of memory which propose that visual working memory has a capacity limit of 3-4 "slots" (Luck and Vogel, 1997; Cowan, 2001; Luria and Vogel, 2011) leading to the prediction that the fidelity of memory will not change below the proposed capacity limit. Instead the results are compatible with a limited memory resource (Bays and Husain, 2008; Bays, Catalao, and Husain, 2009; Bays et al., 2011), where the resource allocated to each item is determined by the number of to-be-remembered items. By extending the scope of the dynamic resource model – which has previously been successfully applied to spatial location, colour and orientation – to the domain of motion, we demonstrate that this model can be taken as a general conceptual framework for visual working memory.

It is important to highlight that in the present study, all participants performed above chance level even for sequence lengths of up to 4 items. However, a previous study (Kawasaki et al., 2008) has reported a small memory capacity for motion directions, i.e., two items, with memory capacity measured using a change detection procedure. Although such paradigms have been very useful in understanding visual working memory, they provide a binary- correct/incorrect response measure. We would argue

that measuring the precision of memory is potentially a more sensitive index of working memory, allowing us also to test any modulations of the *fidelity* of the stored items by set size.

Serial position of target influences precision of memory

Serial position or order at which an item is presented within a sequence can also affect the precision with which it is recalled. Last item in a sequence was remembered with higher fidelity compared to other items in a sequence. This finding is in line with previous studies reporting a benefit for the last item presented in a sequence known as the recency effect (Phillips and Christie, 1977; Wright et al., 1985; Neath, 1993; Hay et al., 2007; Blalock and Clegg, 2010). However, measuring precision of working memory, i.e., a measure sensitive to small changes in fidelity of memory, showed that the recency effect was affected by the number of preceding items, with less precision in longer sequences (Fig. 2.4B). This modulation of last item precision by sequence length appeared to be driven purely by an increase in variability in memory for the last item in longer sequences (Fig. 2.7A).

For items earlier than the last one in each sequence, precision of memory did not vary significantly between different serial positions, but was significantly lower compared to the last item (Fig. 2.4B). This drop in precision cannot be explained by the temporal decay of memory (Fig. 2.5) but rather is a result of interference of other items in the sequence that follow earlier items. Thus it appears that each time an item is added, the resources dedicated to previous items have to be re-distributed to accommodate the added item with enough resources for encoding. Equal precision for all items except the last item in each sequence suggests that memory resource is shared equally between earlier items.

In line with earlier studies investigating working memory (Wright et al., 1985; Neath, 1993; Burgess and Hitch, 1999; Hay et al., 2007; Botvinick et al., 2009; Blalock and Clegg, 2010), we show a recency effect which further was modulated by the number of preceding items (Fig. 2.4B). Several models have been proposed in the literature to account for the well-replicated effect of recency arguing for retroactive interference whenever a new item is added (Nairne, 1988) or a decrease in temporal distinctiveness

for earlier items, resulting in a better available representation for the last item (Glenberg et al., 1983; Burgess and Hitch, 1999; Brown et al., 2000). However, here we show that the magnitude of the recency effect is affected by the number of *preceding* items. Therefore, the recency effect can also be explained in terms of the allocation of a "left over" share of the memory resource that is determined by the number of previous items.

Interestingly, similar decline of precision for longer sequences was observed at other serial positions (last, penultimate, first, etc.), there was a significant decrease in precision for items presented in longer sequences (Fig. 2.4B). Therefore at each serial position, the precision of memory and the amount of resource dedicated to that item is influenced by the overall number of to-be-remembered items in that trial. These results are consistent with research investigating the precision of working memory for sequences of orientations (Gorgoraptis et al., 2011), now extending those conclusions to the domain of visual motion.

Sources of error at recall in working memory

Recently, two alternative models of working memory distinguishing possible sources of error in recall have been proposed. According to the model proposed by Zhang and Luck (2008), one can distinguish between two possible errors that can result in lower precision for larger set sizes. In larger set sizes, variability of memory for the *target* direction is higher. Furthermore, in longer sequences participants are more likely to respond at *random* ('guessing') since the probability of not storing an item beyond the capacity limits of memory, as proposed by Zhang and Luck (2008) and "slot" models of memory, is higher for larger set sizes.

However, in tasks similar to the one used in the present study, successful performance depends not only on remembering target motion direction but also on remembering the correct conjunction of colour and motion direction. This raises the possibility of another type of error that may occur in working memory: misremembering the correct conjunction of colour and motion direction, i.e., *misbinding errors*. In other words, other items in a sequence that are not probed (i.e., non-targets) can systematically bias recall if a feature associated with them (direction of motion) is attributed to the target instead.

This important potential source of error is accounted for in the model proposed by Bays et al. (2009) by adding the probability of non-target responses to the model proposed by Zhang and Luck (2008). In order to find the model that best describes our data we compared to the two models (Fig 2.6). Our analysis demonstrated that the model proposed by Bays et al. (2009) provides a significantly better fit for the data (Tables 2.1 and 2.2), providing evidence for the existence of a source of error in working memory that was not accounted by previous model. In their schema, misbinding errors (those systematically biased by non-targets) would simply have been subsumed under the category of 'random' responses.

Misbinding of object features

As stated previously, successful performance on the precision task used here depends not only on remembering target motion direction but also on remembering the correct conjunction of colour and motion. Therefore, responses to non-target motion directions arise when participants incorrectly bind features across two objects. In this instance, participants may incorrectly bind the colours and motion directions resulting in responses centred around one of the non-target motion directions. Previously, it has been shown that increasing the load of memory, either by increasing the number of items (Bays, Catalao, and Husain, 2009) or by introducing an extra set of features in memory (Bays et al., 2011), results in misremembering the correct conjunction of features between objects.

In the present study, we show that items presented early in a sequence and in longer sequences are more prone to *misbinding* errors as opposed to other items in the sequence. Note that participants did not know before each trial how long the sequence would be, so there is no reason to believe they pre-allocated resources for each item in a sequence prior to each trial. Thus they would be expected to allocate all resources to the first item. But if a new item is presented, according to the resource model, some of the resources devoted to the first item now have to be allocated to that item, and so on if further items follow. The findings presented here suggest that the re-distribution of memory resource for earlier items comes with a cost, specifically making these items more susceptible to *misbinding* errors.

But why would such reallocation of resources lead to misbinding? Some insights into this process might be offered from the results of a recent report which investigated precision of memory for objects of different colour and orientation (Bays et al., 2011). Errors in memory for colour and orientation increased with the number of items to be stored but crucially were not correlated, suggesting that these features are stored separately- i.e., 'unbound'. Further, misbinding errors also increased with memory load but again occurred independently in each feature dimension, suggesting that bound information might in fact be stored independently of feature dimensions. If this is indeed the case, it might explain why, in the present study, increasing number of items to be held in memory is associated with increasing vulnerability to misbinding a non-target motion direction to the target colour. Corruption of feature bindings would be expected to increase in noisy neural representations as the number of items that are stored increases.

Binding and attention

Another situation which gives rise to proportion of *misbinding* errors in working memory is where temporal and spatial information between to-be-remembered items are shared. Simultaneous presentation of motion directions as transparent motion surfaces resulted in a decrease in precision as compared to sequential presentation. Precision of memory for motion directions when presented as transparent motion was observed to be more variable and prone to *misbinding* errors (Fig. 2.9), both of which declined by prioritizing (cuing) a motion surface beforehand (Fig. 2.9).

Although the experiment was designed to minimize motion repulsion, by minimizing the angular separation between the two motion directions (Rauber and Treue, 1999; Braddick et al., 2002), misperceiving target direction nonetheless might have contributed to the increase in memory variability around the target direction. However, *misbinding* errors cannot be explained in terms of such misperception effects. In the transparent motion condition participants had to actively segregate the two directions of motion and encode both directions. Our results demonstrate that this process during encoding has a cost on the precision of memory, explained by an increase in misbinding errors. Conversely, prioritizing one transparent sheet by cuing it in advance led to

improvement in precision of memory associated with a significant decrease in misbinding errors.

These findings suggest that selective attention can have an important role in correct binding of features, extending previous reports demonstrating the importance of attention in binding of features in visual working memory (Wheeler and Treisman, 2002). Previous reports have illustrated the dependence of working memory capacity on the ability to attend to task-relevant information (Awh et al., 2006; McNab and Klingberg, 2008), and elevation of precision by cuing either the location or colour of the relevant items (Bays and Husain, 2008; Gorgoraptis, Catalao, Bays and Husain, 2011). Together these results highlight the close relationship between attention and working memory although the exact nature of this connection remains unclear.

Conclusion

Together the results from the present study point towards a limited memory resource that can be dynamically distributed and re-distributed when presented with novel visual objects over time. The re-allocation of resources comes with a cost, manifested in *misbinding* errors observed for earlier items in longer sequences and the modulation in variability in memory for last items. Furthermore, our results highlight the importance of selective attention in visual working memory specifically for correct binding of visual features in memory. These findings extend previous literature on temporary storage of visual motion and provide further insight into the dynamics of memory distribution for objects presented over time or simultaneously. Results from both experiments challenge item-limit models of memory and provide consistent evidence for the dynamic allocation of resources in memory, now across a range of visual features, including motion.

Chapter 3

Causal evidence for a focus of attention in working memory maintenance

3. 1 Introduction

A comprehensive understanding of visual working memory relies not only on studying behaviour but also investigating the neural correlates of this cognitive process. Research on visual working memory has emphasized the demands of this cognitive process on sensory representation resources. According to the sensory recruitment hypotheses (e.g.

Postle, 2006; Ester et al., 2009; Serences et al., 2009a) retention of visual information in working memory involves *same* brain areas as those involved in perceptual encoding of the visual attributes (Pasternak and Greenlee, 2005; Postle, 2006). In fact, as explained in detail in Chapter 1 (section 1.3), there are a number of psychophysical, animal electrophysiology and human neuroimaging studies that have shown that visual areas responsible for perception and encoding of visual features are also active during the maintenance period of working memory tasks (e.g., Smith and Jonides, 1997; Bisley et al., 2001, 2004; Postle et al., 2003; Ranganath et al., 2004; Serences et al., 2009b). For example, Harrison and Tong (2009) presented a sequence of oriented gratings followed by a cue indicating the grating to be maintained for 11seconds. After the delay interval, a test grating was presented and participants had to indicate whether test grating was rotated clockwise or anti-clockwise relative to the cued grating. They showed that information held in working memory maintenance can be decoded from activity patterns in early visual areas.

However, recently it has been suggested that items maintained in early visual areas may represent only those items in the focus of attention (FOA) rather than the full contents of working memory (Olivers et al., 2011b; Lewis-Peacock et al., 2012). This is based on conceptual models of working memory arguing for functionally distinct regions for maintenance of a limited number of items available for ongoing cognitive processes and an item held in FOA, one that is selected as the object of the next cognitive operation (Oberauer, 2002, 2006). Therefore, as proposed by this model, when working memory is filled, most of the stored items will not be in an active state but instead may be relatively suppressed. Only one item at each given time, however, will acquire the special status of being in the FOA (note that there is currently a controversy regarding the number of items in FOA (see Cowan, 2011; Olivers and Eimer, 2011 for reviews). Moreover, it has been suggested that an item in FOA gains access to sensory input through feedback connections to lower visual areas and hence is the only object represented in these areas (Olivers et al., 2011).

Considering the dissociation between representations inside and outside the FOA, most previous studies, mainly human neuroimaging, have focused on decoding representations in working memory maintenance for items that are most relevant to the task at hand. For example, in the study by Harrison and Tong (2009), only one item, that is the cued grating, was retained and hence information decoded during memory

maintenance might be related to this item only, that is the most relevant item or the one in FOA.

Behavioural evidence for the distinction between the full contents of working memory and those in FOA comes from studies demonstrating object-switch effects. That is when two successive operations require access to an object in working memory, the response time is faster when the operation requires access to the same element compared to when a switch to another object is required (Garavan, 1998; Oberauer, 2003). Further, same studies have reported that recognition of items presented last in the sequence is faster (Wickelgren et al., 1980; McElree and Dosher, 1989; Öztekin and McElree, 2007) and more precise (Gorgoraptis et al., 2011) compared to earlier items - the recency effect. This has been explained in terms of differences in access of the last item compared to previous ones since the last item is represented in FOA and has privileged accessibility (Oberauer, 2006).

The dissociation in recognition judgment for the last item (i.e., the item in FOA) and previous ones was examined recently (Oztekin et al., 2010). In that study participants were presented with a sequence of words followed by a recognition probe. The findings indicated that hippocampal activation was enhanced for all previous items in a sequence compared to last item. This was put forward as evidence for special, privileged state of the last item, with a dichotomy between items maintained in FOA and all other memory representations (Oztekin et al., 2010).

More direct evidence demonstrating the relationship between sustained activity and working memory maintenance comes from an imaging study that distinguishes between the most relevant item and full contents of memory (Lewis-Peacock et al., 2012) . In that study, a retro cue, presented during the delay interval, highlighted the most relevant item for the upcoming cognitive operation. It was shown that delay period activity reflected only the item in FOA. Importantly the neural signature of unattended information in memory was restored when attention was refocused to these items by a second retro cue. These findings challenge the sensory recruitment hypotheses arguing for distinct neural traces for items in working memory and those in FOA.

Together these behavioural and imaging studies have shown that items in working memory can have different “states” according to their relevancy to the task and serial positions in a sequence. Moreover, it has been suggested that items in FOA are those

represented in early visual areas, through feedback connection to these areas (Olivers et al., 2011). Considering these advances in conceptual models of working memory, a question that arises is whether it is possible to disrupt the representation of items inside FOA by applying transcranial magnetic stimulation (TMS) to early visual areas (see Chapter 1, section 1.3.4). Thus, if items in FOA are the representations retained in early visual areas, TMS applied to early visual areas would disrupt maintenance of these items only, without having an effect on other items in working memory.

In order to test this hypothesis, we investigated the effect of TMS applied to an area involved in processing of motion direction (area MT+) on memory for this feature. Visual areas involved in perception and encoding of motion are relatively well-known (Shadlen and Newsome, 1996; Andersen, 1997; Mather, 2011) and hence this visual feature was a perfect candidate for our experiments (e.g., Bisley and Pasternak, 2000; Bisley et al., 2001; Pasternak and Zaksas, 2003; Silvanto and Cattaneo, 2010 for studies showing involvement of MT+ in working memory for motion). In Experiment 3.1, we manipulated the item in FOA using a retro cue, i.e., a cue presented long after the visual array has been extinguished indicating the most probable item that will be probed. In this way, one of the items in memory would be bought into the FOA. TMS was applied to MT+ after the presentation of the cue to examine the causal role of this area in maintenance of item in FOA compared to other items in working memory.

In Experiment 3.2, we manipulated the item in FOA by presenting items sequentially, in light of previous studies that have demonstrated the special case of the last item. Specifically, the last item is in the FOA in an obligate manner. TMS was applied to MT+ after the encoding of items to test the differential effect of TMS for items presented last in the sequence (i.e., the item in FOA) compared to previous items presumed not to be in FOA. Based on current conceptual models of working memory, if only the item in FOA is represented in early visual areas, TMS to MT+ should disrupt performance of these items only, without any effect on other items in working memory.

3. 2 Experiment 3.1

3. 2. 1 Method

3. 2. 1. 1 Participants

Fourteen right-handed participants (8 male) with average age of 25 years (SD = 7) with no history of neurological or psychiatric abnormality participated in this study. All participants were screened to confirm suitability for receiving TMS and gave written informed consent to the procedure of the experiment, approved by the local ethics committee.

3. 2. 1. 2 MT+ Localisation

Localiser task

The localizer task consisted of 16-20s blocks of RDK moving in translational motion interleaved with 16-20s static dots, for 8 blocks in total. The stimuli covered 10º of visual angle and dots were presented at the centre of the screen in low contrast on a black background.

fMRI

Participants were scanned on a 3T Siemens (Siemens Medical System, Erlangen, Germany) using a standard transmit/receive head coil, prior to the experiment. A multislice echoplanar imaging (EPI) sequence was used to acquire BOLD signal (TR= 2.45s, TE= 30ms. 35 slices per volume). Ascending slice acquisition was employed resulting in 132 volume per run (matrix size= 64×64×35; voxel size= 3×3×3mm, 50% gap). In addition to functional scans, aT1 weighted anatomical scan [3D MDEFT sagittal partition direction, matrix size= 256×240×176, voxel size= 3×3×3mm] was acquired for the frameless stereotaxy procedure described below in 3.2.1.3, to localize the TMS coil position on each participant's scalp prior to administration of TMS .

Pre-processing and Analysis

Functional images were reconstructed offline and the first 4 volumes were discarded to account for T1 equilibrium effects. Images were realigned to the middle of the series and were then spatially smoothed using a 6mm full-width-at-half maximum Gaussian kernel. Slice-timing correction was then applied. The next step of pre-processing was correction of magnetic field inhomogeneties via geometric unwarping. High pass filter (100s) was applied to remove low frequency signal fluctuations. Statistical map were generated by constructing a Generalized Linear Model (GLM) which comprised of a boxcaqe regressor (convolved with a canonical haemodynamic response function) with onsets/offsets corresponding to the task.

Statistical maps (Z stats images) for the contrast motion versus static blocks were thresholded at Z= 2.3 (p= 0.05; cluster corrected). Left hemisphere clusters in the vicinity of MT+ (using the anatomical guidelines described by Dumoulin et al., 2000) were identified in the native space of each participant.

3. 2. 1. 3 TMS

Localisation of TMS target: Clusters corresponding to left MT+ as defined above were overlaid onto each participant's native space high resolution T1-weighted scan. A Brainsight frameless stereotaxy procedure (Rogue Research, Montreal, Canada) was used to identify the scalp location overlying left MT+ in each participant.

In each experimental session, TMS was delivered via a Magtism Rapid stimulator using 70-mm figure-of-eight coil. The coil was held in a position over the marked location with a custom holder and was oriented at ~45º with the handle pointing posteriorly. Four TMS pulses at 20 HZ were applied to left MT+ either at 60% of maximum machine output (*"high" intensity*) or at 24% of maximum machine capacity (*"low" intensity*) in each trial. Low intensity trials were included to control for non-specific effects of TMS such as the acoustic artefact and tactile sensation on the scalp.

3. 2. 1. 4 Working memory task Stimuli

Stimuli were generated by Cogent toolbox for MATLAB and were displayed on a 14.1" flat panel display (resolution: 800 × 600 pixels, refresh rate: 60 Hz). Participants were seated approximately 60cm from the monitor in a dimly illuminated room.

In each trial, two Random Dot Kinematograms (RDKs) were presented, below and above the fixation cross at the centre of the screen. The distance between the center of the fixation cross and the center of each RDK was 10° of visual angle. RDKs consisted of 25 dots, each covering 0.1º of visual angle. Dots were displayed within an invisible circular aperture of 150 pixels in diameter (5.7 º of visual angle). Dot lifetime was 500 msec and dots reaching the edge of the circular aperture were re-positioned randomly on the other side of the aperture; therefore dot density was kept constant throughout the presentation.

Motion was 100% coherent (constant speed of 4.5 degrees/sec for all dots). Direction of motion for each RDK was set at a random value between 0-360º with no minimum angular separation between the two motion directions. RDKs were presented in green and red colours, chosen randomly for RDKs presented at different locations.

Following the presentations of the two RDKs, a mask was presented. The mask consisted of 5000 dots, half of them presented in red and half in green, and covering the whole screen. Motion direction of each dot was chosen randomly from 0-360º. Dot life-time was 500 msec, longer than the presentation duration of the mask (100 msec). Dots reaching the boarders of the screen were repositioned randomly on another side of the screen and hence dot density was kept constant throughout the presentation of the mask.

3. 2. 1. 5 Experimental Procedure and design

Figure 3.1 is a schematic representation of a sample trial. Each trial started with a fixation cross (500 msec) followed by the presentation of two RDKs, each presented for 200 msec and followed by a 100 msec mask. After 300 msec of blank interval, a retro cue was presented in which the colour of the fixation cross changed to either red or green, indicating the RDK that was more likely to be probed at the end of the trial. The retro cue was presented for 200 msec and was valid for 80% of the trials. That is in 80%

of the trials, the colour of the probe was the RDK cued by the colour of the fixation cross. The probability of cueing the RDKs above or below the fixation cross was kept constant for both items.

The retro cue was followed by 2600 msec delay interval prior to the administration of TMS (4 pulses at 20HZ). The last TMS pulse was followed by a 300 msec blank interval prior to the presentation of the probe display. The probe stimulus consisted of a circle (5.7 º of visual angle in diameter) presented at the centre of the screen with a line positioned at a random orientation displayed from the centre of the circle- drawn from the uniform distribution [0-360˚] – within the circle. The probe stimulus was presented in the same colour as one of the RDKs (i.e., either red or green). Participants were asked to adjust the orientation of the line within the circle, using a mouse, to match the direction of motion of the RDK presented in the same colour in the sequence.

In 80% of the trials the colour of the probe matched that of the retro cue (*valid trials*). In the remaining trials, the RDK that had not been indicated by the retro cue was probed (*invalid trials*). Probe display was presented until response and participants were asked to respond as accurately as possible, with no time pressure.

Each participant completed 416 trials (208 per TMS intensity condition, randomly interleaved) across 4 experimental blocks. Prior to the start of experiment, participants completed 40 trials to familiarize themselves with experimental procedure.

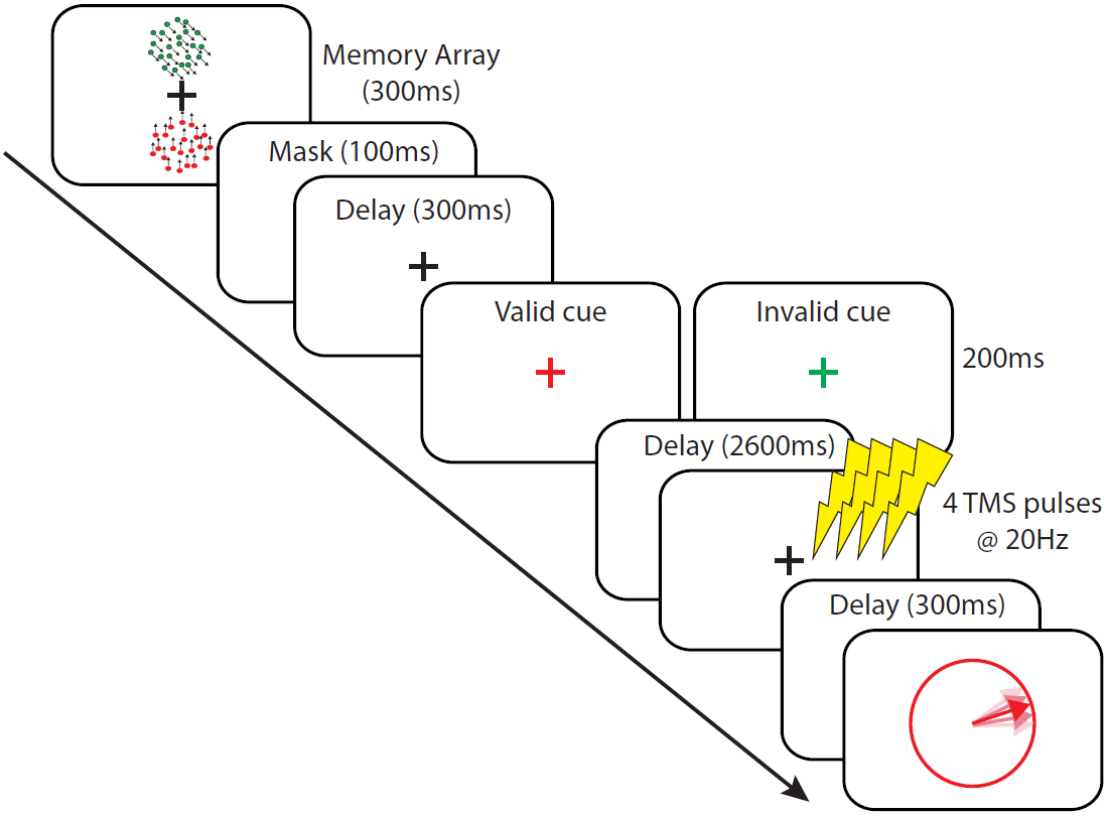

Figure 3. 1: An example of a sample trial.
Two RDKs were presented simultaneously and participants were asked to keep in mind the direction of both of them. During the maintenance period, the colour of the fixation cross changed to indicate the RDK that was more likely to be probed at the end of the trial. A short 4-pulse train of TMS was then applied, followed by a blank interval prior to the presentation of the probe display. Participants were instructed to match the orientation of the probe line to match the direction of motion of the RDK with the same colour as the probe (regardless of whether it matched the colour of the retro cue).

3. 2. 1. 6 Behavioural Analysis

For each trial, precision of memory was calculated as described in Chapter 2, based on previous studies using fidelity of recall of a visual stimulus as an index of working memory performance (e.g., Bays et al., 2009, 2011; Gorgoraptis et al., 2011; Pertzov et al., 2012). In summary, for each trial, the angular deviation between motion direction reported by the participant and the motion direction of the memory target was calculated. Precision was defined as the reciprocal of the circular standard deviation of error across trials within a condition. The value expected for chance was subtracted from calculated values and hence zero precision corresponds to responding at random.

Trials where participants did not move the mouse (i.e., trials in which response angle was identical to probe angle) or their response times were longer than 10000 msec, were excluded from further analysis.

3. 2. 2 Results and Discussion

We first determined the effect of cue validity on performance in the low TMS, i.e., control condition. There was a significant effect of validity on precision of memory. Performance on trials where the probe was validly cued were significantly better than those where the invalid item was later probed (precision for validly cued items: 1.8, precision for unvalid items: 1.15; $t(13) = 3.35$, $p= 0.005$). Therefore the cue was successful in producing a behavioural advantage.

Next we examined the effect of high (versus low) intensity TMS on valid and invalid trial memory precision (Fig. 3.2). There was a significant effect of validity (main effect of validity, $F(1,52) = 6.5$, $p= 0.014$) but no main effect of TMS intensity or an interaction between the intensity and validity. The lack of significant interaction may be because the study was underpowered and therefore, I further checked the effects of high versus low intensity TMS for valid and invalidly cued items separately. t-test comparison demonstrated that precision of memory for validly cued items in high TMS decreased significantly compared to low intensity TMS condition ($t(13) = 2.6$, $p= 0.02$-Fig. 3.2) [change from 1.8 to 1.57 in precision for low to high intensity TMS respectively]. There was no change in precision for invalid items under high compared to low intensity TMS conditions ($t(13) = 0.4$, $p> 0.1$ -Fig. 3.2) [change from 1.18 to 1.13 in precision for low to high intensity TMS respectively].

It is important to note also that performance of invalidly cued items under high TMS was above chance ($t(13) = 4.8$, $p< 0.001$) confirming that these items were indeed maintained in working memory.

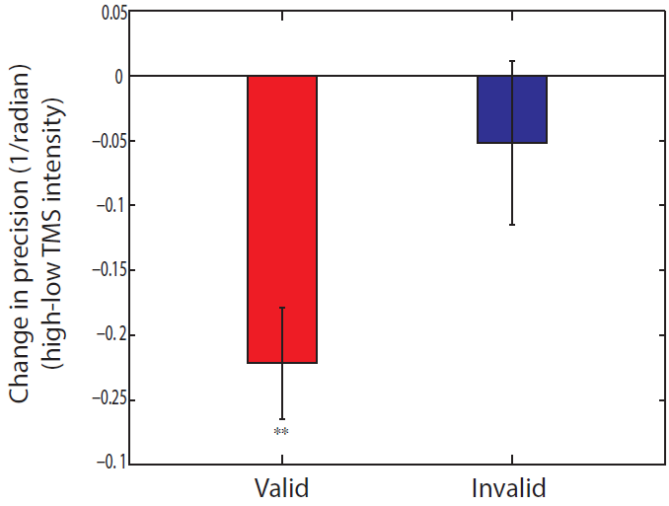

Figure 3. 2: Effect of TMS (high-low intensity TMS) on precision of memory for valid compared to invalid items.
High (versus low) TMS resulted in a decrease in performance for valid items only (within subject error bars).

3. 3 Experiment 3.2

In Experiment 3.1 we used a retro cue to manipulate a memory item to be in or out of a theoretical FOA, i.e., one item was made more accessible by virtue of having more attention focused upon it, rendering higher recall precision for this item.

The question that remains unanswered is whether TMS to early visual areas can modulate representation of items that are *inherently represented at different states* within working memory. Items introduced in working memory sequentially are known to be maintained at different levels of representations according to their serial position within the sequence (e.g. Neath, 1993; Hay et al., 2007; Botvinick et al., 2009; Blalock and Clegg, 2010). More specifically, the last item in a sequence has been shown to be maintained with higher precision (Gorgoraptis et al., 2011), or maintained in a different state than previous items (Oberauer, 2006; Öztekin et al., 2010).

Because several studies have suggested that the last item is represented in the FOA, it might be argued that decrease in precision for earlier items is caused by interference from the last item on earlier ones. This hypothesis is strengthened by a recent report that showed the last item "advantage" is due to decreased recall precision for earlier items, with the last item in sequences of different lengths maintained with similar precision as items presented *simultaneously* for the same set size (Gorgoraptis et al., 2011).

If the last item in a sequence is in FOA, we predict that TMS to early visual areas after the sequential presentation of items would disrupt memory representation for only the last item. Consequently, TMS would interfere with the last item's effect on earlier items resulting in an *increase in precision* of memory for earlier items. In Experiment 3.2, we aimed to test these predictions by presenting 2 RDKs *in a sequence* and to investigate the effect of TMS to MT+ on precision of memory for the last item compared to previous ones.

3. 3. 1 Method

3. 3. 1. 1 Participants

Seventeen right-handed participants (10 male) with average age of 27 years (SD = 5.4) with no history of neurological or psychiatric abnormality participated in this study. All were screened to confirm suitability for receiving TMS and gave written informed consent to the procedure of the experiment, approved by the local ethics committee.

3. 3. 1. 2 Stimuli

Stimuli were generated by Cogent toolbox for MATLAB and were displayed on a 14.1" flat panel display (resolution: 800 × 600 pixels, refresh rate: 60 Hz). Participants were seated approximately 60cm from the monitor in a dimly illuminated room.

In each trial, a sequence of two Random Dot Kinematograms (RDKs) was presented consecutively at the centre of the screen on a black background followed by a mask. After the presentation of the sequence, the probe display was presented. The properties of the RDKs, masks and the probe display were identical to that explained in Experiment 3.1.

3. 3. 1. 3 Experimental Procedure

Figure 3.3 is a schematic representation of a sample trial. The MT+ localizations process and TMS parameters where identical to that described in Experiment 3.1. In a

separate experimental session, TMS was applied to the vertex, identified as Cz based on the International 10-20 system for EEG electrode localization. TMS to the vertex served as an additional control for the non-specific effects of applying TMS to the cortex during task performance.

Each trial started with a fixation cross, followed by a sequence of 2 RDKs. Each RDK was presented for 200 msec followed by a 100 msec mask. Prior to presentation of the 2nd RDK a 900 msec blank display was presented. Similar to the first RDK, the 2nd RDK was presented for 200 msec followed by a 100 msec mask. The probe display was presented after 900 msec blank interval after the presentation of the 2nd RDK. TMS was applied during the delay intervals either in the first delay or the second delay, following a 300 msec blank interval.

After the presentation of a blank interval for either 900 msec (in trials in which TMS was applied in the 1st delay interval) or 300 msec (after TMS in the second delay) the probe stimulus was presented. The probe stimulus was presented in the same colour as one of the RDKs (i.e., either red or green). Participants were asked to adjust the orientation of the line within the circle, using a mouse, to match the direction of motion of the RDK presented in the same colour in the sequence. The probability of probing any of the RDKs within the sequence was kept constant for both items in the sequence. The probe display was presented until response and participants were asked to respond as accurately as possible, with no time pressure.

The intertrial interval (ITI) was set to a minimum of 2000 msec but varied to ensure a minimum of 5000 msec between TMS applied in the second delay and the start of the next trial.

3. 3. 1. 4 Design

We used a fully factorial, balanced design with four factors: TMS location (MT+ and Vertex), TMS intensity (high and low), TMS position (1st or 2nd delay) and target position (1st or 2nd delay) resulting in a total of 16 conditions. Participants completed two testing sessions, in which TMS was applied either to left MT+ or vertex only. Participants completed 448 trials, 56 trials per condition per testing session. Prior to the

experimental session participants received training of up to 40 trials to familiarize themselves with the task.

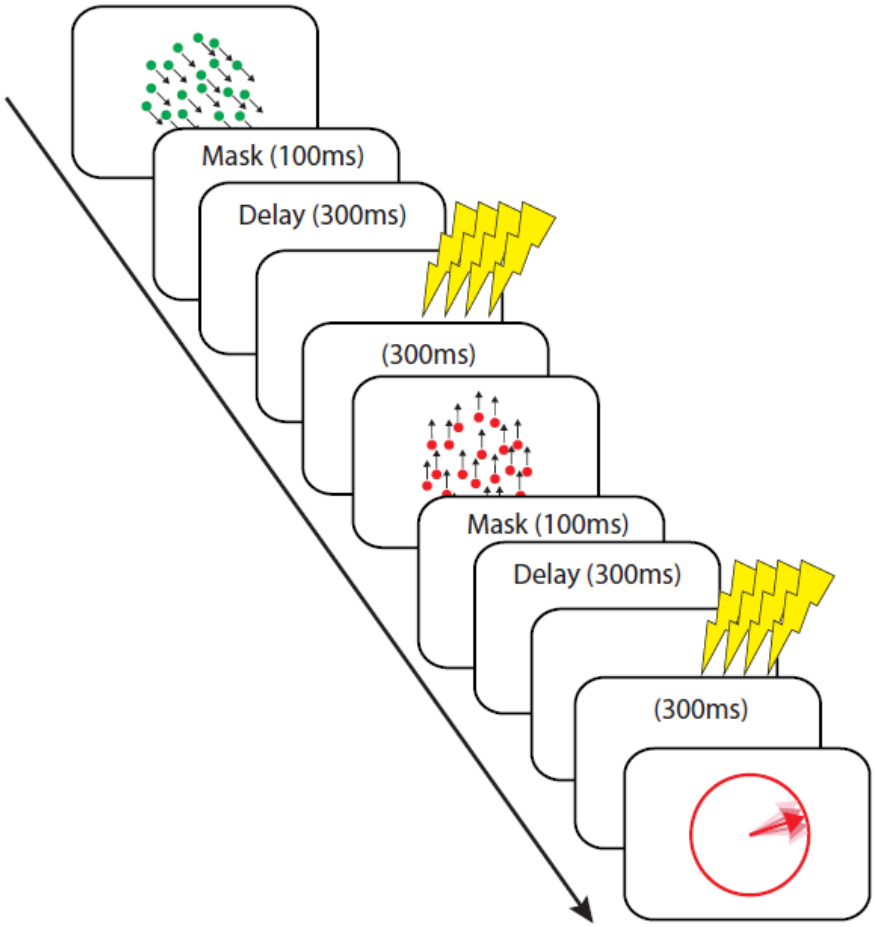

Figure 3. 3: A schematic presentation of a trial in Experiment 3.2.
In each trial a sequence of 2 RDK patterns in two different colours (green and red) moving in different directions are presented. TMS was applied 300 msec after the start of the delay interval either in the first delay (i.e., between the 1st and 2nd RDKs) or after the presentation of both RDKs (i.e., prior to the presentation of the response stimuli). At the end of each trial a probe stimulus was presented and participants had to adjust the line within the response circle to match the direction of the motion of the RDK with the same colour as the probe.

3. 3. 1. 5 Behavioural Analysis

In each trial, precision of memory was calculated as described in Experiment 3.1 based on previous studies using fidelity of recall of a visual stimulus as an index of working

memory performance (e.g., Bays et al., 2009, 2011; Gorgoraptis et al., 2011; Pertzov et al., 2012). Trials in which participants did not moved the mouse or their response times were longer than 10000 msec were excluded from further analysis.

To quantify the contribution of different sources of error to working memory performance, we applied the probabilistic model introduced in Chapter 2 by Bays et al. (2009). This model attributes errors in adjustment tasks to the following sources of error: 1) Gaussian variability in memory for target motion direction, 2) probability of misreporting the non-target motion direction and 3) probability of responding with a random direction. Maximum likelihood estimates of these parameters were obtained separately for each experimental condition.

3. 3. 2 Results

3. 3. 2. 1 Effect of TMS to MT+ in working memory precision

We first investigated the causal effect of TMS applied to MT+. There was a significant main effect of target position on precision of recall from memory ($F(1,16) = 12.3$, $p= 0.003$) confirming that last items in sequence were remembered with higher precision than earlier items, regardless of TMS intensity and time of TMS. Moreover, there was a significant interaction between TMS intensity and target position ($F(1,16) = 7.79$, $p= 0.013$). Therefore TMS intensity influenced working memory precision differentially depending upon the position of the target within the sequence.

TMS was applied either in the first delay interval (prior to presentation of the 2nd RDK) or after the presentation of both RDKs during the maintenance period. Therefore the effects of TMS separately on these two conditions are further explored.

We first sought to examine the effect of high versus low intensity TMS applied to MT+ in the first delay interval. There was a significant interaction between target position and intensity of TMS ($F(1,16) = 5.62$, $p= 0.031$). In trials where TMS was applied in the first delay interval, the serial position of the target determined the direction of high (versus low) TMS effects on performance. There was a significant TMS-induced improvement in performance when *first* item in the sequence was the target ($t(17)=$

2.37, p= 0.015- Fig. 3.4A). Therefore in trials where TMS was applied prior to encoding of the 2nd item, there was an improvement in precision of memory for the 1st item in the sequence and a decrease in performance for the 2nd item in the sequence.

We next examined the role of TMS to MT+ when applied in the second delay interval, that is after both items have been encoded into working memory. There was a significant interaction between TMS intensity and target position (F(1,16) = 6.7, p= 0.020) demonstrating that TMS applied in this delay interval also had differential effects on target representation depending upon its position in the sequence. There was a significant improvement in performance in high TMS condition for items presented first in the sequence (t(17)= 2.09, p= 0.026- Fig. 3.4A). As illustrated in Figure 3.4A, high TMS to MT+ resulted in an increase in precision of memory for the first item and a decrease in precision for the last item compared to low intensity TMS.

By contrast, analysis of the effects of the effects of TMS to the vertex (high and low intensity) revealed no significant main effect of TMS intensity on performance (F(1,16) = 0.001, p> 0.8) as well as no significant interaction between TMS intensity and target position (F(1,16) = 1.34, p> 0.27). Change in precision of memory under high TMS condition for all conditions was not significantly different than performance under low TMS condition (all p>0.1- Fig. 3.4B).

Together these findings support our predictions (and results from the previous experiment), showing that TMS applied to MT+ during the maintenance period for two sequential RDKs disrupts recall of the last item in the sequence. Furthermore, due to such disruption, precision of memory for the 1st item improved after high intensity TMS, which we interpret as a decrease in interference from the item in FOA. High TMS applied in the 1st delay interval, that is before the presentation of the 2nd RDK, also resulted in a similar pattern of results.

One possibility, however, is that the similar pattern of results for different TMS positions within the sequence may have been due to disruption of encoding of the 2nd item when applied in the 1st delay interval and disruption of memory representation of the item in FOA when applied in the 2nd delay interval. This is a question that I aim to address in the next section.

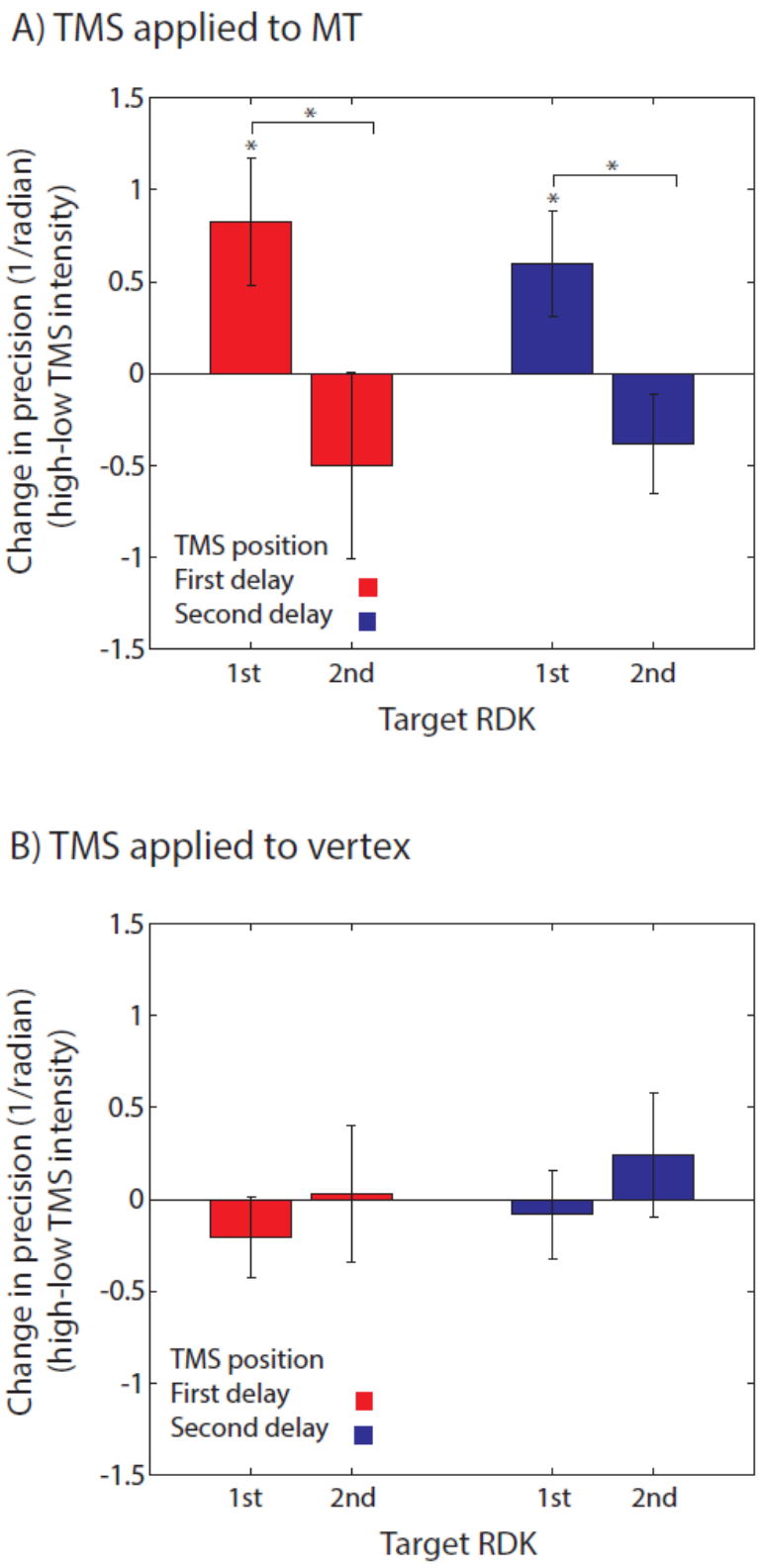

Figure 3. 4: Changes in precision in high TMS condition compared to low administered to MT+ (A) and vertex (B). Positive values correspond to improvement in performance for high versus low TMS. A) TMS applied to MT+ in either 1st or 2nd delay resulted in an increase in precision of memory for the first item. B) For TMS applied over the vertex, there were no significant TMS-induced changes in recall precision (within subject error bars).

3. 3. 2. 2 What source of error is modulated by TMS to MT+

In order to investigate whether TMS applied in the first delay interval affected the encoding of the last item (i.e., the item following TMS), I examined the sources of error affected by high TMS to MT+ in this condition. Modulation in precision of memory in tasks similar to the one employed in this experiment can occur as a result of changes in variability of the maintained representations, random responses or a systematic bias by the non-target item in the sequence (Bays et al., 2009a). If TMS affects the encoding of the 2nd item, any change in precision of memory should be explained by modulations in proportion of *random* responses since failure to encode any information would be expected to result in guessing at recall.

There was a significant interaction between TMS intensity and target position for proportion of random responses ($F(1,16) = 16.42$, $p= 0.001$). Therefore, proportion of random responses, i.e., the amount of guessing was modulated by TMS intensity differentially for items presented at different serial positions (Fig. 3.5).

In trials in which TMS was applied in the 1st delay, there was a significant interaction between TMS intensity and target position ($F(1,16) = 11.7$, $p> 0.004$). In trials when TMS was applied to MT+ in the first delay interval, the proportion of random responses on high TMS significantly decreased for the 1st item in the sequence ($t(17)=2.1$, $p= 0.026$) and increased for the 2nd item in the sequence ($t(17)=3.013$, $p= 0.004$ -Fig. 3.5). Similarly, in trials in which TMS was applied in the 2nd delay, there was also a significant interaction between TMS intensity and target position for proportion of random responses ($F(1,16) = 6.69$, $p> 0.020$, Fig. 3.5) but no significant change in performance for items presented 1st and 2nd in the sequence in high compared to low intensity TMS.

Modulations in the proportion of random responses were accompanied by modulations in proportion of target responses (interaction between TMS intensity and target position; $F(1,16) = 6.69$, $p> 0.020$). For each TMS position (i.e., 1st or 2nd delay interval), there was a significant interaction between TMS intensity and target position (TMS in 1st delay, $F(1,16) = 7.63$, $p> 0.014$;TMS in 2nd delay $F(1,16) = 7.23$, $p> 0.016$).

There was no significant interaction between intensity of TMS and target position for variability in target memory ($F(1,16) = 2.09$, $p> 0.05$). Similarly, there was no

modulation of responses biased by non-target responses, that is no interaction between TMS intensity and target position for the proportion of non-target responses ($F(1,16) = 0.95$, $p > 0.05$).

The results suggest that changes in the precision of memory were driven by modulation of random responses, suggesting that in trials where TMS was applied in the 1st delay, the motion direction that followed TMS may have been encoded with less success resulting in more random responses, i.e., guesses.

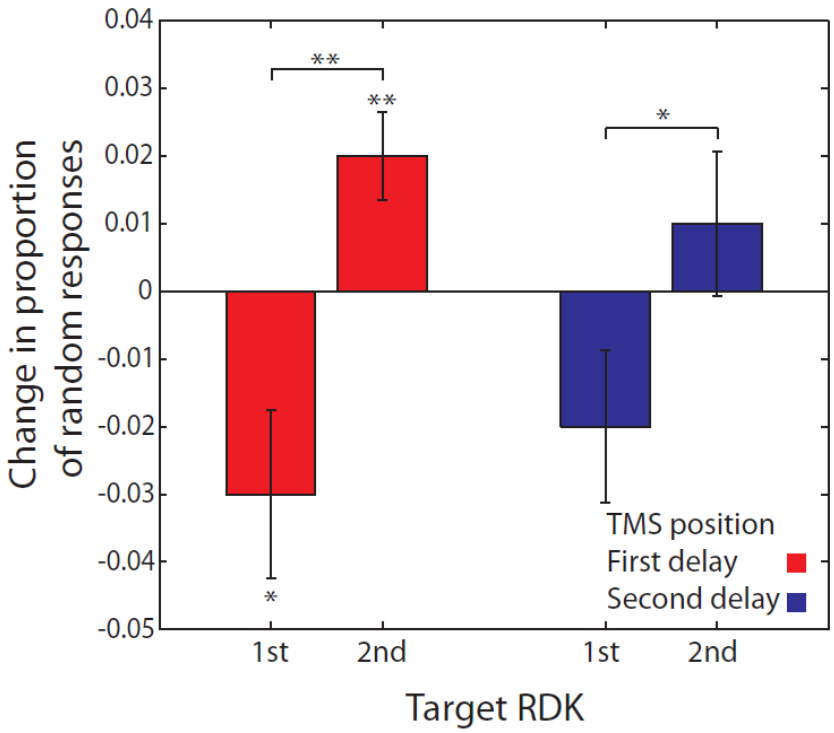

Figure 3. 5: Changes in proportion of random responses in high versus low TMS conditions. There was a significant decrease in random responses for items presented 1st in the sequence while for items presented 2nd, there was an increase in random responses (within subject error bars).

3. 4 Discussion

Recent conceptual models of working memory argue for different states of retention in working memory; either all the contents are represented to the same level, or that one (or several) items are represented with more fidelity in a FOA (Cowan, 2001; Oberauer, 2006; Olivers et al., 2011). Within this conceptual framework, it has been proposed that the item in FOA is represented by delay-activity in early sensory areas (Olivers et al., 2011).

In the studies presented in this chapter, I firstly provide evidence towards the sensory recruitment hypothesis (Postle, 2006; Ester et al., 2009; Serences et al., 2009a), demonstrating that TMS applied to MT+ can disrupt memory for motion directions. Further, we also investigated the possibility of a FOA, manipulating items inside and outside FOA. To the best of my knowledge, these studies are the first to show a causal role of MT+ in maintenance of the item in FOA.

TMS impairs working memory precision for items in FOA

Previously it has been suggested that one way of manipulating items in FOA, is to make them most relevant to the next cognitive operation (Oberauer, 2002, 2006). In line with these suggestions, in Experiment 3.1 we manipulated the most relevant item in working memory using a retro cue with 80% validity. TMS applied to MT+ after the presentation of the cue disrupted memory representation of the cued item (i.e., the item in FOA).

By contrast, in Experiment 3.2, the item in FOA was manipulated by sequential presentation of items, because of the known privilaged "state" of last item compared to previous ones (Wickelgren et al., 1980; McElree and Dosher, 1989; Öztekin and McElree, 2007). Similar findings were observed in this condition, showing decreased precision for last item (that is the one in FOA) compared to earlier items caused by TMS administered during working memory maintenance.

These findings are in line with recent behavioural (e.g., Oberauer, 2006) and imaging (Öztekin et al., 2010; Lewis-Peacock et al., 2012) studies which show that items in working memory can have different "states" according to their task relevancy and temporal context of items. Thus, when working memory contains several items, most of

them will not be in an "active" state but one will acquire the special status of being in FOA: the item most relevant for the next cognitive operation or alternatively the item presented last in the sequence.

These findings have important implications for the sensory recruitment hypothesis of working memory (e.g. Postle, 2006; Ester et al., 2009; Serences et al., 2009). Unlike the predictions of this hypothesis, not all items in working memory might be maintained through persistent delay period activity (e.g., sustained firing rates, increased BOLD responses) in early sensory areas. Most studies on the role of sensory areas in working memory retention have confounded working memory content with attention in a way that the item most relevant to the task is that maintained in working memory (e.g., Harrison and Tong, 2009). Therefore, the observed sustained activity observed in these studies might instead reflect better an interaction between attention and working memory content, rather than working memory content alone. In the studies reported in this chapter, I have attempted to provide more causal evidence for dissociation between the neural trace of an item presumably in FOA, and the full contents of working memory, suggesting that only the item in FOA is retained in early visual areas.

Impaired encoding of upcoming item by TMS

In Experiment 3.2, TMS applied to MT+ in the first delay interval, that is prior to presentation of 2nd item in the memory array, impaired performance for the upcoming item. The decrease in precision of recall of this stimulus was accompanied by an improvement in memory for the first item. Further investigation of the nature of errors in recall in these trials demonstrated that changes in precision were driven by modulation of random responses (guesses). Thus, the RDK that followed TMS may have been encoded with less success. Noisier encoding of the 2nd item may, in turn, have led to an increase in precision of memory for the first RDK because of greater allocation of resources to it. Future studies should examine the time course of influences of TMS applied before presentation of items on subsequent memory of them.

Improved performance for items outside FOA after TMS

An important finding in Experiment 3.2 was the observed *improvement* in working memory performance for items presented first in the sequence and hence the item outside FOA when TMS was applied in the 2nd delay. This seemingly paradoxical result could be explained by understanding the effect of the last item on the representation of earlier items. Some investigations have reported the "special" case of last item, showing that earlier items in the sequence are represented with lower *precision* compared to this item (Gorgoraptis et al., 2011; Zokaei et al., 2011). A recent study demonstrated that the resolution in memory of an item presented last in a sequence was similar to the resolution of simultaneously-presented items for the same set size (Gorgoraptis et al., 2011). In other words, for each set size, precision of memory for items presented simultaneously is identical to precision of memory for item presented last in the sequence in a similar set size. Thus, the last item advantage can instead be viewed as *decreased* precision for earlier items. It can therefore be argued that the last item in a sequence interferes with memory representation for earlier ones, resulting in a decrease in fidelity of memory representation for these items. In Experiment 3.2, one possibility is that TMS disrupted the last (i.e., 2nd) item resulting in a decrease of its interfering effect on the 1st item, and thereby increased recall precision of the 1st item.

Improved performance for items presumably outside FOA was only observed in Experiment 3.2. This can be explained considering the differences in methodologies in the two experiments reported here. In Experiment 3.2, both items were probed with equal probability at the end of the trials and hence the memory resource was distributed more equally between the two items. In Experiment 3.1 however, the cue was valid for 80% of the trials and thus participants were more likely to re-allocate more memory resources to the cued item. This is demonstrated in the low TMS control condition in which performance for a validly cued item was significantly more precise compared to the invalid item. Hence the disruption of item in FOA does not influence the representation of the un-cued item since prior to administration of TMS, lower share of memory resource was allocated to this item and hence it was retained with lower precision.

Memory for items outside FOA

The findings presented here do raise several interesting questions. If the full contents of working memory are not represented in sensory areas through persistent activity, then where are they represented?

In the present chapter we did not investigate the neural correlates of these items. It is possible that these items are also maintained in sensory regions, which are not affected by TMS-induced depolarisation. Moreover, these items can be maintained in other areas associated with working memory maintenance, e.g., prefrontal or parietal cortex (e.g., Fuster and Alexander, 1971; Watanabe, 1981; Funahashi et al., 1993; Miller and Cohen, 2001). Alternatively, researchers have recently suggested that items, retained for short durations of time, are not maintained through persistent firing of neurons but rather through modulations in temporary weight changes in the "hidden states" of neuronal populations (Mongillo et al., 2008; Buonomano and Maass, 2009). Therefore, all items maintained in working memory may not be represented through persistent activity observed during delay intervals but through changes in synaptic weights of neurons.

Conclusion

The findings presented in this chapter challenge the notion that all items are retained in working memory with equal fidelity (as stated by e.g., a fixed resolution item limit model). Instead they provided evidence to support recent theoretical concepts of working memory that suggests that items in working memory are represented in different states (i.e., in or out of a FOA). The representations in FOA, regardless of how they achieved their "special" state, can be disrupted with TMS applied to early sensory areas. These findings have important theoretical applications, highlighting the need to dissociate and control for items in working memory and those in focus of attention. The results also provide evidence that only one item might be in the FOA, rather than multiple (as suggested by Cowan's model of working memory).

(Fuster and Alexander, 1971; Fuster, 1973, 1990; Watanabe, 1981; Miller and Cohen, 2001)

Chapter 4

Role of attention in feature binding in visual working memory

4. 1 Introduction

What do working memory and attention systems share? Highlighted by previous chapters is the close relationship between attention and working memory. While many authors have pointed out the intimate connections between these two processes - both in terms of behaviour and neural substrate (Awh & Jonides, 2001a; Chun, 2011; Chun,

Golomb, & Turk-Browne, 2011; Cowan, 1998) - it remains unclear how much overlap there is between them. Recently, an important controversy has arisen about whether attention is required for the maintenance of feature-bound objects in working memory (e.g., Luck and Vogel, 1997; Wheeler and Treisman, 2002; Yeh et al., 2005; Fougnie and Marois, 2009; Allen et al., 2006; Johnson et al., 2008; Baddeley et al., 2011).

A central quality of working memory is its limited capacity (Cowan, 2001b), a property shared by attention processes (Chun et al., 2011). Cowan has argued for a capacity-limited system for maintenance of information available for conscious awareness, with a limit of about four chunks of information in healthy adults (Cowan, 1988, 1998, 2001). In the visual domain, the chunks are expressed as the number of *integrated* objects, i.e., with all features that belong to an object correctly bound together. In fact, in line with this framework, object-based theories of visual working memory propose that there are a limited number of discrete memory slots, each storing or maintaining information regarding an individual object consisting of different features (Luck and Vogel, 1997; Anderson et al., 2011; Luria and Vogel, 2011).

However, within object-based theories of working memory, the role of attention has yet to be established. One line of research has argued that maintenance of bound features in working memory is *automatic* and no more resource demanding than maintaining individual features (Luck and Vogel, 1997; Vogel et al., 2001). In a series of pioneering experiments Luck and Vogel (1997) reported that working memory performance was unaffected by the number of features in the objects to-be-remembered. Therefore, according to these object-based models of working memory, although initial feature-binding relies on attention, *maintenance* of stored items can be achieved in the absence of attention resources.

Support for such a proposition comes also from studies that employ working memory and attention tasks concurrently. The rationale behind such dual-task studies is to demonstrate overlap in cognitive processes. For example, if memory for binding depends more on attention resources, loading these resources should result in larger impairments in memory in trials where information was stored in a bound form compared to memory for 'disintegrated' features. Some previous studies have reported similar levels of impairment in memory for independent features and feature-bound objects using dual working memory and attention tasks (Allen et al., 2006; Johnson et

al., 2008; Baddeley et al., 2011). These findings would, therefore, be consistent with automatic maintenance of bound features in working memory.

On the other hand, contrary to these claims, other researchers have argued for a role of attention in working memory maintenance, emphasizing that in situations where attention is withdrawn, object representations collapse into disintegrated features in working memory (Rensink, 2000; Wheeler and Treisman, 2002). Wheeler and Treisman (2002) proposed a two-stage model of working memory: within each feature dimension, working memory is limited to a few items but binding is maintained only by relying on attention processes. This model was based on the results of a study where participants were asked to detect either a change among individual features or a change in feature conjunction (binding condition) following a retention period. Crucially, they found that change-detection performance was impaired in trials where participants were asked to detect a change in the binding condition compared to changes in individual or multiple features (Wheeler and Treisman, 2002a). The authors argued that since maintenance of integrated objects is more attentionally demanding, more errors in performance arise under the binding condition.

More recently, Chun and colleagues have put forward a taxonomy for attention, arguing that attention can be directed to internal representations – in the absence of sensory information –to maintain feature-binding in integrated objects (Chun, 2011; Chun et al., 2011). According to this view, maintenance of bound features within a limited set of objects is dependent on 'internal attention' resources. Consistent with this proposal, some studies using dual-task designs have shown large decrements in memory performance for integrated objects, compared to disintegrated features (Stefurak and Boynton, 1986; Yeh et al., 2005; Fougnie and Marois, 2009).

In resource framework of working memory, however, it has been suggested that visual features might in fact be stored in independent memory stores (Bays, Wu, & Husain, 2011). Therefore, it has been suggested that a further mechanism is needed to maintain the bound information of independently-stored features. Failures in this mechanism should result in misbinding errors in working memory maintenance

As a result of these contradictory findings in the literature, there still remains a lack of consensus on the role of attention in maintenance of bound objects, despite its highlighted role in many theories of working memory (Wheeler and Treisman, 2002;

Chun, 2011). One reason for divergent results might lie in the methodology used. Until now, working memory performance has been measured using change-detection tasks with a fixed magnitude of change and comparing across varied difficulty (memory for disintegrated features vs. bound objects).

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Here, we applied the method of adjustment (Bays et al., 2009; Fougnie, Asplund, & Marois, 2010; Wilken & Ma, 2004; Zhang & Luck, 2008) to investigate whether executive resources are needed for maintenance of bound objects. Crucially, instead of examining memory performance under working memory tasks of varied difficulty (i.e., by increasing working memory load), we kept the working memory task constant and instead systematically manipulated the demand of the attention task during the maintenance period using a method previously shown to successfully load attentional resources (Lavie, 2005, 2010; Forster and Lavie, 2008; Lavie et al., 2009). Moreover, by applying a recent analytical technique (Bays et al., 2009) we can report the proportion of errors arising as a result of failure to maintain correct bound features of objects in memory – *misbinding errors* – under different attentional load. This allows us to directly test whether the demand of the attention task affects feature binding of objects maintained in working memory.

In Experiments 4.1 to 4.3, we examined the effect of systematically increasing difficulty of a visual search task during working memory maintenance while in Experiment 4.4 we extend the findings to a cross-modal effect of executive resources on maintenance of bound objects by increasing the levels of a secondary auditory task.

4. 2 Experiment 4.1

In Experiment 4.1, we investigated whether systematic increase in attentional load of a visual search task during working memory maintenance influences memory precision. Specifically, we tested whether this manipulation results in an increase in the proportion of misbinding errors, in this case for colour and direction of motion.

4. 2. 1 Method

4. 2. 1. 1 Participants

Twelve healthy individuals (5 male) with an average age 25 years (range: 20- 35) participated in this experiment. All had normal or corrected to normal vision and reported normal colour vision. They provided written consent to the procedure of the experiment, which was approved by the local ethics committee.

4. 2. 1. 2 Stimuli and Procedure

A schematic representation of a trial of our dual-task design is presented in Figure 4.1. Each trial started with a fixation cross (500 msec) followed by the presentation of two Random Dot Kinematograms (RDKs) on either side of fixation cross (10° of visual angle away from the center) for 500 msec. Each RDK consisted of dots of a single colour, presented on a grey background on either side of the fixation cross. RDKs were presented in a randomly selected colour from a selection of 5 easily distinguishable colours (White, Red, Green, Blue and Yellow). Participants were asked to hold in memory the directions of motion of these coloured RDKs (memory array).

Each RDK consisted of 50 dots, each covering 0.1° of visual angle. Dots were displayed within an invisible circular aperture of 150 pixels in diameter (5.7° of visual angle). Dot lifetime was 500 msec equal to the presentation duration of RDKs. Dots reaching the edge of the circular aperture were re-positioned randomly on the other side of the aperture; therefore dot density was kept constant throughout the presentation. Motion was 100% coherent (constant speed of 4.5 degree/sec for all dots). Motion direction was chosen randomly from a value between 0-360° for both RDKs.

In 2/3 of the trials, following a blank interval (800 msec), the visual search array was presented briefly for 195 msec (to prevent eye movement) and participants were asked to perform a letter search task. They were required to press X and Z keys on the keyboard if they detected the letter X or Z respectively, across both high and low load conditions.

In low and high load conditions, the search array consisted of an array of six letters, each positioned on a virtual circle at a radius of 2.5cm from the center of the screen. The letters were one of the two target letters (Z or X) and five non-targets or distractors (five "O"s in *low load condition* and letters R, K, V, S, L in *high load condition*). Different distractor letters made discrimination more difficult in the high load condition. Letters were presented in "Ariel" font and were 40pt in size. In 50% of the trials the target letter was letter "Z" and in the remaining of the trials the target letter was "X". Participants were asked to respond as fast and as accurately as they could. Auditory feedback (correct or incorrect) was provided on performance in this task. Following the visual search task, a blank interval was presented for 800 msec before the presentation of the working memory probe.

In the remaining 1/3 of trials, no visual search task was presented (Fig. 4.1, no load condition). Following the presentation of the two RDKs, a blank interval of 1795 msec was displayed before the presentation of the probe display. All trial types were randomly interleaved within a block.

The probe stimulus consisted of a circle (5.7° of visual angle in diameter) presented at the center of the screen with an arrow positioned at a random orientation – drawn from the uniform distribution [0-360°]- within the circle. The probe stimulus was presented in the same colour as one of the two RDKs in the memory array. Participants were asked to adjust the orientation of the arrow, using a mouse, to match the direction of motion of the RDK presented in the same colour in the memory array. The probability of probing any of the RDKs was kept constant for each RDKs. The probe display was presented until response. Participants were informed to give equal weight to both the working memory and visual search task in each trial.

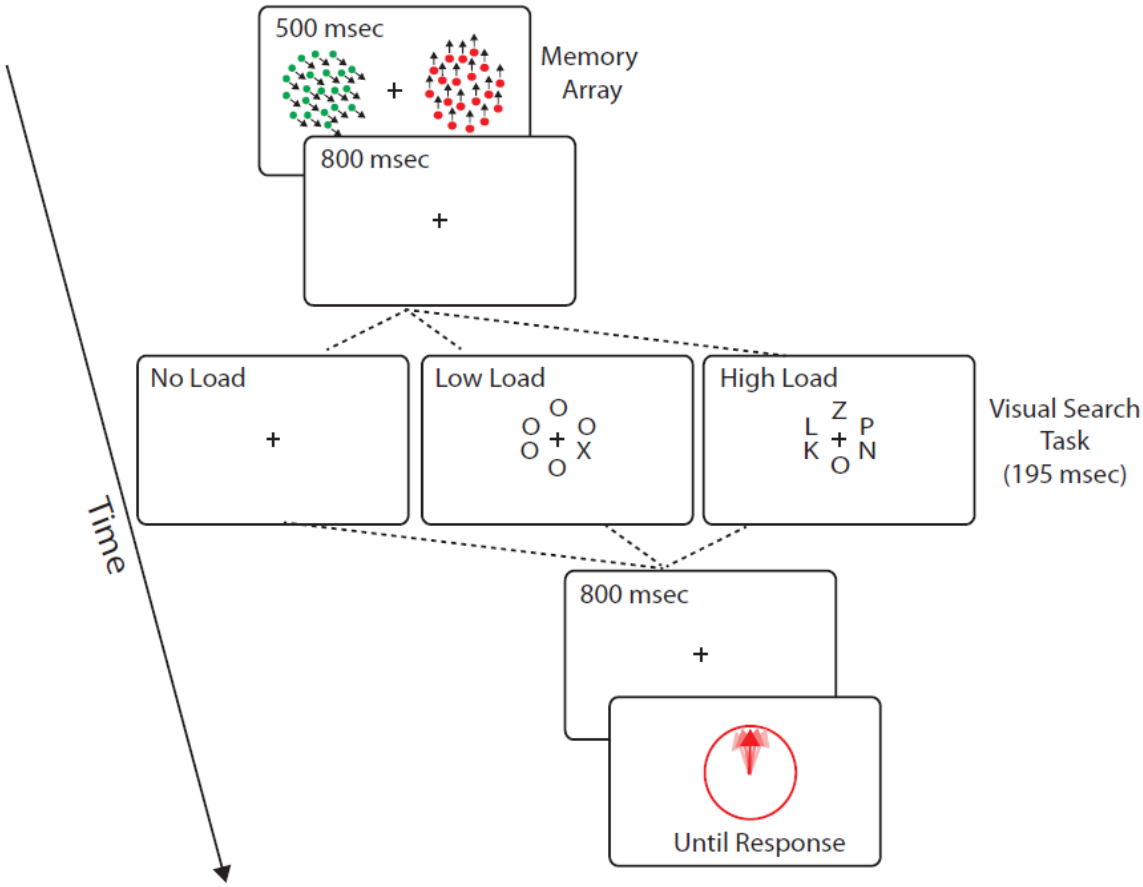


Figure 4. 1: An example of a sample trial in Experiment 4.1
Two coloured RDKs were presented simultaneously. In 1/3 of the trials, the probe display was presented following a long retention period (no load). In the remaining 2/3 of the trials, a visual search task of varied difficulty (low vs. high load) was presented before the presentation of the probe display. Participants were asked to respond as fast and as accurately as they can to the visual search task. Following the retention period, participants were asked to adjust the probe display to match the target motion direction.

Stimuli were generated by Cogent toolbox (www.vislab.ucl.ac.uk/Cogent/) for MATLAB and were displayed on a 21-inch CRT monitor (refresh rate: 60Hz). A chin rest, positioned at 60cm from the screen ensured a 60cm distance from the monitor.

Participants completed 3 blocks of 60 randomly intermixed trials per visual search condition (i.e., no, low and high conditions) in a dimly illuminated room. Prior to the start of the experiment, participants were acquainted with the experimental apparatus and conditions by gradually increasing the complexity of the practice trials.

4. 2. 1. 3 Analysis

In each trial, both reaction times (RT) and accuracy in the visual search task under both load conditions were calculated. In addition, precision of working memory report was computed for each attention load condition (see Chapter 2). Chance level precision was subtracted from precision values, therefore zero precision corresponds to chance level precision.

In order to distinguish different sources of error in memory precision across different experimental condition, we applied a probabilistic model proposed previously by Bays et al. (2009) (see Chapter 2 Section 2.2.2 for detailed description of the model).

4. 2. 2 Results and Discussion

Effect of load manipulation on visual search performance

High load visual search task resulted in significantly longer mean reaction times (RT) and decrease in mean accuracy compared to the *low load* condition (744 vs 596 msec and 83% vs 94%; $t(11)= 6.168$, $p<0.001$ for accuracy and $t(11)= 9.368$, $p<0.001$ for RT). This confirmed that attentional load was successfully manipulated in the visual search task. Trials with an incorrect response in the visual search task were excluded from analyses of the working memory task performance.

Working memory performance

The key question we wished to address is whether increasing attention load in the search task would affect memory for items already stored in working memory. We first examined the distribution of errors in relation to the target direction under different conditions (i.e., no, low and high load conditions). As illustrated in Figure 4.2A, the proportion of responses falling close to the *target* direction *decreased* systematically as the attentional load increased. This is illustrated as a decrease in the peak of response distribution around zero, i.e., target value under high load condition. Furthermore, the longer tails of the distribution under high load condition provide evidence for additional source of error (either guessing or misbinding errors) that may occur in this condition

(Fig. 4.2A). Importantly, the proportion of responses centered on the *non-target* motion direction *increased* in the high load condition (Fig. 4.2B). Under high load conditions, increased errors arose as a result of responding to the non-target direction. In other words, participants erroneously misbound the colour of the probed RDK (target) with the direction of motion of the RDK that was not probed (non-target). This is clearly illustrated in an increase in the peak of response distributions around the non-target value under high attention load.

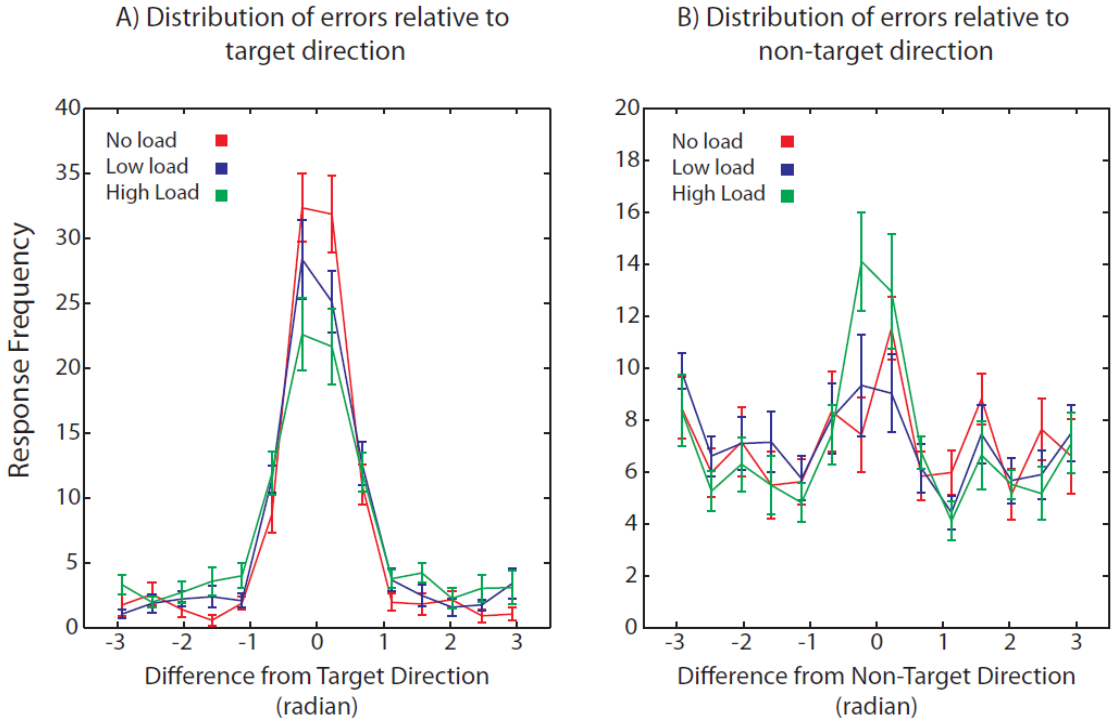


Figure 4. 2: Distribution of errors relative to target and non-target motion direction.
A) Frequency of response as a function of the difference between the response and the target motion direction. Under high load condition, the variability in recall of the target direction (width of the distribution) increase and the peak of the distribution centered around target value (zero) decreases. B) Frequency of response as a function of the difference between the response and the non-target motion direction. There is a larger proportion of responses around the non-target direction under high load condition compared to the other two conditions. Error bars indicate SEM (N= 12).

We then investigated whether precision of memory for motion direction was affected by visual search load manipulations. There was a significant decrease in precision under high load compared to no load ($t(11)= 3.688$, $p= 0.004$) and low load conditions ($t(11)= 2.454$, $p= 0.032$) (Fig. 4.3A). There was no significant difference in precision in

working memory between no load and low load search conditions ($t(11)= 0.949$, $p> 0.05$).

To distinguish three possible sources of error in memory we applied a three-component model of response error to our data (see Analysis). Maximum likelihood estimates of the probability of responding at random, the probability of responding with the target and non-target motion direction as well as variability (concentration parameter, κ) in recall of target direction were estimated. Subsequent to model fitting, outlier values were excluded. Model estimates for κ and random responses for 1 participant were 2.5 standard deviation above the mean values and the probability of target responses for the same participant was 2.5 standard deviation below the mean value. Therefore for the remaining analysis, this participant was excluded.

Proportion of *target* responses varied significantly under different load conditions ($F(2,30)= 3.61$, $p< 0.039$). There was a significant decrease in proportion of target responses under high load compared to no load ($t(10)= 4.9$, $p< 0.001$) and low load conditions ($t(10)= 2.291$, $p= 0.045$). Further there was a marginally significant decrease in proportion of target responses under low load compared to no load condition ($t(10)= 2.303$, $p= 0.052$). The modulation in proportion of target responses under different load conditions was accompanied by modulations in the proportion of *non-target* responses. There was a significant increase in proportion of non-target responses under high load condition compared to no load ($t(10)= 6.5$, $p< 0.001$) and low load condition ($t(10)= 3.5$, $p= 0.006$) (Fig. 4C). There was no significant difference in κ and the proportion of random responses under different search conditions (Fig. 4.3B).

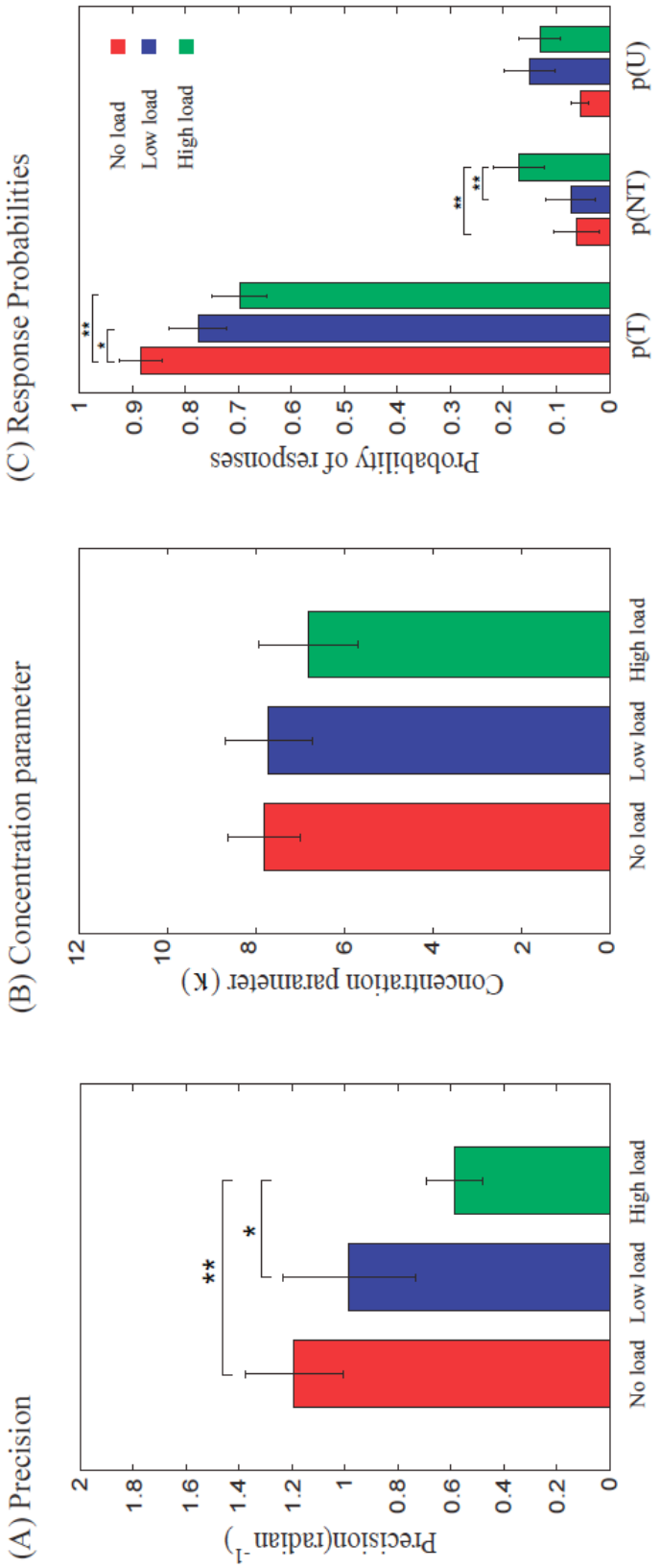


Figure 4. 3: Precision of memory and model estimates for different sources of error in the visual working memory task for different search conditions. A) Precision of memory decreased significantly as visual search task difficulty increased from no load to high load conditions. B) Concentration parameter did not differ significantly between different visual search conditions. C) Probability of target responses (p(T)) decreased significantly under visual search conditions compared to no search condition. Probability of target responses (p(NT) increased significantly under high load condition compared to no load and low load conditions and probability of random responses (p(U)) did not differ significantly between different conditions. Error bars indicate SEM (* $p< 0.05$, ** $p< 0.01$).

The results from Experiment 4.1 demonstrate a decrease in precision of working memory in trials where the visual search load of the secondary task was high. This decrease in precision was accompanied by an increase in the proportion of responses centered on the *non-target* motion direction, not in random responses. Therefore, loading visual attention (by a secondary visual search task) during working memory maintenance for motion directions, specifically results in feature-binding failures for items maintained in memory.

4. 3 Experiment 4.2

In order to establish the generality of the relationship between attention and feature-binding in working memory, we aimed to extend these findings to another visual feature. In Experiment 4.2, we applied similar methodology to a visual working memory task but now for oriented coloured bars, rather than moving stimuli.

4. 3. 1 Method

4. 3. 1. 1 Participants

Fifteen healthy individuals (7 male) with an average age of 25 years (age range: 18-37 years) participated in this experiment. All participants reported normal colour vision and had normal or corrected to normal vision.

4. 3. 1. 2 Stimuli and Procedure

Stimuli and procedure in this experiment was similar to Experiment 4.1, except for the following changes. In each trial, two coloured oriented bars (2° × 0.3° of visual angle) were presented 10° of visual angle away from the center on either side of fixation point for 500 msec (memory array). The colours of the bars were chosen randomly from a selection of 5 easily distinguishable colours (similar to those in Experiment 4.1). The

angles of the two bars were chosen randomly from a value between 0-180°. Participants were asked to keep in mind the orientation of the two coloured bars.

Following an 800 msec delay, in 2/3 of trials a visual search task with varied difficulty (low or high load condition) was presented for 195 msec. Participants were asked to perform a letter search task under low and high load conditions (similar to that in Experiment 4.1). Participants were asked to respond as fast and as accurate as they could in the visual search task. In the remaining 1/3 of the trials, after the presentation of the memory array a delay interval (1795 msec) was displayed before the presentation of the probe display.

The probe stimulus consisted of an oriented bar (2° × 0.3° of visual angle) at the center of the screen, presented at a random orientation drawn from a uniform distribution [0-180°]. The probe bar was displayed in the same colour as one of the oriented bars in the memory array. Participants were asked to adjust the orientation of the probe bar, using a mouse, to match the orientation of bar presented in the same colour in the memory array. The probability of probing any of the oriented bars was kept constant for both bars. The probe was displayed until response.

Participants completed 3 blocks of 60 randomly intermixed trials per visual search task difficulty (i.e., no load, low load and high load conditions) in a dimly illuminated room. Reaction times (RT) and accuracy on the visual search task as well as accuracy in the working memory task were calculated. Prior to the start of the experiment, participants were acquainted with the experimental apparatus and condition by gradually increasing the complexity of the practice trials.

4. 3. 2 Results and Discussion

Effect of load manipulation on visual search performance

We replicated the findings in Experiment 4.1 on the effects of load on RT and accuracy in the visual search task. *High load* resulted in significantly longer mean RT and decrease in mean accuracy compared to *low load* condition (548 vs 449 msec and 78% vs 92%; $t(14)= 4.463$, $p=0.001$ for accuracy and $t(14)= 9.307$, $p<0.001$ for RT). Trials

with an incorrect response in the visual search task were excluded from analyses of the working memory task performance.

Working memory performance

Precision of working memory was significantly affected by the visual search condition ($F(2,42)= 7.028$, $p= 0.002$). Pair-wise comparison between the three visual search conditions showed that precision was significantly lower under high load condition compared to no load condition ($t(14)= 6.515$, $p<0.001$) and low load condition ($t(14)= 4.535$, $p=0.001$), replicating the findings from Experiment 4.1 (Fig. 4.4). There was also a significant decrease in precision under low load condition compared to no load condition ($t(14)= 4.11$, $p=0.001$) (Fig. 4.4).

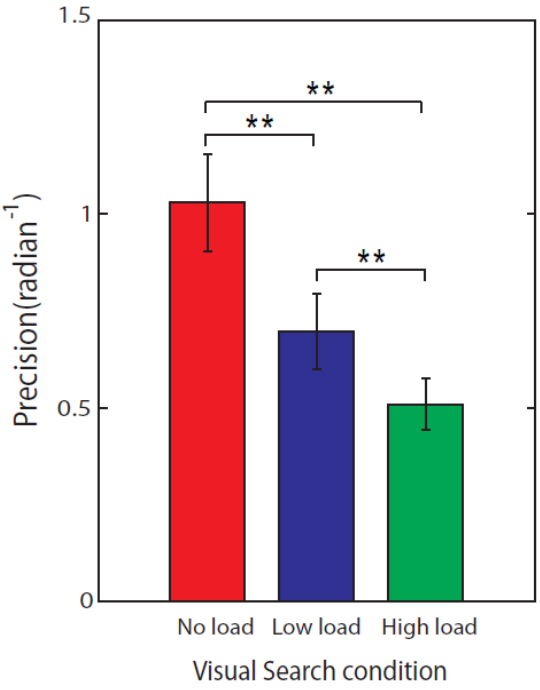


Figure 4. 4: Precision of memory under different visual search load conditions
Precision was significantly lower under high load condition compared to no and low load conditions. Low load condition further resulted in a decrease in precision of memory compared to no load condition (** p< 0.01).

We then applied the three-component model of response error to our data and maximum likelihood estimates of κ and proportion of target, non-target and random responses were calculated. Table 4.1 shows the model estimates under different visual search load conditions.

There was a significant effect of search condition on proportion of target responses, main effect of condition: $F(2,42)= 3.46$, $p< 0.041$. Pair-wise comparison of precision under different load conditions revealed a significant decrease in proportion of *target* responses under low load compared to no load condition ($t(14)= 2.505$, $p=0.025$) and under high load compared to no load condition ($t(14)= 5.683$, $p<0.001$). This was accompanied by a significant modulation in the proportion of *non-target* responses. There was an increase in proportion of non-target responses under high load condition compared to no load ($t(14)= 3.23$, $p=0.006$) and low load condition ($t(14)= 2.873$, $p=0.012$). There was no effect of visual search difficulty on proportion of random responses ($F(2,42)= 1.8$, $p> 0.1$) and κ ($F(2,42)= 0.9$, $p> 0.3$).

Table 4. 1: Model estimates under different visual search condition; mean (SD). κ refers to concentration parameters, while p(T), p(NT) and p(U) correspond to proportion of target, non-target and random responses respectively.

	κ	**p(T)**	**p(NT)**	**p(U)**
No load	4.54 (1.7)	0.89 (0.14)	0.03 (0.05)	0.08 (0.1)
Low load	3.55 (1.4)	0.83 (0.18)	0.07 (0.05)	0.10 (0.14)
High load	3.6 (1.8)	0.72 (0.19)	0.13 (0.04)	0.14 (0.17)

The results from Experiment 4.2 replicate the findings of Experiment 4.1; increasing the visual search difficulty resulted in an increase in proportion of binding failures. Therefore, across a variety of visual features (colour-motion and colour-orientation) these findings suggest that attention plays a crucial role in maintenance of bound representations in working memory. Increasing the load of visual attention results in failures in binding for features of objects maintained in memory.

4. 4 Experiment 4.3

Binding failures in high attentional load conditions might be due to the specific role of attention in maintenance of feature-bound objects. Alternatively, they might occur because search difficulty is not high enough to influence other sources of error. Therefore, in Experiment 4.3, we increased the load of the visual search task even further (by adding more distractor letters in one of the visual search conditions which we have termed 'hyper load') to investigate whether we can further increase binding-failures or affect other sources of error.

4. 4. 1 Method

4. 4. 1. 1 Participants

Thirteen healthy individuals (6 male) with an average age of 24 years (age range: 18-29 years) and normal or corrected to normal vision participated in this experiment. All participants reported normal colour vision.

4. 4. 1. 2 Stimuli and Procedure

Stimuli and procedure in this experiment was identical to Experiment 4.1 except for the following changes. After the presentation of the memory array (identical to Experiment 4.1), in 3/4 of the trials a visual search task was presented. The visual search display in the low and high load conditions were identical to those in Experiment 4.1. A 3rd load condition was also included in this experiment, the *hyper load condition*. In this condition, the search array consisted of two circular arrays (5 cm and 6.5 cm in diameter) of 6 letters each; 11 distractor letters (R, K, V, S, L, W, N, P, Y, F, J) and 1 target letter (either X or Z- Fig. 4.5). The visual search array was presented for 195 msec. Participants were asked to perform a letter search task and press X or Z keys of the keyboard when detecting the letters X or Z respectably amongst the search array. Participants were asked to respond as fast and as accurately as they can. Auditory feedback was provided on performance in this task.

Identical to Experiments 4.1 and 4.2, the visual search task was followed by an 800 msec delay and the probe display. In 1/4 of the trials, no visual search task was presented and the memory array was followed by a 1795 msec delay before the presentation of the probe.

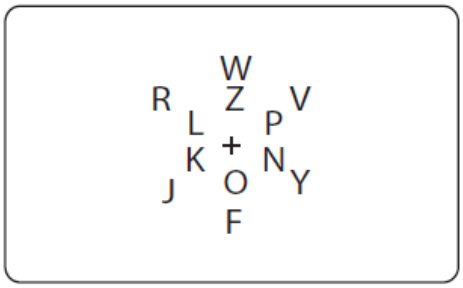


Figure 4. 5: Example of hyper load visual search condition
In this condition 2 circles of letters (1 target and 11 distractors) are presented around the fixation cross for 195 msec. Participants are asked to report the nature of the target letter as fast and as accurately as possible.

4. 4. 2 Results and Discussion

Effect of load manipulation on visual search performance

Accuracy of search was significantly higher in the low load condition compared to high load ($t(12)= 3.354$, $p=0.01$) and hyper load conditions ($t(12)= 9.264$, $p<0.001$). Furthermore, there was a significant decrease in accuracy under hyper load condition compared to high load condition ($t(12)= 7.832$, $p<0.001$).

RTs were significantly faster in the low load condition compared to high load ($t(12)= 8.387$, $p<0.001$) and hyper load conditions ($t(12)= 11.241$, $p<0.001$). Moreover, RTs were faster in the high load condition compared to hyper load condition ($t(12)= 4.739$, $p<0.001$). The findings from Experiment 4.1 and 4.2 were replicated and the findings from the hyper load condition confirms that the load manipulation in this new condition was successful. For the rest of the analysis on performance in the visual working memory task, trials with incorrect responses in the visual search task were excluded from the analysis.

Working memory performance

The distribution of responses around the target direction under different visual search conditions replicated and extended the findings from Experiment 1. The results illustrate that as the difficultly of the visual search increases, from no load to hyper load, the peak of responses in the working memory task around the *target* direction decreased. This was accompanied by an increase in the width of the distribution and the proportion of responses away from the target direction as search difficulty increased (Fig. 4.6A).

The proportion of responses around the *non-target* motion direction increased as search difficulty increased (Fig. 4.6B) illustrating that in trials were the visual search condition was more difficult, participants were more likely to respond to the non-target motion direction.

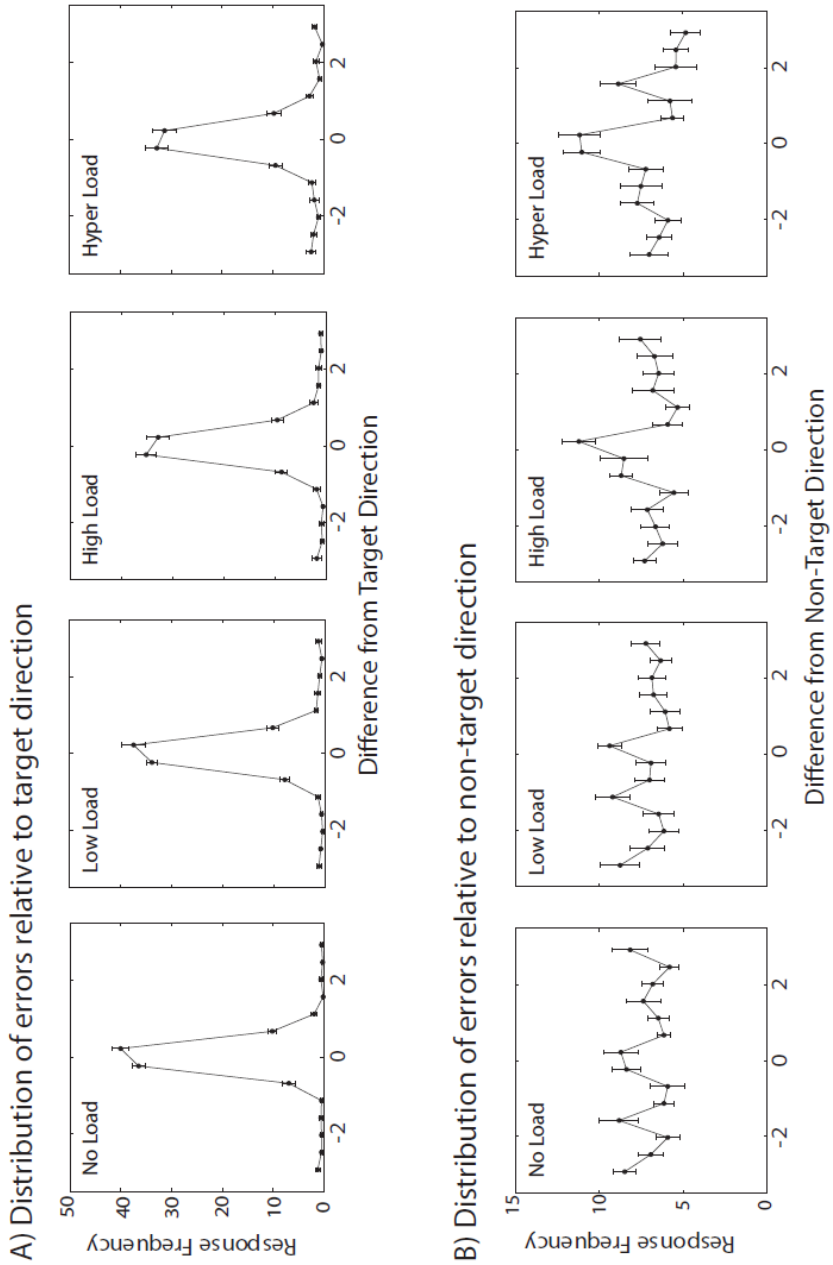


Figure 4. 6: Distribution of errors relative to target and non-target directions.
A) Frequency of response as a function of the difference between the response and the target direction. As visual search difficulty increased, the variability in recall (width of the distribution) around the target direction increased and the peak of distribution decreased. B) Frequency of responses as a function of the difference between the response and the non-target direction. There is an increase in proportion of non-target responses as visual search difficulty increased from no load to hyper load conditions. Error bars indicate SEM.

We then investigated the effect of visual search load on resolution of memory in the working memory task. There was a significant effect of visual load on precision of memory; $F(3, 48)= 4.624$, $p<0.01$. There was a significant decrease in precision of memory, compared to no load condition, in the low ($t(12)= 2.951$, $p=0.012$), high ($t(12)= 4.546$, $p<0.002$) and hyper load ($t(12)= 6.017$, $p<0.001$) conditions, replicating the findings from Experiment 4.1. Precision of memory was significantly lower under hyper load condition compared to low load condition ($t(12)= 3.254$, $p<0.01$- Fig. 4.7A).

We further applied the three-component model of response error to our data and maximum likelihood estimates of κ and the proportion of target, non-target and random responses were calculated. Table 4.2 shows the model estimates under different visual search load conditions.

Table 4. 2: Model estimates under different visual search condition; mean (SD). κ refers to concentration parameters, while p(T), p(NT) and p(U) correspond to proportion of target, non-target and random responses respectively.

	κ	**p(T)**	**p(NT)**	**p(U)**
No load	10.2(3.3)	0.93 (0.06)	0.014 (0.02)	0.06 (0.05)
Low load	10.6 (3.6)	0.85 (0.12)	0.013 (0.02)	0.13 (0.12)
High load	9.1 (4.6)	0.82 (0.1)	0.07 (0.07)	0.10 (0.09)
Hyper load	9.2 (5.1)	0.79 (0.14)	0.09 (0.07)	0.11 (0.11)

There was an effect of load condition on proportion of *target* responses, one-way ANOVA, $F(3,48)= 3.252$, $p< 0.05$. Probability of target responses, as compared to no load condition, decreased significantly in the low ($t(12)= 3.146$, $p=0.008$), high ($t(12)= 4.297$, $p<0.002$) and hyper load ($t(12)= 4.38$, $p<0.002$) conditions (Fig. 4.7C). The changes in probability of target responses were accompanied by changes in the proportion of *non-target* responses under different load conditions; $F(3,48)= 6.097$, $p= 0.001$. There was a significant increase in non-target responses in high load condition compared to no load ($t(12)= 2.55$, $p=0.025$) and low load conditions ($t(12)= 2.452$, $p=0.03$). Importantly, there was a significant increase in non-target responses in the hyper load condition compared to no load ($t(12)= 3.718$, $p=0.003$) and low load

conditions ($t(12)= 4.224$, $p=0.001$). There was no significant difference in κ ($F(3, 48)= 0.401$, $p> 0.5$-Fig. 4.7B) and *random* responses ($F(3, 48)= 1.465$, $p> 0.2$) under different visual search conditions.

In Experiment 4.3 we show systematic increase in failures to maintain bound features in working memory alone as the attentional load of the secondary task increases; replicating and extending the findings from Experiments 4.1 and 4.2. Although the estimated proportion of random responses increased in trials where the visual search task was present, it's important to note that this increase was not systematically modulated by attentional load.

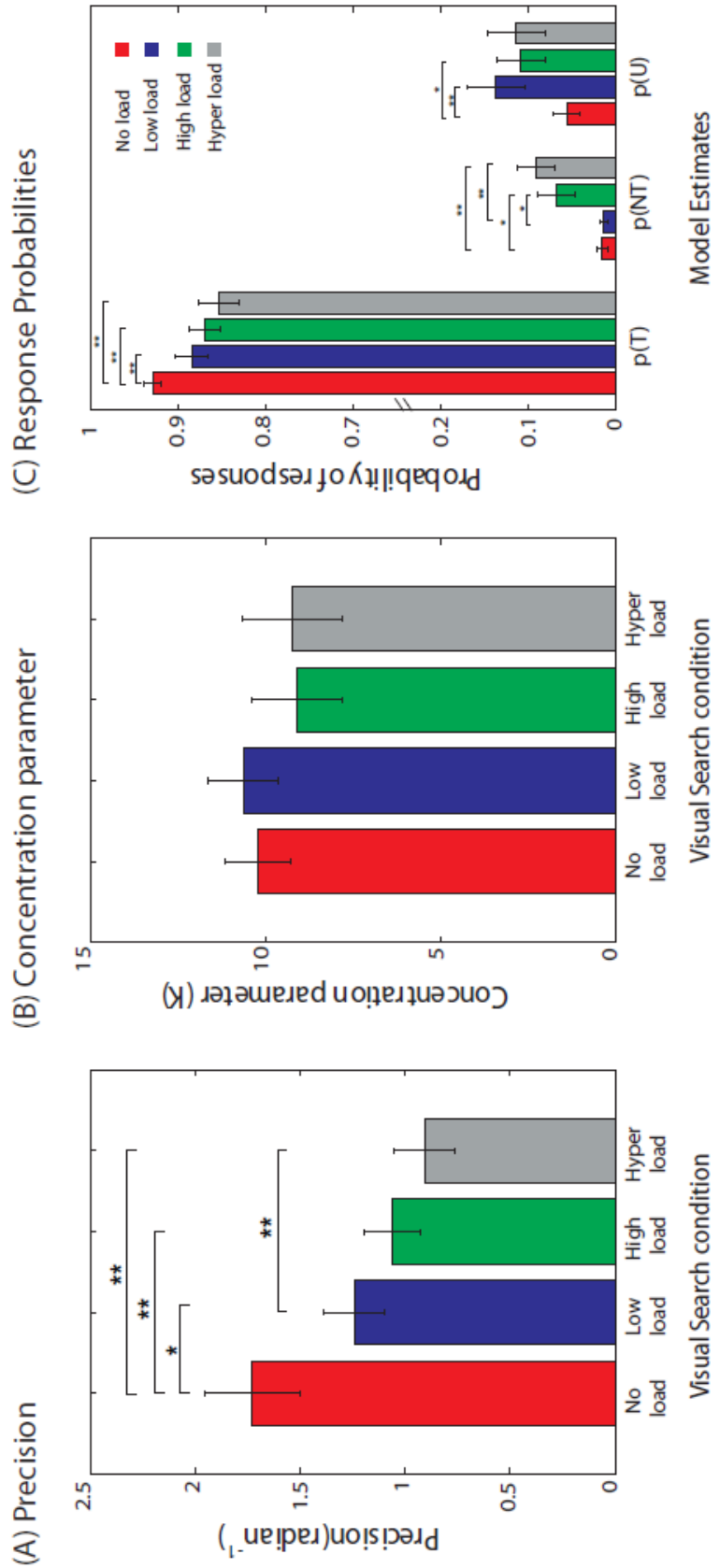


Figure 4. 7: Precision of memory and model estimates for different sources of error in the visual working memory task for different search conditions. A) Precision of memory decreased significantly as visual search task difficulty increased from no load to hyper load conditions. B) Concentration parameter did not differ significantly between different visual search conditions. C) Probability of target responses (p(T)) decreased significantly under visual search conditions compared to no search condition. Probability of target responses (p(NT) increased significantly under high and hyper load condition compared to no load and low load conditions and probability of random responses (p(U)) increased significantly under low and high load conditions compared to no load condition only. Error bars indicate SEM (* $p<0.05$, ** $p<0.01$).

4. 5 Experiment 4.4

In Experiments 4.1-4.3 we provided evidence for the central role of visual attention in maintenance of bound features in working memory. In Experiment 4.4, we investigated a more general role of attention resources on object maintenance by testing whether auditory attention load would also result in failures of binding in visual working memory.

Previously, studies have applied continuous verbal tasks to investigate the role of attention resources on working memory encoding and maintenance. When participants were asked to count backwards in three from a 3-digit number during the encoding phase of each trial, a significant reduction in memory performance was observed (Dell'Acqua and Jolicoeur, 2000; Morey and Cowan, 2004, 2005; Stevanovski and Jolicœur, 2007). However, these studies have not found specific impairment in memory for bound objects under continuous verbal task performance (Allen et al., 2006).

In Experiment 4.4 we introduced a novel auditory task that is closely related to the visual search task in Experiments 4.1-4.3, with varied difficulty in the maintenance period of a visual working memory task.

4. 5. 1 Method

4. 5. 1. 1 Participants

Twelve healthy native English speakers (5 female) with an average age of 26 (range: 19-47) participated in this experiment. All participants reported normal colour vision and had normal or corrected to normal vision.

4. 5. 1. 2 Stimuli and Procedure

Stimuli and procedure in this experiment was similar to Experiment 4.1, except for the following changes. Following a blank interval of 800 msec delay after the presentation of memory array (2RDKs), participants were presented with an auditory stimuli (a word) spoken either by a male or a female voice. The words were chosen from a

selection of words previously used (Meteyard et al., 2008), and had either a negative (e.g., decay) or positive (e.g., increase) meaning. The words from both groups were matched on number of letters. The maximum length of audio files were 1 sec, if an audio file was shorter than this time, a blank interval was added to match the delay interval within all trials.

In 1/3 of the trials, participants were asked to make a gender judgment on the spoken word, that is to press a key (Z key) if the word was presented in a male's voice and press another key (key X) if the word was presented in a female's voice. This acted as the low auditory load condition. In another 1/3 of the trials participants were asked to make a judgment regarding the meaning of the words, they were asked to press the Z key if the word had a negative meaning and press X if the word had positive meaning. This condition acted as the high auditory load condition. Participants were asked to respond as accurately and as fast as possible. Auditory feedback was provided for performance in the visual search task.

In the remaining 1/3 of the trials, no audio stimuli was presented to the participants (no load task). After a blank delay of 800 msec following the presentation of the audio file, the probe display for the working memory task was presented (similar to Experiment 4.1). The probe remained until response and probability of probing any of the RDKs was kept constant for both RDKs.

Participants completed 3 blocks of 60 trials; one block per auditory load condition. Reaction times (RT) and accuracy on the auditory task as well as accuracy in the working memory task were calculated. Prior to the start of the experiment, participants were acquainted with the experimental apparatus and condition by gradually increasing the complexity of the practice trials.

4. 5. 2 Results and Discussion

Effect of load manipulation on auditory attention task

We first examined whether auditory load manipulations were successful. RTs were calculated from the onset of audio files since decision making on the gender of the speaker could be made before the word was fully spoken. The results showed that high

auditory load resulted in significantly longer RTs and decrease in accuracy compare to low load condition (1500 v.s. 1300 msec, $t(12)= 2.7$, $p=0.02$ for RT; 91% vs 96%, $t(11)= 2.549$, $p=0.027$ for accuracy). These results confirm that our auditory load manipulations were successful. Trials with incorrect response in the auditory load task were excluded from the remaining analysis.

Working memory performance

Firstly, we looked at the effect of load manipulation on distribution of responses in the working memory task around target and non-target responses. The proportion of responses away from the target direction increased under high load condition (Fig. 4.8A). Moreover, there was an increase in proportion of non-target responses under high load condition only (Fig. 4.8B) as illustrated by an increase in the peak of distribution around the non-target value.

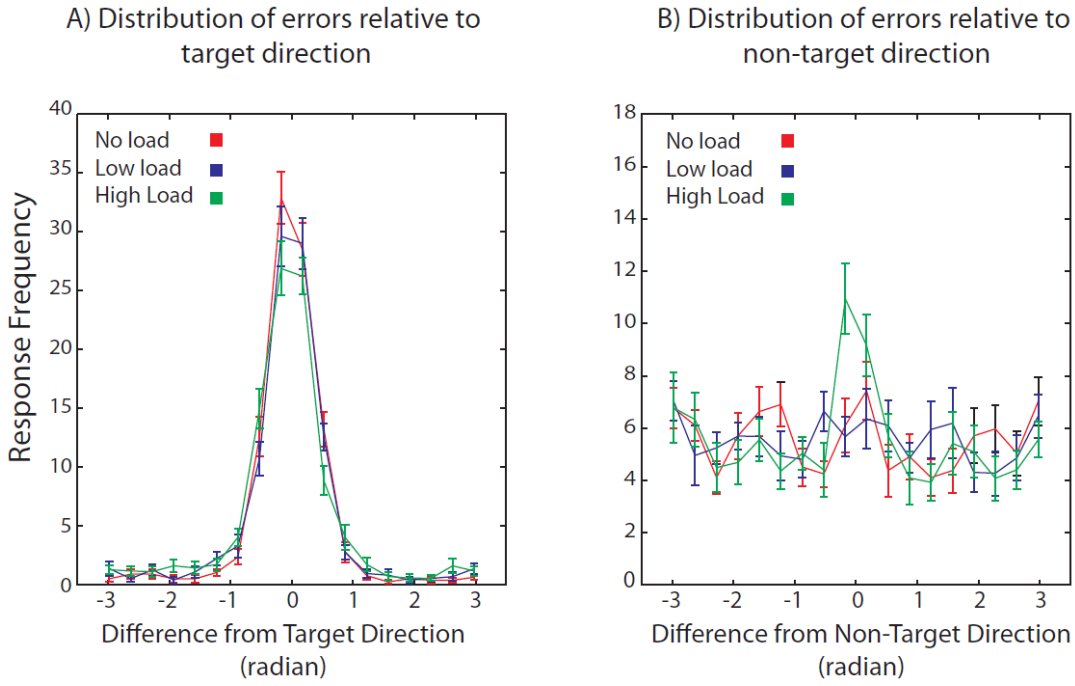


Figure 4. 8: Distribution of errors relative to target and non-target motion directions.
A) Frequency of response as a function of the difference between the response and the target direction. Under high auditory load condition, the variability in recall of the target orientation (width of the distribution) increased. B) Frequency of response as a function of the difference between the response and the non-target orientation. Proportion of responses around the non-target direction increased under high auditory load condition only. Error bars indicate SEM.

Precision of working memory under all conditions were calculated. There was a significant decrease in precision under high load compared to no load ($t(11)= 3.454$, $p=0.005$) and low load conditions ($t(11)= 3.175$, $p=0.009$) (Fig. 4.9A). There was no difference in precision of memory between no load and low load conditions ($t(11)= 0.338$, $p>0.3$) (Fig. 4.9A).

This decrease in precision under high load condition was accompanied by a decrease in proportion of *target* responses under high load compared to no load condition ($t(11)= 3.381$, $p=0.006$). Importantly, proportion of *non-target* responses was also modulated by auditory load condition ($F(2,33)= 3.697$, $p= 0.036$). There was a significant increase in proportion of non-target responses under high load compared to no load condition ($t(11)= 2.684$, $p=0.021$). A similar pattern of results was observed when comparing non-target responses under high load and low load conditions ($t(11)= 2.243$, $p=0.046$) (Fig. 4.9C). There was no significant difference under different load conditions in either κ ($F(2,33)= 0.68$, $p>0.5$) (Fig. 4.9B) or proportion of *random* responses ($F(2,33)= 0.554$, $p>0.5$).

Increasing the demand of an attentionally-demanding auditory task during working memory maintenance resulted in an increase in failures in correct maintenance of integrated visual objects. Thus the recourses essential for maintenance of feature-bound visual objects may be shared across modalities.

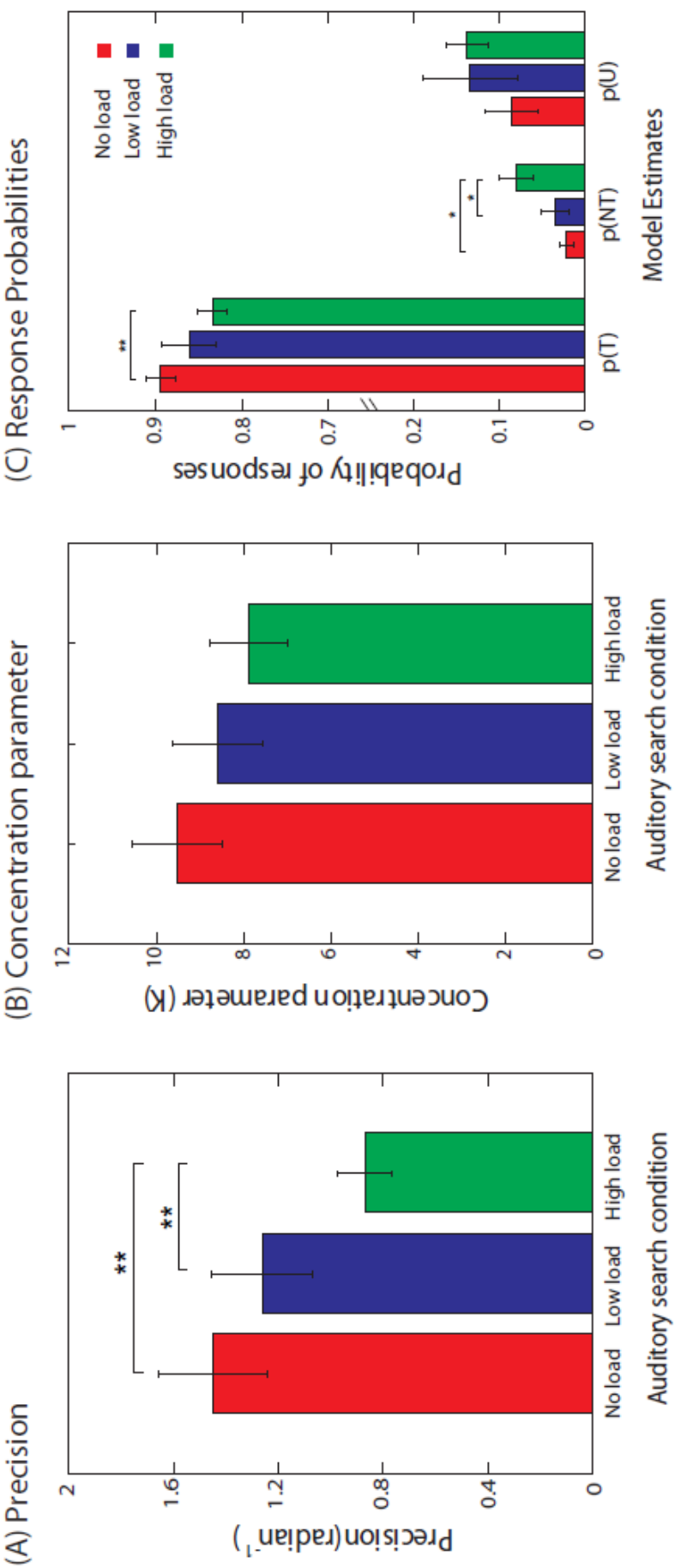


Figure 4. 9: Precision of memory and model estimates for different sources of error in the visual working memory task for different auditory load conditions.

A) Precision of memory decreased significantly as auditory task difficulty increased from no load to high load conditions. B) Concentration parameter did not differ significantly between different load conditions. C) Probability of target responses (p(T)) decreased significantly under auditory load conditions compared to no load condition. Probability of target responses (p(NT) increased significantly under high load condition compared to no load and low load conditions. Probability of random responses (p(U)) did not differ significantly under different conditions (* $p<0.05$, ** $p<0.01$).

4. 6 Discussion

The present study focused on understanding the role of attention in maintenance of feature-bound objects in working memory. Despite the highlighted close connection between attention and working memory (Rensink, 2000; Awh and Jonides, 2001; Wheeler and Treisman, 2002b; Chun, 2011; Chun et al., 2011), the extent of overlap between the two processes remains unclear. Here, we investigated this issue by employing a relatively new technique that allows us to decompose the types of error made when participants retrieve an item from working memory (Bays et al., 2009; Zhang & Luck, 2008).

Our findings point to a central role of a general resource that extends across visual and auditory attention, in maintaining correct conjunction of features in visual working memory. Loading attention resources in either the visual or auditory modality resulted in an increase in incorrect binding of visual features belonging to items already stored in working memory. Memory for conjunction of motion direction and colour (Experiment 4.1 and 4.3) as well as orientation and colour (Experiment 4.2) was impaired when an unrelated visual search task with high attentional load was performed during memory maintenance. Therefore systematic increase in visual search difficulty resulted in a decrease in precision of working memory. Importantly this was accompanied by an increase in the frequency of binding failures, i.e., the proportion of responses attributed to *non-target* values. In other words, participants incorrectly bound the colour of the probed item (i.e., the target item) with either motion direction or orientation of the non-target item retained in working memory. Moreover, the results demonstrated above chance performance in both tasks (working memory and attention) and in all conditions confirming that participants were performing to the best of their abilities in the two tasks performed in each trial.

Role of attention resource in current models of working memory

The literature provides conflicting evidence concerning automatic vs. resource demanding maintenance of bound objects in working memory. Existing models invoke very different functional roles of attention in working memory processes. On one hand, some researchers propose that the process of memory maintenance is automatic for

integrated objects (Luck and Vogel, 1997; Hollingworth, 2003; Johnson et al., 2008; Luria and Vogel, 2011) while others argue for a strong case of attention – or resources shared with attention to sensory stimuli – playing a crucial role, stating that remembered objects will collapse into disintegrated features in the absence of attention (Wheeler and Treisman, 2002; Chun, 2011).

Resource models of memory (Wilken and Ma, 2004; Bays and Husain, 2008) further highlight the need for a mechanism to maintain binding information amongst features stored in independent memory stores. These models propose that there is a limited resource that is shared amongst all to-be-remembered items. Therefore the fidelity of memory representations is dependent on the proportion of memory resource dedicated to each item. Recently it has been shown that errors in recalling the colour and orientation of an object can be uncorrelated, i.e., an error can be made with respect to one feature independently of the other (Bays et al., 2011). Uncorrelated errors such as these – between features belonging to one object – provide evidence for independent storage of each feature category. Hence feature binding to maintain integrated objects in working memory may be required (Bays et al., 2011). The findings from present study, which allowed us to decompose the types of error in recall (full details in Bays et al, 2009), would further suggest that maintenance of integrated objects (comprising different features) depends heavily on available attention resources.

Binding failures in working memory caused by taxing attention resource

The present findings suggest a rather selective overlap between visual working memory and attention processes since other sources of error (i.e., variability in feature representations) were not affected by loading the attention resource. Many authors have pointed out the close relationship between the two processes (e.g., Awh & Jonides, 2001; Chun, 2011; Chun, Golomb, & Turk-Browne, 2011; Lavie, 2005; Rensink, 2000; Wheeler & Treisman, 2002b), even defining working memory as active maintenance of attention to information (Chun, 2011). However, the findings reported here demonstrate restricted overlap between the two systems since loading attention resources resulted in a very specific and limited working memory impairment in feature binding. Our findings would therefore be consistent with both previous arguments: while there is

some overlap in resources used by attention and working memory, there also appear to be separate resources that were not vulnerable to interference in our dual task paradigm.

It might be argued that maintenance of bound features is simply more difficult than retaining features alone and therefore more vulnerable than other aspects of working memory (and hence more prone to interference upon loading attention). It is worth highlighting though that even in our "hyper load" condition where attention resources were taxed heavily, no change in variability of feature representations (kappa or concentration parameter) was observed (Fig. 7B). Therefore, the levels of visual search load employed in studies reported did not appear to influence the fidelity of feature representations. However, the extent to which other sources of error, including variability in representations, rely on attention resource remains to be fully established. The methodology and analytical techniques used here provide a potentially important means to probe how general our findings might be.

Shared working memory and attention processes

Rather than invoking a resource shared by attention and working memory, it might be argued that the results reported here might be explained by a specialized, separate mechanism that is involved in both processes, but is not part of an attention or working memory module. For example, it might be part of an 'executive' system that deploys the control or allocation of resources. Loading such a mechanism through either attention or working memory would result in impairments in the alternative mechanism. This is certainly a logical possibility. However, considering our findings, such a mechanism would seem to be very specialized because taxing this resource results in very specific impairments, leading to errors in feature-binding of objects retained in memory. Imaging techniques might help to resolve this question in the future, but the behavioural data presented here cannot distinguish between a separate or overlapping resource.

By applying dual task designs, previous studies have also provided evidence pointing to an overlap between attention and working memory processes. For example, investigations have demonstrated that *loading working memory* also influences visual search (Woodman et al., 2001; Emrich et al., 2010). Similarly researchers have shown larger impairment in memory for bound objects in the presence of a attentionally

demanding secondary task (Stefurak and Boynton, 1986; Yeh et al., 2005; Fougnie and Marois, 2009); (Brown and Brockmole, 2010). Therefore, loading either system (i.e., attention or working memory resource) can result in impairments in the other process.

Positive findings using dual task designs on the role of attention on working memory maintenance, however, have been inconsistent. There are many example in the literature with contrary findings to those mentioned above (Allen et al., 2006b; Johnson et al., 2008). The observed discrepancy in the research on this topic might potentially be explained by the methodology that has been applied here. Change detection performance varies across different visual features, with better performance for detecting colour changes compared to those in orientation (Johnson et al., 2008) or shape (Fougnie and Marois, 2009). In binding conditions, a change occurs in one of the features within the target object. However, change-detection performance for features of different categories is varied. That is, change-detection performance for some features (e.g., orientation) is better than others (e.g., shape). In the binding condition, a change occurs in one of the object features and as a result of baseline difference in change-detection performance *for individual features*, performance in the binding condition is subject to averaging across a varied baseline. Measuring the precision of recall – not binary responses ('change' or 'no change') – provides a more sensitive means to probe feature recall that also potentially avoids such issues.

Conclusion

Taken together, the results from the present study point to a cross-modal recourse that is essential for maintenance of bound representations in working memory. Taxing this resource while participants are asked to maintain bound representations, results in a specific type of error: *feature binding failures*. Based on these findings, we propose a limited overlap in resources recruited in speeded visual search and auditory word comprehension and those essential primarily for maintenance of integrated features in working memory. An important challenge for future research will be to clarify the neural and psychological qualities of this resource, and determine its capacity limitations.

Chapter 5

Working memory impairments in Parkinson's disease

5. 1 Introduction

Neurological patients with specific impairments in the dopaminergic system provide a great opportunity to investigate the role of this neurotransmitter in different cognitive processes, specifically working memory. Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of midbrain dopaminergic neurons and

subsequent depletion of dopamine in basal ganglia (e.g., Rafal et al., 1984; Albin et al., 1989; German et al., 1989; Damier et al., 1999; Obeso et al., 2000). Considering the important role of dopamine in working memory (see Introduction section 1.4), it is perhaps no surprise that this group of patients exhibit impairments in this cognitive function, although in the past PD has been considered to be a purely motor disorder by some investigators. In the present chapter we examined impairments in visual working memory precision in PD patients pre-medication and later (after 3 months) on medication.

Cognitive impairments have long been associated with PD (Bradley et al. 1989; Owen et al. 1992; Owen et al. 1993; Owen et al. 1997; Owen 2004); however the prevalence estimates of cognitive impairments vary widely (Janvin et al., 2003; Verbaan et al., 2007). Prior to manifestation of motor symptoms, PD patients can suffer from non-motor cognitive impairments including hyposomia, rapid eye movement sleep disorder and deficits in executive functions (Verbaan et al., 2007; Savica et al., 2010; Schapira and Tolosa, 2010). Cognitive dysfunctions reported in early PD include poor planning, sequencing, cognitive flexibility and problem solving, and impairments in working memory and attention (Cooper et al. 1991; Owen et al. 1993; Owen et al. 1997; Dujardin et al. 1999; Muslimovic et al. 2005; Foltynie et al. 2004).

One of the most prominent cognitive deficits observed in early PD, is deficits in visual working memory (Bradley et al. 1989; Postle et al. 1997; Owen et al. 1997; Morris et al. 1988). Working memory impairments have been reported in a variety of visuospatial tasks (e.g. Owen 2004; Cools & D'Esposito 2011). Compared to healthy controls, medicated patients with either mild or severe PD have been reported to be significantly impaired in complex spatial working memory tasks (Owen 2004; Owen et al. 1997; Owen et al. 1992). In such paradigms, participants are asked to search through a number of coloured boxes presented on a computer screen and by touching each box, find tokens that are hidden inside the boxes. Observers have to avoid the boxes in which the tokens had already been found and hence the task relies heavily on manipulation and updating of information retained in working memory. A trend towards impairment in this task has also been observed in non-medicated patients with extremely mild PD (Owen 2004; Owen et al. 1997; Owen et al. 1992).

Moreover, there is some research showing improvement in working memory performance in PD patients on dopamine medication (e.g., Lange et al., 1992; Owen et al., 1992; Mattay et al., 2002). Dopamine has been shown to improve performance on spatial (Lange et al., 1992) and N-back working memory tasks in PD patients (Mattay et al., 2002). Improvements on dopamine however, have not been easily replicated. Owen and colleagues (1992) have failed to report any difference in performance on a spatial span task between control participants, medicated and un-medicated PD patients. Further, medicated PD patients on dopaminergic medication with severe clinical symptoms were significantly impaired in spatial working memory task compared to healthy controls. Therefore, the role of dopamine and disease progression on working memory processes is highly complex and remains unclear.

It has also been suggested that PD patients primarily have impaired attentional abilities that in turn may influence their working memory performance. The basal ganglia have been shown to be engaged during working memory tasks (Skeel et al., 2001; Lewis et al., 2004; Cools et al., 2008). More specifically, they have been involved in filtering distractors in order to provide more space for relevant information to be stored in working memory (McNab and Klingberg, 2008). Medicated PD patients with mild and severe symptoms are reported to be impaired on set shifting attention tasks (Owen et al. 1993; Owen et al. 1992; Muslimović et al. 2005). Moreover, PD patients have been found to be more distractible, within a working memory task compared to healthy controls. Lee and colleagues (2010) examined both working memory capacity and attentional abilities of PD patients. Their findings point to both reduced working memory capacity and filtering deficits manifested in these patients. It therefore remains unclear whether the reported impairments in working memory are secondary to attention deficits observed in these patients.

The complicated relationship between attention and working memory impairments is further highlighted in a study by Cools and colleagues (2010). Early to moderate stage PD patients were tested both on and off dopaminergic medication on both a delayed response task with or without the presence of distractors and backwards digit span (a measure of verbal working memory- see section 5.2.2.1 for more details). Off medication, distractor resistance was enhanced while backwards digit span was impaired. These effects were restored back to normal on medication. Based on such findings it was hypothesized that in mild PD, any changes in cognitive performance are

due to low dopamine levels in the striatum and possible increase in dopamine levels in prefrontal cortex (Cools et al. 2010). The latter might be due to chemical reciprocity between striatum and prefrontal cortex (Pycock et al., 1980; Roberts et al., 1994; Akil et al., 2003; Meyer-Lindenberg et al., 2005) resulting in cognitive enhancement in these patients. Such effect might be observed in mild PD only, since dopamine depletion might have not yet extended to prefrontal cortex.

Thus there is complexity of both the temporal development of different deficits and the relationship between working memory and attention impairments in PD patients. In order to understand the role of dopamine in working memory processes, establishment of impairments at early stages of the disease and their development as the disease progresses is essential. This will not only allow us to gain knowledge on the role of dopamine in working memory, but will also aid our understanding of the cognitive profile of PD patients.

Knowledge of the cognitive profile of PD serves several important purposes. Of theoretical importance is how this research will contribute to our knowledge about the relationship between brain dysfunction, structure and key cognitive processes. Moreover, cognitive assessment may be used as a tool to identify individuals at early stages of the disease so that neuroprotective therapies might potentially be used before the onset of widespread neurodegeneration.

In the present chapter, we aimed to firstly examine the nature of impairments in both working memory and filtering abilities in newly-diagnosed, un-medicated PD patients. We measured working memory performance using the method of adjustment (see Introduction, section 1.2), which potentially provides a more sensitive measure of performance than tasks with binary responses (such as change detection tasks). All patients were also tested on a variety of neuropsychological tests to compare the sensitivity of different measure of working memory and correlations that may exist between these tasks. Furthermore, we aimed to establish the effects of dopaminergic medication on performance by testing all patients after being established on dopaminergic medication.

5. 2 Methods

5. 2. 1 Participants

Eight newly diagnosed PD patients (Table 5.1) were tested twice, once prior to administration of any medication (pre-medication condition), within few weeks of diagnosis, and once approximately 3 months after being on daily dopaminergic therapy. Of the eight patients, four were on the dopamine agonist Ropinirole (1mg × 3 per day) and the remaining four patients were on Levodopa Sinemet (1.25mg × 3 per day), at the time of second session of testing.

From the eight PD patients, five were asked to come back to participate in two further testing sessions, once on and once after 12 hour withdrawal from medication 2 weeks apart (Table 5.1 For demographics of the 5 patients). The on/off medication sessions were counterbalanced between the patients and 3 of the patients had the off session 2 weeks after completing the on session.

Eleven healthy individuals (3 females) with no history of mental illness also participated in this study. Information regarding these participants is presented in Table 5.1. Patients and healthy controls were matched on age and years of education (see Table 5.1). Of 11 controls, 8 were also tested approximately 3 months after their first testing session to investigate any effects of practice in healthy controls, regardless of any medication. All patients and healthy controls had normal or corrected to normal vision and reported normal colour vision.

Table 5. 1: Participants' demographics.

Groups	**Age (years)**	**Gender**		**Years of education**
	Mean(std)	**Male**	**Female**	**Mean (std)**
Patients (N= 8) Pre/post medication	68 (8)	3	5	14.5 (3)
Patients (N= 5) On/off medication	70.5 (3)	4	1	13 (2.6)
Controls (N = 11)	66 (7)	8	3	15.5 (3)

5. 2. 2 Materials and Measures

Both patients and age-matched controls performed the following tasks.

5. 2. 2. 1 Neuropsychological tasks

Forward and backward digit span (for verbal working memory): letter sequences of 2 to ≤ 8 digits (two sequences per list length) were used.

Forward and backward Corsi spatial span (for visuospatial working memory): spatial sequences of 2 to ≤ 8 (two sequences per list length) were employed.

For both digit and spatial spans, we calculated span as the maximum sequence length in which participants reported a minimum of one sequence per list length correctly. Half a score was deducted if participants performed only one of two correct per sequence length.

***Mini Mental State Examination (MMSE)*:**

MMSE is a brief 30-point questionnaire test that is commonly used to screen for cognitive impairment, for example dementia (Folstein et al., 1975).

Unified Parkinson's Disease Rating Scale (UPDRS):

UPDRS is a 44-question measure of severity of the clinical symptoms of PD. It consists of 5 parts including the evaluation of behaviour and mood, self-evaluation of daily life, motor evaluation, Hoehn and Yahr severity of PD and Schwab and England activities of daily living scale respectively. PD patients pre and post medication completed the UPDRS (see Table 5.2 for results).

5. 2. 2. 2 Computer-based tasks

All Stimuli were presented on a 21-inch CRT monitor at a viewing distance of approximately 60cm.

Experimental 4-item working memory task:

The task was adapted from that previously used by Gorgoraptis et al. (2011) in healthy young people. A schematic representation of the task is shown in Figure 5.1A. In each trial, a sequence of 4 coloured bars (2° × 0.2°) was presented at screen centre on a grey background. This was the sample array presented as a sequence. Each bar was presented for 500 msec followed by a 500 msec blank interval, prior to the presentation of the next bar in the sequence. The colours in each trial were selected randomly- but with no repetition within a trial- from five easily distinguished colours (red, yellow, green, blue and purple). Minimum angular separation between the orientations of bars within the same sequence was 10°; the orientations were chosen randomly otherwise. Participants were asked to remember the orientation of each bar.

At the end of each trial, a probe bar which was the same colour as one of the bars in the sequence was presented at screen centre. Its orientation was randomly selected and a circle surrounding this probe made it easier to distinguish from the bars in the previous sequence. Participants were instructed to use a rotating dial (which controlled the orientation of the probe bar on the screen) to match the orientation of the probe with the same coloured bar in the sequence, i.e., the target item. Stimuli presented in any of the serial positions within the sequence were probed with equal probability and participants did not know beforehand which item would be tested.

Patients completed 100-200 trials of this condition depending on their ability pre-medication and approximately 3 months after being established on a dopaminergic medication. Five patients on and off medication performed 100 trials of this condition in each testing session. All age-matched controls performed 200 trials per condition; from this group 8 came back 6-8 weeks after first testing session and completed another 200 trials per condition.

Attentional filtering or pre-cueing condition:

Stimuli were identical to those in the experimental 4-item working memory task except for the following. At the beginning of each block, a 100% valid cue would inform participants to maintain the orientation of a bar presented in a specific colour in the subsequent sequence. In each trial, participants were presented with a sequence of 4 oriented bars, one of which was presented in the cued colour. Following the presentation of the sequence, a probe consisting of a randomly oriented bar presented in the cued colour and surrounded by a black circle was displayed. Participants were asked to rotate the probe bar using a response dial to match the orientation of the item in the sequence presented at the cued colour. This task was employed to control for any deficits in attentional filtering across groups (Fig. 5.1B).

Patients completed 100-200 trials per 1-item working memory or pre-cuing conditions depending on their ability pre-medication, approximately 3 months after being established on a dopaminergic medication and on and off medication. All age-matched controls performed 200 trials per condition; from this group 8 came back 6-8 weeks after first testing session and completed another 200 trials per condition.

Control tasks

It is possible that poor performance on our experimental 4-item working memory task might be due to factors other than the ability to maintain four items in working memory. These include difficulties in attending to stimuli presented in sequences; simple temporal decay of information over short durations even if only one item had to be maintained; and sensory or motor impairments (e.g., in turning the response dial). Some of these problems might be more evident in PD patients than in the healthy controls. The following tasks, administered in random order across participants, were therefore used as controls to ensure that such issues were not a concern for subsequent interpretation.

1-item working memory task: In each trial, participants were presented with a single oriented target bar (2° × 0.2°) at screen centre on a grey background for 500 msec.

Following a blank variable delay, a probe bar of the same colour surrounded by a black circle appeared at the centre of the screen. Participants were asked to rotate a dial to adjust the probe bar's orientation to match the orientation of the target bar (Fig. 5.1C). The maintenance period preceding the probe was randomly chosen from one of the following delays: 500, 1500, 2500 and 3500 msec. The duration of the retention periods matched the durations from presentation of target bars at different serial positions within 4-item sequences used in the experimental working memory task. This task was used to control for temporal decay of information in working memory.

Sensorimotor Control Task: In each trial a coloured oriented 'target' bar (2° × 0.2°) was presented at screen centre on a grey background. The colour of the bar was chosen randomly from 5 possible colours (red, yellow, green, blue and purple). 500 msec following the presentation of the bar, a probe bar of the same colour surrounded by a black circle appeared below the target bar. Participants were asked to rotate a dial to adjust the probe bar's orientation on screen to match the orientation of the target *which remained on screen* until a response was made. The black circle surrounding the probe item disappeared upon rotating the dial. The orientation of the target and the probe were independently randomised on each trial. Participants could click on the dial to confirm their response when they were satisfied with the orientation of the probe bar. Note that in this task, the target bar was presented on the screen throughout the trial until response. The inter-trial interval was 500 msec. Six PD Patients pre and post medication, all 5 patients on and off medication and 8 of the age-matched controls completed 20 trials of this sensorimotor task (Fig. 5.1D).

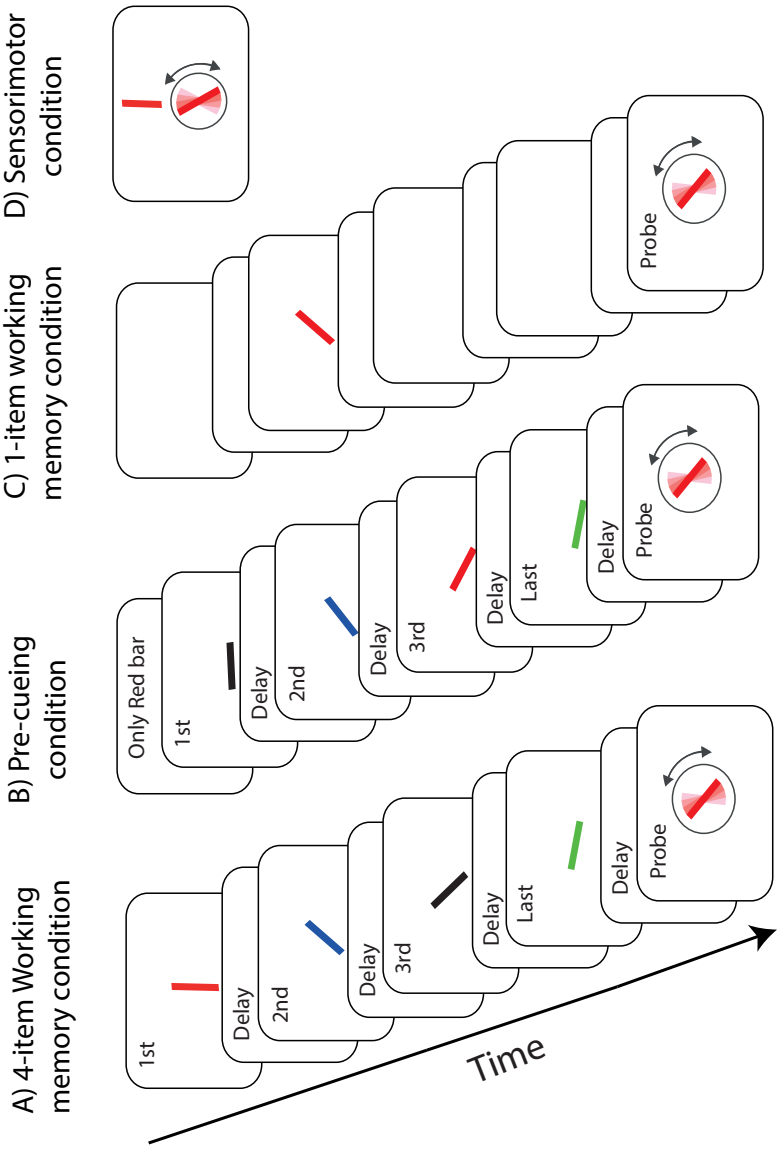


Figure 5. 1: Example of sample trials for different conditions in this study. A) Experimental 4-item working memory condition. A sequence of 4 coloured oriented bars were presented sequentially. Any of the bars could be probed by colour of the response stimuli. B) Pre-cueing condition. At the beginning of each trial, one colour was highlighted (pre-cued) as the target. Participants were asked to only remember the orientation of that coloured bar. C) 1-item working memory condition. A rotating dial is used to orient the probe bar to match the orientation of the target bar. The delay period matched the duration each of the 4 possible serial positions of the previous condition. D) Sensorimotor task. A rotating dial is used to orient the probe bar (surrounded by circle) to match the orientation of the target bar presented above the probe while the target bar remained on screen.

5. 2. 3 Analysis

For the computer-based tasks (experimental 4-item working memory, pre-cueing, 1-item working memory and sensorimotor conditions), precision was calculated as described in Chapter 2. In summary, precision was defined as the reciprocal of the standard deviation of error. Error was calculated as the deviation of the response value (i.e., the reported orientation of the target) from the target value (i.e., the real value of the target's orientation) in each trial. Similar to previous chapters, the value expected for chance was subtracted from the obtained values. Hence a precision score of zero corresponds to responding at random.

For the 1-item working memory condition, error was calculated for each delay interval separately as well as overall performance. In the 4-item working memory conditions as well as the pre-cueing condition, error was calculated for overall performance and additionally for each serial position of the target in the sequence. In order to distinguish different sources of error in memory in the working memory condition, we applied a probabilistic model proposed previously by Bays et al. (2009) (See Chapter 2 for details).

We firstly examined whether pre-medication, newly diagnosed PD patients show impairments in any of the tasks employed in this study, in both neuropsychological and computer-based tasks. Further, we investigated the effect of dopaminergic medication by comparing performance in PD patients pre- and post-medication as well as compared to healthy controls. Lastly, we established the effects of dopaminergic medication by looking at performance in five patients on and off medication.

5. 3 Results

5. 3. 1 Preserved performance in neuropsychological tasks

We first examined performance of PD patients (pre and post medication) in common neuropsychological tasks compared to healthy control participants. None of the participants or healthy controls exhibited evidence of dementia as assessed by the MMSE (Table 5.2). Moreover, PD patients, pre and post medication scored similarly in all sub-scales of the UPDRS. Hoehn and Yahr ratings in PD patients ranged from I to II.

Further, there was no significant change in performance in PD patients after medication in both forwards and backwards digit and spatial spans. Therefore, there is no effect of medication on these tasks. Compared to controls, there was no significant difference in performance in forwards and backwards digit and spatial spans in patients pre and post medication; demonstrating that in these tasks patients performed similarly to healthy age-matched controls. Table 5.2 illustrates the mean performance under these tasks in patients and healthy controls.

Table 5. 2: Mean performance in neuropsychological tasks in all groups

Groups	MMSE	UPDRS	Digit span		Spatial span	
			Forwards	Backwards	Forwards	Backwards
Patients (pre-med)	30	22	4.8	3.5	3.5	3
Patients (post-med)	30	22.5	5.4	3.5	3.5	3.5
Controls	30	N/A	4.6	4.3	3.5	3

5. 3. 2 Working memory impairment in PD patients pre-medication

In order to compare performance in the 4-item working memory task across groups, we first examined the distribution of responses in relation to the target orientation in this condition, in patients pre and post medication as well as healthy controls. As shown in Figure 5.2A, PD patients pre medication responded less to the target orientation

compared to controls. This is illustrated by a decrease in the peak of response distribution around zero in these patients. In PD patients post medication however, there was an increase in proportion of responses around the target value, highlighted by an increase in peak of distribution in patients post-medication. The pattern of responses points to possible impairments in working memory in PD patients pre-medication that is then restored back towards normal post medication.

We then calculated overall precision in performance in this condition- that is the standard deviation of error in response. Compared to controls, overall precision of memory in PD patients pre-medication was significantly worse ($t(17)= 2.73$, $p= 0.014$). There was a significant improvement in working memory precision in PD patients after approximately 3 months on dopaminergic medication ($t(7)= 4.88$, $p= 0.002$). Post medication, there was no significant difference in performance between PD patients and age-matched controls ($t(17)= 1.6$, $p= 0.122$) (Fig. 5.2B). Thus, the precision of working memory representations is lower in un-medicated newly diagnosed PD patients; and restored back towards normal levels on dopaminergic medication.

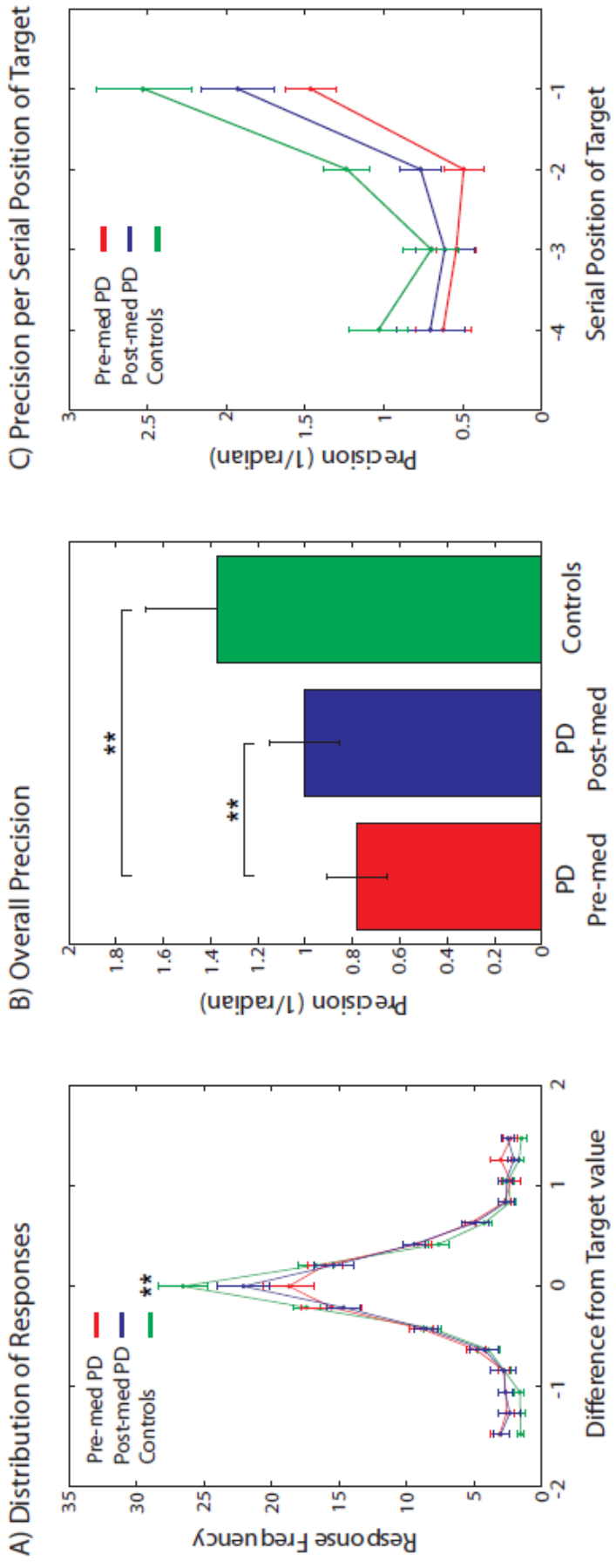


Figure 5. 2: Performance of patients pre and post medication in the 4-item working memory task.
A) Distribution of responses around the target orientation. Peak of distribution around the target value was lower in PD patients pre medication compared to both patients post medication and healthy controls. B) Overall precision in performance. PD patients pre medication were responding less precisely compared to both PD patients post medication and healthy controls. C). Precision of recall at each serial position of the target. For later items in the sequence, PD patients pre medication were responding less accurately compared to patients post medication and healthy controls.

Items were presented sequentially. We therefore investigated the effect of serial position of the target stimulus on precision of memory recall next. We compared memory precision at each serial position of target in patients pre-medication, compared to controls. There was a main effects of serial position on performance ($F(3,68)= 19.8$, $p< 0.001$). Both groups performed significantly better for the last item in the sequence compared to earlier items; a strong example of the well-documented recency effect (Phillips and Christie, 1977; Nairne, 1988; Hay et al., 2007; Botvinick et al., 2009; Blalock and Clegg, 2010).

Comparison of PD patients pre-medication to healthy controls, revealed a main effect of group on performance ($F(1,68)= 18.03$, $p< 0.001$). t-test comparisons of precision of memory between healthy controls and PD patients pre-medication at different serial positions of the target demonstrated a significant impairment in PD patients pre-medication for items presented later in the sequence. PD patients pre-medication performed significantly worse for target item presented both penultimate and last in the sequence ($t(17)= 3.64$, $p= 0.002$ and $t(17)= 2.75$, $p= 0.014$ respectively).

Comparison of performance in patients pre and post medication, demonstrated a significant improvement in performance in PD patients post medication (repeated measures ANOVA; main effect of drug: $F(1,7)= 23.8$, $p= 0.002$). Direct comparison of memory precision in patients pre- and post- medication at each serial position of the target demonstrated a significant improvement post medication at the penultimate position ($t(7)= 2.44$, $p= 0.045$) and a marginally significant improvement for the last item ($t(7)= 2.33$, $p= 0.052$). Working memory performance of PD patients post medication did not vary significantly compared to healthy controls for all serial positions of the target except for items presented at the penultimate position in the sequence ($t(17)= 2.27$, $p= 0.037$, however n.s. after Bonferroni correction).

Together these findings highlight significant impairments in working memory performance in un-medicated PD patients which is restored back towards levels comparable to healthy control after approximately 3 months of dopaminergic medication (Fig. 5.2B-C).

5. 3. 3 Preserved attentional abilities in PD patients

As highlighted previously, it has been suggested that PD patients are also impaired in attentional abilities although the exact temporal development of these deficits are less clear. In order to investigate whether early diagnosed, un-medicated patients are impaired in filtering abilities, we examined performance of patients (pre and post medication) compared to healthy controls in the pre-cueing condition where participants are asked to selectively encode and maintain 1 item while ignoring the distractors. There was no significant difference in performance in this condition in PD patients pre and post medication and compared to controls in both overall performance and at different serial positions of the target within the sequence (all $p>0.05$). Hence, PD patients can use the pre-cue to encode an item in memory and later protect this retained information from upcoming distractors. Thus, at early stages of PD, in our sample, there is no evidence for deficits in filtering abilities within a working memory task.

5. 3. 4 Sources of error in working memory impairments in PD patients pre and post medication

Although the analysis reported previously reveals that PD patients pre-medication are impaired on 4-item working memory task, a question that remains unanswered is the sources of error that result in working memory impairments in PD patients pre-medication and how these alter on dopaminergic medication. In tasks similar to the one we used, participants can make 3 different types of error (explained in more detail in Chapter 2, section 2.2.2). In brief, error can arise because of variability in memory for the items maintained in memory or simple guessing due to failure to encode or retrieve the target item from memory. Finally participants may be misreporting the features of the non-target items instead of the correct features. This last type of error is a result of systematic biasing of the target item by other items held in memory.

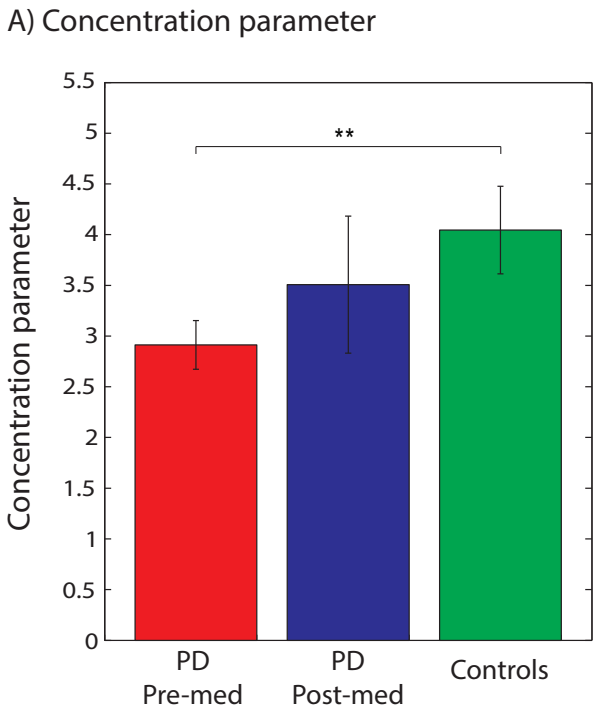
In order to gain an understanding on the possible sources of error that may have occurred, we applied a three-component probabilistic model of error (previously explained see Chapter 2, section 2.2.2, for details of model) to the data. Maximum likelihood estimates of the probability of responding to random, probability of responding to the target and variability of target orientation (i.e., concentration

parameter, κ) were estimated. Subsequent to model fitting, individuals with any parameter value as an outlier (i.e., 2.5 standard deviation away from the mean of each parameter) were excluded from further analysis. One elderly control and one PD patient were excluded.

There was a significant difference in concentration parameter in PD patients pre-medication compared to healthy controls ($t(15)= 2.8$, $p= 0.014$). However, there was no signficiant difference in concentration parameter between patients on medication and healthy controls. Concentration parameter captures variability in memory for the retained information and has an inverse relationship with standard deviation meaning that high concentration parameter corresponds to lower variability in memory. Hence, resolution of maintained items was less variable in both healthy controls and PD patients on medication compared to PD patients prior to administration of medication (Fig. 5.3A). Furthermore, probability of random responses was also significantly higher in un-medicated PD patients compared to healthy controls ($t(15)= 2.2$, $p= 0.043$- Fig. 5.3B). This was accompanied by a marginal decrease in probability of target responses in un-medicated PD patients compared to elderly controls ($t(15)= 2.1$, $p= 0.054$- Fig. 5.3B). Probability of random responses and target responses in PD patients *on medication* however did not vary from that observed in healthy controls.

The remaining comparisons between all model estimates, comparing patients pre and post medication as well as compared to healthy controls failed to reach significance. This can be explained by either lack of power due to small number of participants or noisy model estimates due to small number of trials accomplished by each participant.

These results demonstrate that working memory representations in un-medicated PD patients are firstly noisier than healthy controls- as observed by a decrease in concentration parameter in these patients. Secondly, these patients are more likely to respond randomly whether it is due to faster decay of information or limited encoding of information- a question that remains to be answered. On medication, however, PD patients respond similarly to healthy controls.



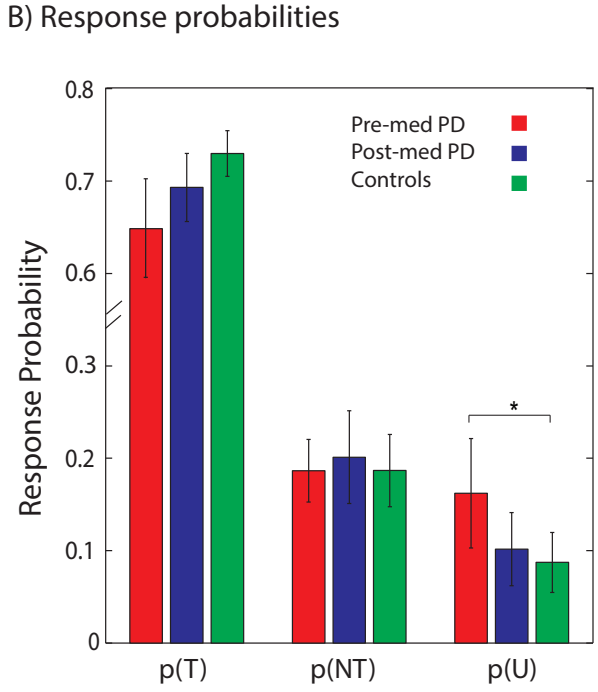


Figure 5. 3: Model estimates for different sources of error in the 4-item working memory task.

A) Concentration parameter was significantly lower in PD patients pre medication compared to healthy controls. B) Probability of random responses (p(U)) were significantly higher in PD patients pre medication compared to controls. There was a marginal decrease in probability of target responses (p(T)) in PD patients pre medication. Probability of non-target (p(NT)) responses was not different in PD patients pre and post medication and compared to healthy controls (error bars indicate SEM).

5. 3. 5 Working memory deficits cannot be explained by impairments in temporal decay or sensorimotor performance

To examine whether difference in performance on the 4-item working memory task were caused by impairments in factors other than impairments in working memory, we analysed performance of patients and controls on our control tasks. Overall performance on the 1-item working memory task at different delay intervals did not differ in PD patients pre and post medication and compared to controls. Therefore, we conclude that impairments in our experimental 4-item working memory task cannot be attributed simply to difference between the groups in how information decays over time (although, of course, this does not mean that there is no influence of maintenance duration on precision of memory).

Furthermore, there was also no significant difference in performance between groups on the sensorimotor control task (Fig. 5.1D). This result is particularly important since PD patients might have difficulties with dexterity in using the response dial, but our findings show this is not a confounding factor in interpreting the data.

5. 3. 6 Effect of repeated testing on working memory performance in healthy controls

Since PD patients were tested twice, once pre medication and once post medication, it is be possible that any improvements observed in the 4-item working memory task post medication may be the result of repeated testing in these patients, i.e., due to practice effects. In order to investigate this, we asked 8 of the 11 healthy controls to come back approximately 3 months after their first session of testing.

There was no significant difference in overall performance in the working memory task between the two sessions of testing in these healthy controls (repeated measures ANOVA, main effect of session: $F(1,7)= 1.123$, $p= 0.325$). Pair-wise comparisons between performances across two sessions at each serial position of the target demonstrated no significant change in precision of memory at all positions. Therefore, any improvement observed in PD patients post medication is unlikely to be explained by

the effect of repeated testing/practice effects, if we can extrapolate from healthy controls.

5. 3. 7 Working memory precision on and off medication in PD patients

It can be concluded that the improvements observed in PD patients post medication are most likely to be a result of the effect of dopaminergic medication on working memory performance. Therefore, dopamine appears to enhance working memory performance in patients who were otherwise impaired in this task. If this is the case, withdrawal from dopaminergic medication should result in impairment in working memory. In order to test this hypothesis, we asked 5 of the 8 PD patients to return for 2 more testing sessions, once on and once after 12 hour withdrawal from dopaminergic medication. For clarity, these two testing session are labelled on and off medication while previous sessions are labelled pre and post.

There was no significant change in performance in patients on and off medication in forwards and backwards digit and spatial spans, 1-item working memory and pre-cueing conditions. Therefore, 12 hour withdrawal from dopaminergic medication did not have an effect on performance in these tasks. However, patients off medication performed significantly worse on the 4-item working memory task compared to when on medication (repeated measures ANOVA, main effect of medication: $F(1,4)= 10.035$, $p= 0.034$- Fig. 5.4A). There was also a significant interaction between medication and serial position of the target ($F(3,12)= 7.14$, $p= 0.005$). Pair-wise comparison of performance in on and off testing sessions at all serial position of the target demonstrated significant impairment in performance for the last item in the sequence in the off medication session for these five patients ($t(4)= 6.6$, $p= 0.003$- Fig. 5.4B). Lack of an effect for other serial positions might be due to low power in this small sample size.

There was no significant difference in performance between pre-medication and off medication conditions ($F(1,4)= 0.21$, $p= 0.7$- Fig. 5.4A) highlighting that even after 12 hour of withdrawal from dopaminergic medication, performance is impaired to the extent observed pre-medication (Fig. 5.4A).

All in all, these findings point to the conclusion that newly diagnosed, un-medicated PD patients have specific working memory impairments that is normalized on dopaminergic medication. Importantly, 12 hour withdrawal from medication causes performance to drop back to levels comparable to prior medication.

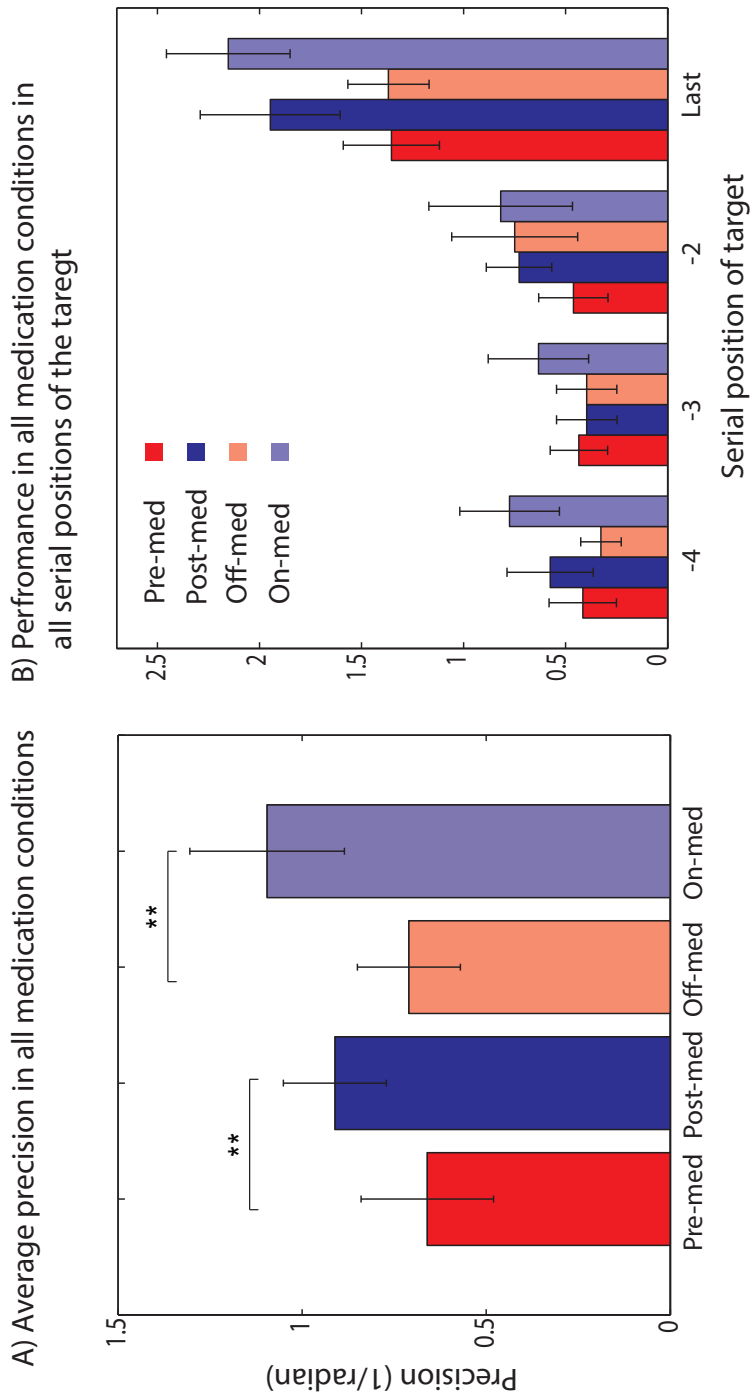


Figure 5. 4: Performance of patients, pre, post , on and off medication in the 4-item working memory task. A) average precision was significantly lower in both pre-medication and off-medication conditions compared to post-medication and off-medication conditions respectively. B) Precision of memory in all serial positions of the target. As illustrated clearly, in trials where target is presented last or first in the sequence, there is an increase in performance in post-medication compared to pre-medication. 12 hour withdrawal from medication impaired performance to levels comparable to pre-medication condition (shaded red bar). Taking up medication, however, improves performance (N=5).

5. 4 Discussion

The findings from this chapter demonstrate visual working memory impairments associated with *de novo* untreated, recently-diagnosed PD patients. Using an analogue, continuous report procedure, which potentially provides a more sensitive measure of working memory performance than change-detection paradigms, we were able to detect working memory deficits in PD patients that were restored back towards normal on dopaminergic medication. These findings help establish the temporal development of cognitive impairments in PD patients and further our understanding of the role of dopamine in visual working memory precision.

Working memory impairments in de novo untreated PD patients

PD patients prior to administration of any medication were tested on a sequential working memory task. We demonstrated that these patients, compared to healthy age-matched controls, were significantly impaired. The deficits were observed in overall performance and at different serial positions of the target (more pronounced for items presented later in the sequence). These findings extend previous literature, showing that working memory deficits are detectable at early stages of PD.

Moreover, deconstructing possible sources of error allowed us to investigate the sources of error affected by impaired dopamine function. Memory representation of the target item in un-medicated PD patients was noisier than healthy controls. Dopamine is known to be crucial for determining neuronal signal-to-noise ratios specifically in prefrontal cortex during working memory tasks (Sawaguchi, 1987, 2000; Newman and Grace, 1999; Winterer and Weinberger, 2004; Bertolino et al., 2006; Kroener et al., 2009). Therefore, in early stages of PD, deficits in the dopaminergic system might influence the signal to noise ratio manifested by less precise/noisier representations of the target orientation.

Further, pre-medicated patients made more random responses. Increase in random responses may be due to faster decay of information when multiple items are retained in working memory. Although decay of information when 1 item was maintained in memory was not impaired in patients, this does not mean that there is no influence of

number of maintained items on rate of decay of information (Pertzov et al., in press, *JEP:HPP*). Alternatively, increase in proportion of random responses in these patients can arise as a result of limited encoding of information. Although all patients performed significantly above chance level at all serial positions of the target, it may be possible that due to coarse encoding of items, at the time of recall, responses fall within the random range.

Preserved filtering abilities in working memory

Unlike working memory, un-medicated PD patients performed similar to healthy controls in the filtering condition when a 100% pre-cue highlighted the target item amongst a sequence of 4 items. Therefore these patients were firstly able to selectively encode the target item and then protect the retained information from distractors. Previously it has been reported that PD patients off medication show enhanced resistance to distractions (Cools et al. 2010). In that study, PD patients off medication performed a delayed response task with stimuli consisting of faces and scenes and distractors presented during the delay interval. Compared to controls and PD patients on medication, distractor-related slowing was absent off medication. In light of these findings, it was suggested that such enhancement may reflect up-regulation of dopamine levels in prefrontal cortex as a result of reciprocity between striatum and prefrontal cortex (Pycock et al., 1980; Roberts et al., 1994; Akil et al., 2003; Meyer-Lindenberg et al., 2005).

It is important to note that the two studies (present chapter and Cools et al., 2010) cannot be directly compared due to differences in methodology. In the experiment conducted by Cools and her colleagues, enhanced cognitive function was reported in response times. However, in the present chapter speeded responses were discouraged and hence response times could not be used as a dependent variable. Furthermore, here we report preserved performance in a task where the target item had to be selected from an array of items presented sequentially. Enhanced distractor resistance, however, has only been reported for distractors that were presented after the encoding of target items (Cools et al., 2010). These differences point to the complexity of cognitive abnormalities, whether manifest as enhanced or impaired performance in different tasks. From the results reported here, we can conclude that early-diagnosed PD patients can

dynamically allocate their working memory resources to a target item; which is then protected from any bias/influence from non-target/distractor items. However, they encounter significant difficulty in maintaining four items in memory.

Improved working memory performance on dopaminergic medication

One of the principal findings of this chapter is that after 3 months of dopaminergic medication, performance in the working memory task is improved to levels comparable to healthy controls without any observable differences in sensorimotor performance as measured by our control tasks.

These findings are in line with previous literature which show that dopaminergic medication improves working memory performance on a variety of visuo-spatial tasks (Lange et al., 1992; Malapani et al., 1994; Fournet et al., 2000; Mattay et al., 2002; Costa et al., 2003b). Evidence from cortical signal-to-noise enhancement effects of dopamine (Sawaguchi, 1987, 2000; Lewis and O'Donnell, 2000; Meyer-Lindenberg et al., 2005b) support the hypothesis that lack of dopamine may be responsible for decreased efficiency of prefrontal cortex function in patients with early PD only, and subsequent enhanced efficiency after dopaminergic medication targeting.

Improvement of working memory function by dopamine however, is not always replicated, more specifically in patients at later stages of the disease. Higher doses administered later in the disease for developed motor symptoms have been reported to exacerbate different cognitive deficits (e.g., working memory and attention) in patients (Owen et al., 1997; Barch, 2004; Owen, 2004; Cools and D'Esposito, 2011). This may be caused by excessive dopamine receptor stimulation in striatum and PFC which in turn impairs PFC functions (Williams and Goldman-Rakic, 1995b; Murphy et al., 1996b; Verma and Moghaddam, 1996; Arnsten, 1997, 1998). Although the study reported in this chapter highlights the positive influence of dopaminergic medication on working memory function in early PD, the exact effect of these medications as the disease progresses remains to be established.

Sensitive measures of working memory function

Modulations in working memory performance were detected by investigating the *precision* of memory in PD patients. Common neuropsychological measures of verbal and spatial working memory, i.e., digit and spatial spans, were not sensitive enough to pick up such modulations. Recently, studies have highlighted the importance of employing more sensitive measures of working memory performance using tasks similar to the one used here (Bays, Catalao and Husain, 2009; Gorgoraptis, Catalao, Bays and Husain, 2011). Such tasks not only provide a more sensitive measure of performance but also allow us to differentiate between the sources of error that are influenced by different experimental manipulations. Future studies examining working memory performance in different patient groups should aim to employ these measures as classical ways may not be informative regarding the resolution with which items are stored in working memory and the mechanisms of processes affected.

Conclusions

The present findings help to improve our understanding of the relationship between dopamine function and working memory. These results extend previous literature on the temporal development of PD and the influences of dopaminergic medication on working memory precision. The findings might have important implications for clinicians who should consider the cognitive influences of medication administered.

One of the aims of PD research is to identify a cognitive marker for neurodegenration. We suggest that visual working memory impairments, observed in de novo untreated PD patients, might be a good candidate for such a cognitive marker to identify those who are at risk of developing PD, for example due to genetic factors.

Chapter 6

Effect of Cabergoline on working memory and attentional filtering abilities

6. 1 Introduction

In Chapter 5 I demonstrated modulation of working memory performance in individuals with dopaminergic dysfunction, i.e., PD patients pre and post medication. A question that rises naturally is whether dopamine can also be used to improve precision of memory in healthy participants. In the present chapter I aim to test this hypothesis,

investigating the effects of Cabergoline (a D2 dopamine agonist) on working memory and attentional filtering abilities in healthy individuals.

Dopamine has previously been shown to improve performance in different working memory tasks in healthy people (Luciana et al., 1992; Luciana and Collins, 1997; Mehta et al., 2001). For example, Luciana and colleagues have demonstrated that Bromocriptine (a D2 agonist) enhanced spatial working memory in a task that required participants to remember and maintain four spatial locations chosen from 16 possible positions. Similarly, Mehta and colleagues (2001) reported improvement on both spatial span and self-ordered spatial memory tasks on Bromocriptine. Considering that there are currently no D1 agonists available for use in humans, studies employing the subtraction design (see Chapter 1, section 1.4.2 for details) have shown that mixed D1/D2 agonists compared to D2 agonist alone result in improved visuospatial delayed match to sample (Müller et al., 1998) as well as object match to sample tasks in healthy participants (Kimberg and D'Esposito, 2003).

However, some investigations have failed to report enhancement on *non-spatial* working memory tasks using dopaminergic medication- e.g., bromocriptine (Luciana and Collins, 1997; Bartholomeusz et al., 2003b). It has been demonstrated that participants did not benefit from dopamine on a task that required them to maintain information about the shape of objects presented sequentially (Luciana and Collins, 1997) or a 2-back working memory task (Kimberg et al., 2001). There are also several psychopharmacology studies with D2 and D1 agonists in healthy participants that have yielded mixed results, with findings of both cognitive enhancement and impairment associated with different doses, task conditions and populations (Kimberg et al., 1997; Mehta et al., 1999, 2004; Luciana et al., 2004).

The discrepancy between studies may be accounted by differential directions of change in performance on dopamine depending on individuals' baseline performance (e.g., Cools and D'Esposito, 2011 for review). Such baseline-dependent effects might not be observable when considering overall performance due to averaging. There is currently evidence to support this hypothesis from animal, patient and pharmacology studies, as reviewed in Chapter 1 (section 1.4) of this thesis. It has been proposed that the relationship between cognitive performance and dopamine follow an "inverted U-shaped" relation with both hypo and hyper dopaminergic states resulting in impaired

working memory performance (Cools and D'Esposito, 2011). Hence in individuals with optimal levels of dopamine, further administration of dopamine may result in overdosing the system and impaired performance. Contrary to this, working memory can be enhanced in individuals with reduced baseline dopamine function (as observed in Chapter 5 with PD patients). Thus, considering individuals' baseline performance is critical to understanding the direction of change in performance after administration of dopamine.

Human pharmacological studies have confirmed baseline-dependency of dopaminergic medication. In a recent study (Frank and O'Reilly, 2006), participants were asked to perform a working memory task and respond when a target sequence was presented within a sequence of letters and numbers. The task relied heavily on both maintenance and updating of information in working memory. The researchers also included distractors to the task in additional conditions. Cabergoline enhanced working memory performance in low-span participants as measured by reading span (Daneman and Carpenter, 1980) in the no distractor condition. Further, in the same participants, Cabergoline impaired working memory when distractors were present during the delay, demonstrating increased distractibility on Cabergoline. This study firstly highlights the importance on considering baseline performance on the direction of change on dopaminergic medication and secondly the effects of dopamine on filtering abilities i.e., filtering out distractors, within a working memory task.

In the present Chapter we aimed to examine the effects of Cabergoline on performance in both working memory and filtering abilities (i.e., magnitude of distractability) in healthy controls. We employed the same task as previously used in Chapter 5 to be able to provide a more sensitive measure of performance using precision as an index of performance. This would allow us to pick up small changes in performance on Cabergoline and sources of error that are modulated by this drug. Moreover, the pre-cueing condition (where the target item was cued prior to presentation of items in memory- Figure 5.1) allowed us to extend previous research on the role of Cabergoline on distractibility within a working memory task. In line with previous research we predicted different effects of Cabergoline on performance in both working memory and attentional filtering tasks depending on baseline performance of participants.

6. 2 Method

6. 2. 1 Participants

Eighteen healthy male individuals with an average age of 26.5 (range: 18-36) participated in this study. All participants had normal or corrected to normal vision and reported normal colour vision, no neurological, psychiatric or active medical conditions. None of the participants used recreational drugs more than once per month.

Prior to the main testing sessions, on a separate day, participants were briefed that Cabergoline could rarely cause headache and nausea, were given the opportunity to ask questions and completed forwards digit span and Raven's progressive matrices (see section 6.2.2).

All participants then completed two more testing sessions, on drug or placebo with randomised order between individuals. On each session, participants attended the lab at 08:00 and took 20 mg of the drug domperidone to prevent the possible side effect of nausea. At 08:20 participants drank a glass of orange squash consisted of either a crushed placebo tablet or crushed Cabergoline, 1.5 mg tablet. Both participants and the experimenter were blinded to the randomisation of drug. Participants were then free for two hours and at 10:30 their pulse and blood pressure (BP) was checked by a qualified medical doctor. There was no effect of Cabergoline on BP and pulse (Fig. 6.1).

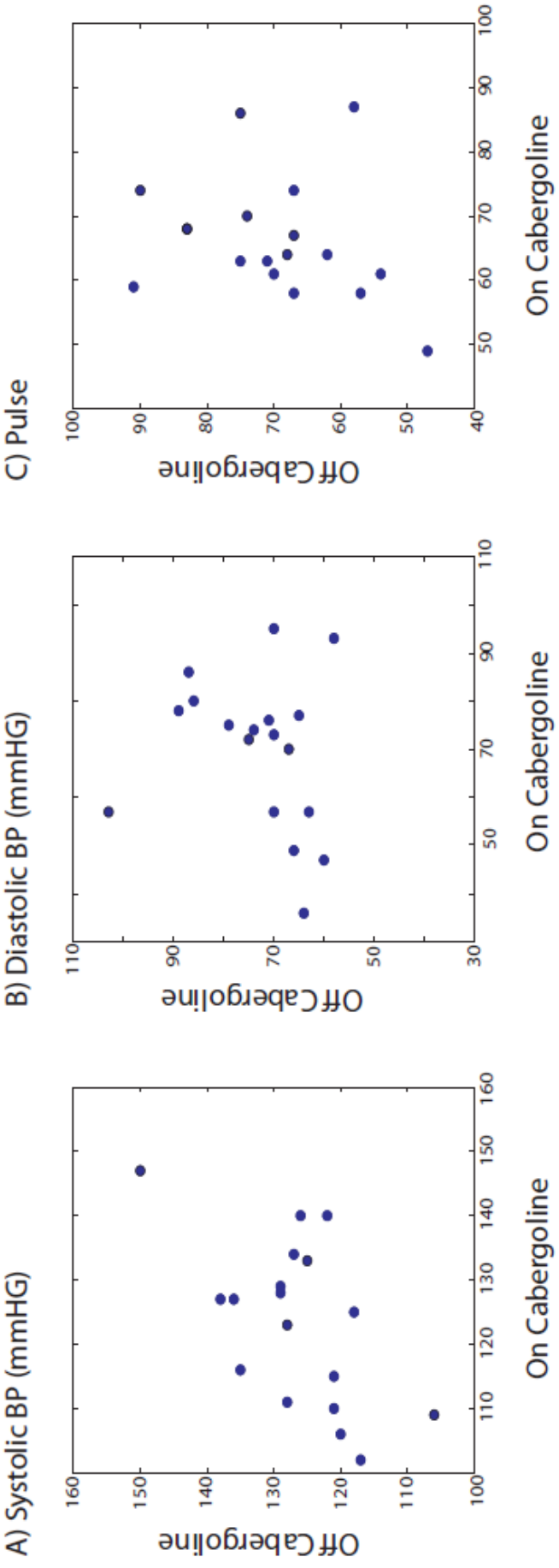


Figure 6. 1: Individuals' pulse and blood pressure on and off Cabergoline
There is no effect of Cabergoline on A) Systolic BP, B) Diastolic BP and C) Individuals' pulse.

Participants then completed three 1.5 hour sessions of experiments (11-12:30; 14-15:30; 16-17:30). The reported experiments in this chapter are those completed in one of these testing sessions. The time of the day that each participant was tested was constant between the two sessions and randomised between participants. In the breaks between testing sessions subjects completed a computer-based visual analogue scale questionnaire to document any side-effects, mood and state anxiety, and whether participants thought they had taken drug or placebo on that day.

6. 2. 2 Materials and measures

Visual Analogue Scale questionnaires

Prior to start of the first experimental session of both testing days (approximately at 11 in the morning, 2 hours after the administration of the drug) participants completed two questionnaires using Visual Analogue Scales (VAS). VAS is a psychometric response scale that is used in questionnaires and is used to measure the subjective characteristics or attitudes that cannot be measured directly. The first VAS questionnaire was used to measure individuals' subjective measure of different mental states (Fig. 6.2). Participants were asked to indicate on the VAS scale how they felt at that moment in time on various emotions and states, for example whether they felt alert vs. drowsy, happy vs. sad or interested vs. bored. The second VAS questionnaire focused on the physical state of participants. Similar to the first questionnaire participants were asked to indicate on a scale how they were feeling physically on questions like, presence of headache vs. no headache (Fig. 6.2).

The visual scale was divided into scales ranging from -500 to 500. The ends of the scale represent the extremes of each question. Each individual's response along the scale was transformed into a score (ranging from -500 to 500). Figure 6.2 illustrates the difference in VAS1 and 2 scores on and off Cabergoline. There was no significant change in VAS scores on and off Cabergoline after correcting for multiple comparisons (corrected p= 0.0019). Therefore any changes in performance in other tasks is unlikely to be explained by changes in the physical or emotional state of these individuals by Cabergoline.

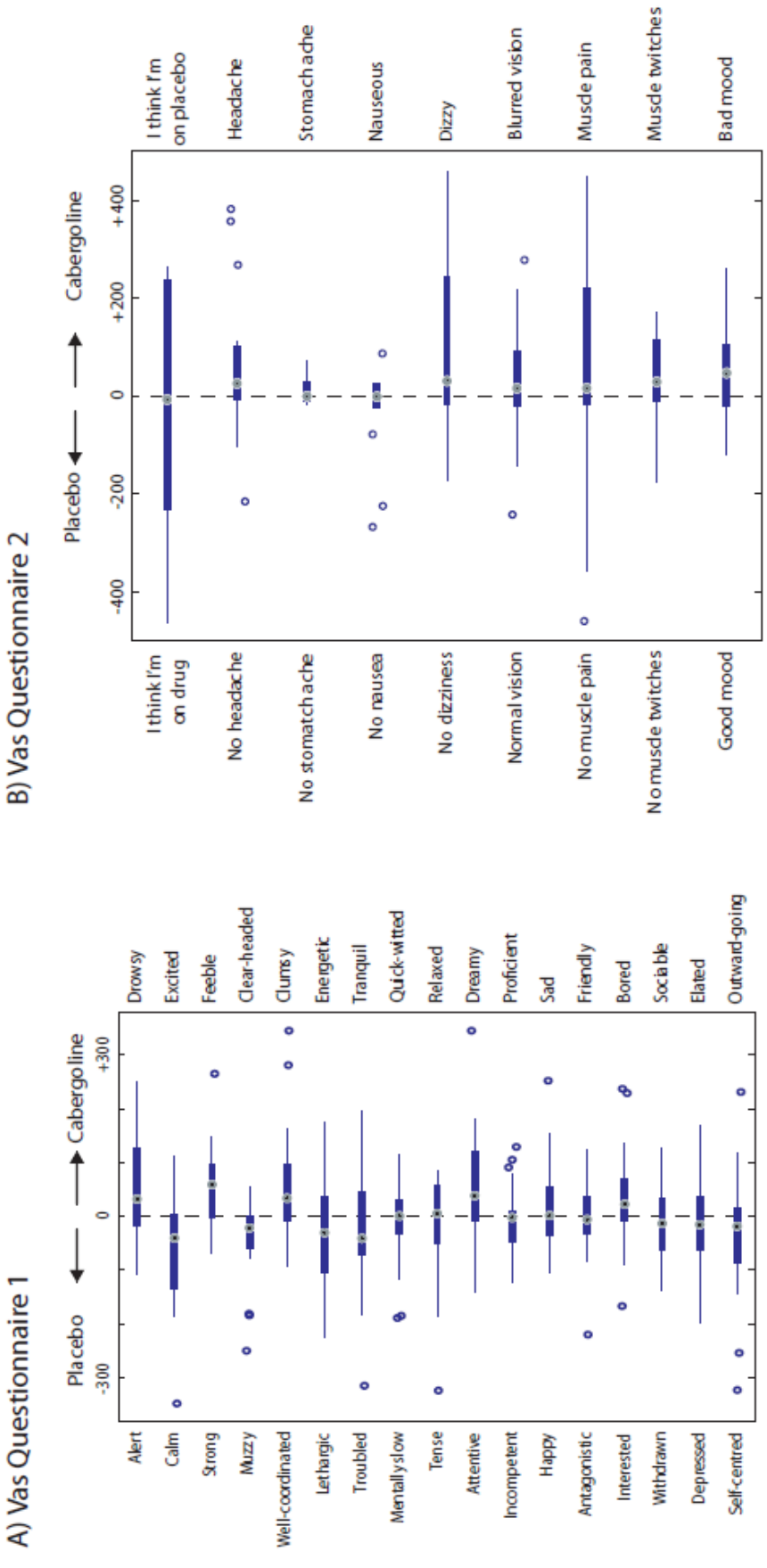


Figure 6. 2: Boxplots of changes in VAS ratings on Cabrgoline and Placebo for items in both VAS 1 (A) and VAS2 (B) questionnaires.

Computer-based tasks

On each testing day, participants performed the 1-item working memory, pre-cueing and 4-item experimental working memory conditions, similar to those explained in Chapter 5 (section 5.2.2). It's important to note that although the tasks were similar between the two testing sessions, they were not identical. The orientation of the target bars were randomly selected on each trial of each condition in each testing session.

Precision of working memory was calculated for overall performance in all conditions, different delay intervals in the 1-item working memory task and different serial positions of the target in the 4-item working memory and pre-cueing conditions.

Raven's Progressive Matrices

All participants were also administered a short version of Raven's progressive matrices prior to the two drug sessions (i.e., before both Cabergoline and Placebo sessions). Raven's matrices provide a non-verbal multiple choice for measuring reasoning (see Fig. 6.3 for an example) and it correlates strongly with general intelligence (Marshalek et al., 1983; Alderton and Larson, 1990; Bors and Stokes, 1998). It consists of fifteen 3×3 matrices with one item missing and participants are asked to choose the missing pattern from a choice of 8 items. Twelve matrices were administered and participants had 15 minutes to complete as many as they could. Performance in this task was later used to see whether general intelligence correlates with changes in performance on Cabergoline in working memory and pre-cueing conditions.

Forward digit span

Similar to the Raven's matrices, participants also completed the forwards digit span where they had to repeat sequences of digits with increasing length (2 sequences per length) until performance broke down. We calculated forward digit span as the maximum sequence length in which participants reported a minimum of one sequence per sequence length correctly. Half a score was deduced if participants performed one out of two correct per sequence length.

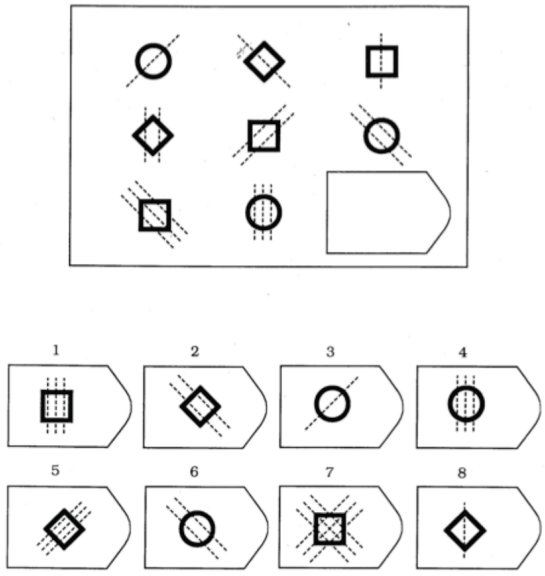


Figure 6. 3: Example of a Raven's progressive Matrix.
Participants are asked to find the relationship between items in the matrix, horizontally, vertically and orthogonally, to find the correct missing item from the 8 choices presented below the matrix. Here the correct answer is item number 5.

6. 3 Results

6. 3. 1 No effect of repeated testing on performance in computer-based tasks

We first looked at any effect of repeated testing under different conditions to investigate any changes in performance *independent of Cabergoline*, as a result of practice effects, since participants performed similar tasks twice, 2 weeks apart. There was no effect of repetition on performance in the 1 item working memory, pre-cueing and 4-item working memory conditions. This was also true for different delay intervals in the 1 item memory condition and for all serial positions of the target in the pre-cueing and the 4-item working memory conditions ($p > 0.05$ for all comparisons). These results confirm that there was no change in performance due to practice effects. In other words, repeating similar tasks twice in succession, 2 weeks apart, did not have any influence on performance. Below I will provide the information regarding all comparisons between different session and for different tasks in more detail.

1-item working memory condition- There was no difference in precision of memory in the 1-item working memory condition (repeated measures ANOVA, main effect of

session, $F(1,17)= 0.4$, $p= 0.5$) and no interaction between testing session and delay interval between target and probe (session* delay interval interaction, $F(3,51)= 0.7$, $p= 0.6$). Pair-wise comparison between precision of memory in session 1 and 2 for delay interval 3500 msec ($t(17)= 1.8$, $p= 0.085$), 2500 msec ($t(17)= 0.17$, $p= 0.9$), 1500 msec ($t(17)= 0.2$, $p= 0.8$) and 500 msec ($t(17)= 0.45$, $p= 0.7$) further confirmed that there was no significant effect of repetition in performance in this condition.

Pre-cueing condition- In the pre-cueing condition, there was no effect of repeated testing on overall precision (main effect of session, $F(1,17)= 0.001$, $p= 0.98$) and no interaction between session and serial order of the target in the sequence ($F(3,51)= 0.14$, $p= 0.93$). Paired-sample comparisons between precision of memory at each serial position of target between two testing sessions confirmed no significant difference for targets presented at different serial position of the target [serial position -4 (1^{st} in the sequence): $t(17)= 0.035$, $p=0.97$, serial position -3 (2^{nd} in the sequence): $t(17)= 0.02$, $p=0.98$, penultimate item: $t(17)= 0.41$, $p=0.69$ and last item: $t(17)= 0.36$, $p=0.72$].

4-item working memory condition- Precision of memory in the 4-item working memory condition was unaffected by repeated testing (main effect of session, $F(1,17)= 4.15$, $p= 0.06$), even when considering the serial position of the target in the sequence (session* delay interval interaction, $F(3,51)= 1.023$, $p= 0.4$). Comparing performance at each serial position of the target further confirmed our results; there was no significant change in performance on second session of testing, at different serial positions of the target [serial position -4 (1^{st} in the sequence): $t(17)= 0.6$, $p=0.5$, serial position -3 (2^{nd} in the sequence): $t(17)= 1.6$, $p=0.12$, penultimate item: $t(17)= 0.87$, $p=0.4$ and last item: $t(17)= 1.3$, $p=0.23$].

Therefore, we can conclude that mere repetition of these tasks, 2 weeks apart, has no effect on precision of memory. It is important to note that although the conditions were repeated on both sessions, the orientation of target and non-target bars were randomly selected on each trial and hence the exact trials with identical orientations were not repeated on both sessions.

6. 3. 2 Effect of Cabergoline on 4-item working memory task

We next sought to investigate the effect of Cabergoline on performance in the 4-item working memory task. Precision of memory was calculated as the reciprocal of standard deviation of error in response for both overall performance and for performance at each serial position of the target, i.e., when in the sequence the target was presented. There was a significant effect of serial position of target on performance ($F(3,51)= 56.75$, $p<0.001$), i.e., higher performance for items presented last in the sequence; the recency effect. However, there was no overall effect of drug on performance in this condition in the overall performance (main effect of Cabergoline, $F(1,17)= 0.03$, $p= 0.8$). This was also true for performance at all serial position of the target within the sequence, i.e., no change on memory precision of Cabergoline in different target position (all $p>0.05$).

As stated previously studies have shown that changes in performance on dopaminergic drug is dependent on individuals' baseline performance. Therefore, we examined the effect of baseline performance (that is average performance on both testing sessions) on any change in precision of memory on Cabergoline. Change in precision on Cabergoline was calculated as:

(precision on Cabergoline) – (precision on placebo).

Therefore, a negative value of change translates into impaired performance on Cabergoline. We divided the participants (median split) depending on their average performance into high and low performers. There was no significant interaction between individuals' baseline performance and the effect of Cabergoline ($F(1, 16)= 0.035$, $p=0.85$). Further, there was no correlation between baseline precision and change in performance on Cabergoline ($r= 0.034$, $p=0.9$- Fig. 6.4) in this condition.

Moreover, there was no correlation between change in performance on Cabergoline and performance in both Raven's matrices (Pearson Correlation= 0.43, $p= 0.075$) and forward digit span (Pearson Correlation= 0.124, $p= 0.63$).

Together these findings suggest that Cabergoline does not influence working memory precision, even when baseline performance of individuals is considered. Further, the magnitude of the change does not correlate with standard measures of working memory (digit span) and intelligence (Raven's Matrices) in young, healthy individuals.

6. 3. 3 Effect of Cabergoline on pre-cueing condition

We then examined the effect of Cabergoline on performance in the pre-cueing condition, comparing performance on and off Cabergoline. There was a significant effect of serial position of the target on performance ($F(3,51)= 24.9$, $p<0.001$); participants both on and off Cabergoline were better at remembering the cued item if it was presented later in the sequence. However, there was no effect of Cabergoline on overall performance ($F(1, 17)= 0.9$, $p=0.35$) and no interaction with serial positions of the target ($F(3, 51)= 2.469$, $p=0.63$).

We next investigated the effect of baseline performance (i.e., average performance on both testing sessions) on any change in precision of memory on Cabergoline in this condition- similar to the procedure done previously on performance in the 4-item working memory condition. We divided the participants (median split) into two groups of low and high performers based on their average performance. There was a significant interaction between individuals' baseline performance and the effect of Cabergoline on performance ($F(1, 16)= 7.583$, $p=0.014$) demonstrating that low and high performers benefited differentially from Cabergoline. More specifically, high performers were significantly impaired in the pre-cueing condition on Cabergoline compared to placebo ($t(8)= 3.78$, $p=0.005$- Fig. 6.4). There was a significant difference in magnitude of change on Cabergoline between high and low performers at different serial positions of the target; for items presented last in the sequence ($t(16)= 2.75$, $p= 0.014$) and first in the sequence ($t(16)= 3.026$, $p= 0.008$). Magnitude of change in performance on Cabergoline was marginally different between low and high performers for the penultimate item ($t(16)= 1.89$, $p= 0.078$- Fig. 6.4). These findings illustrate that the effects of Cabergoline on performance on a pre-cueing working memory task depends highly on individuals' baseline performance.

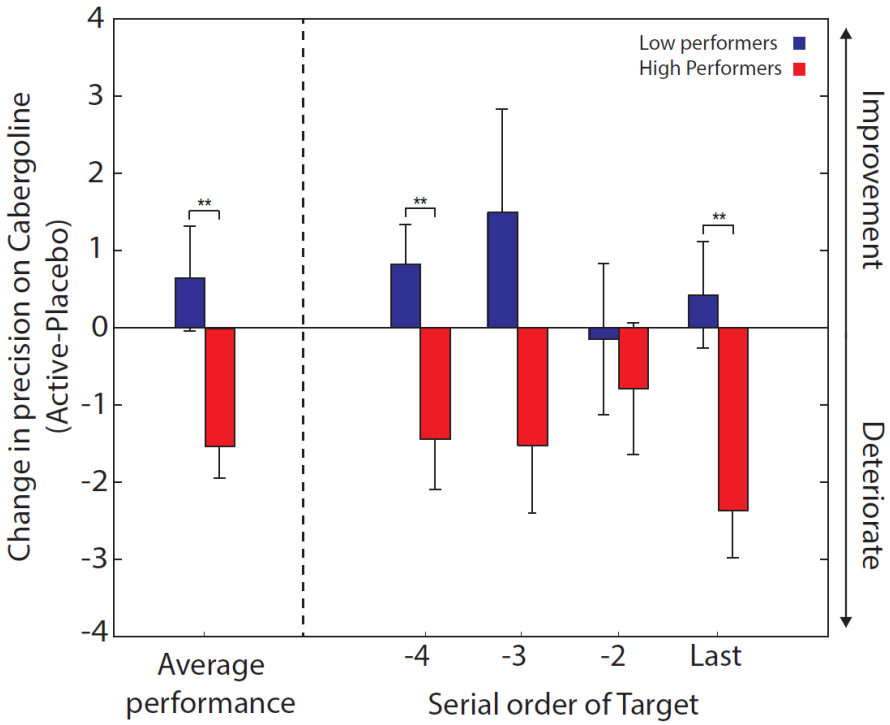


Figure 6. 4: Change in performance on Cabergoline (Active-Placebo) in the pre-cueing conditions. Average performance was significantly improved in low performers compared to high performers. Similar pattern of results was observed at different serial positions of the target (within subject error bars).

This was also demonstrated by the marginally negative correlation between performance on placebo and change in performance on Cabergoline (r= -0.47, p= 0.051-Fig. 6.5). Hence performance on placebo determined the extent and direction of change in performance on Cabergoline in this condition.

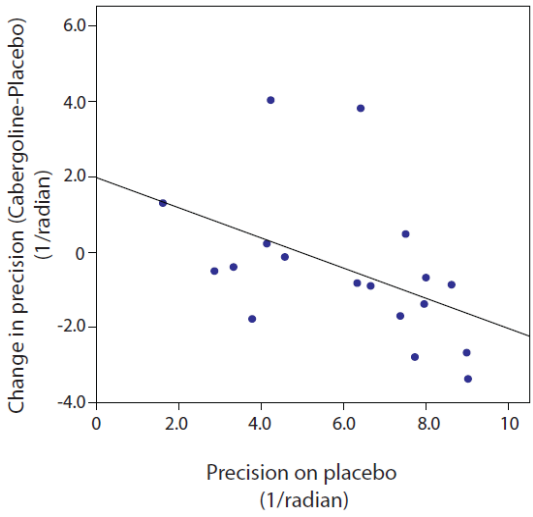


Figure 6. 5: Negative correlation between performance in the pre-cueing condition on placebo and change in performance on Cabergoline.

There was no significant correlation between changes in precision of memory for the cued item and performance in Raven's matrices (Pearson Correlation= 0.043, p= 0.8) and forward digit span (Pearson Correlation= 0.10, p= 0.70). Hence, baseline performance in the pre-cueing condition was the only determinant on the extent and direction of the effect of Cabergoline in different individuals.

6. 3. 4 Model estimates for the pre-cueing condition

Considering the behavioural findings, it is important to further investigate the source of error modulated in low and high performers upon administration of Cabergoline in the pre-cueing condition. On Cabergoline, high performers were performing significantly less to the target orientation, highlighted by the decrease in peak of the distribution around the target orientation (Fig. 6.6A). However, there was no observable difference in response *distributions* in low performers.

In order to examine the sources of error, we applied the three-component model of response error to our data (see Chapter 2, section 2.2.2). Model estimates were not calculated for each serial position of the target due to limited number of trials per condition.

In all participants, both on and off Cabergoline, the probability of responding to non-target orientations and making random responses was close to zero (i.e., 1% of trials). There was no significant difference in probability of target, non-target and random responses on and off Cabergoline in both low and high performers. However, there was a significant interaction between changes in κ on Cabergoline and baseline performance ($F(1,16)$= 5.52, p= 0.032). Pre-cued items maintained in memory in high performers were significantly more variable on Cabergoline compared to placebo, illustrated as a decrease in kappa in this condition (Fig. 6.6B). Considering both the model estimates and the distribution of responses, one can conclude that impaired performance in high performers on Cabergoline is a result of increase in variability for the target item in memory.

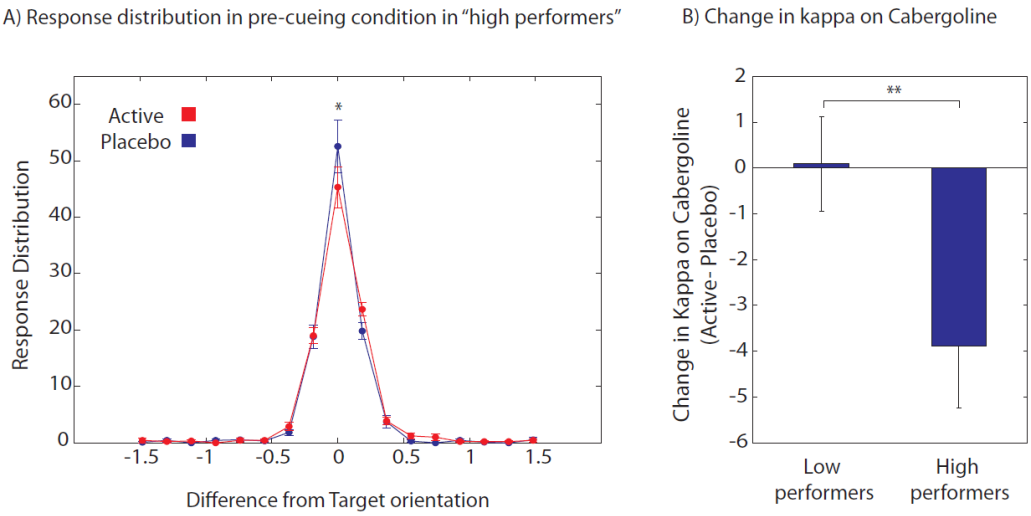


Figure 6. 6: Changes in variability of memory for the target orientation on Cabergoline.
A) Distribution of responses around target orientation in the pre-cueing condition, in high performers. As illustrated in the graph, there is a decrease in peak of the distribution when high performers were on Cabergoline compared to when on Placebo. B) Changes in κ (Active-Placebo) in both low and high performers. There is a decrease in κ in high performers on Cabergoline while no change is observed in low performers (within subject error bars).

6. 3. 5 No effect of Cabergoline in sensorimotor precision or rate of decay

The changes observed in both pre-cueing and working memory condition may be caused by changes in sensorimotor performance or simple decay of information over time. In order to investigate changes in the sensorimotor precision and rate of decay, we can examine changes in performance in the 1-item working memory task.

Any effect of Cabergoline on sensorimotor precision can be examined by looking at the effect of this drug on performance in the condition where 1 item was presented followed by a 500 msec (i.e., short) delay. There was no effect of Cabergoline on performance in this condition (paired t-test; $t(17)= 0.5$, $p>0.5$), and no correlation between change in performance in this condition and baseline performance ($r= 0.15$, $p>0.05$).

Moreover, there was no effect of Cabergoline in overall performance in this condition and at different delay intervals ($p>0.05$ for all comparisons). Therefore, maintenance of 1 item, in the absence of distractors was unaffected by Cabergoline. There was no

significant correlation between performance on placebo in this condition and change in performance on Cabergoline (r= 0.17, p> 0.05).

We then divided the participants into high and low performers based on performance in the pre-cueing condition and looked at any modulations in performance in the 1-item working memory task in these two groups of participants. There was no effect of Cabergoline on low and high performers. Any changes observed in the pre-cueing condition cannot be attributed to changes in the sensorimotor precision or changes in the rate of decay. Hence, Cabergoline appears to have specifically affected the magnitude of distractibility within a working memory task.

6. 3. 6 Interference from last items in working memory

In light of findings from the pre-cueing condition, one can argue that filtering irrelevant information in working memory is modulated by Cabergoline although the direction of this effect is dependent on individuals' baseline performance. Studies have previously highlighted the special case of last item in sequences, demonstrating that this item in the sequence is in a privileged position and is remembered better compared to earlier items (Phillips and Christie, 1977; Wright et al., 1985; Neath, 1993; Hay et al., 2007; Blalock and Clegg, 2010; Wickelgren et al., 1980b; McElree and Dosher, 1989; Öztekin and McElree, 2007; Gorgoraptis, Catalao, Bays and Husain, 2011, Chapter 3). Concurrently, previous items in a sequence are remembered with lower precision (e.g., demonstrated in Chapter 2) presumably due to interference from last item in the sequence. Performance in the working memory condition, in the present chapter, can therefore be viewed differentially for last item compared to earlier items in the sequence.

We examined the effect of Cabergoline on the extent to which precision of memory for previous items are affected by the last item in the 4 item (no pre-cueing) working memory condition. A simple measure was computed for the magnitude of interference (i.e., magnitude of distractibility caused by last item), defined as:

Equation (6.1): p(last)- p(previous)/p(total)

where p(last) is working memory precision for the last and most recently displayed item, p(previous) is average precision for all previous items and p(total) is average

precision for all items in the sequence. Therefore, a positive value for this index translates into higher interference/distractibility from the last item in the sequence.

There was no significant correlation between baseline distractibility (i.e., on placebo) and change in the magnitude of distractibility in this index on Cabergoline (r= -0.31, p<0.2). However, when participants were divided into two groups (median split based on average performance), those with high and low baseline distractibility on placebo, there was a significant effect of Cabergoline in those with low distractibility on placebo; Cabergoline increased the magnitude of distractibility in these individuals ($t(8)$= 3.1, p= 0.015- Figure 6.7). There was no significant change in performance in those with high baseline distractibility.

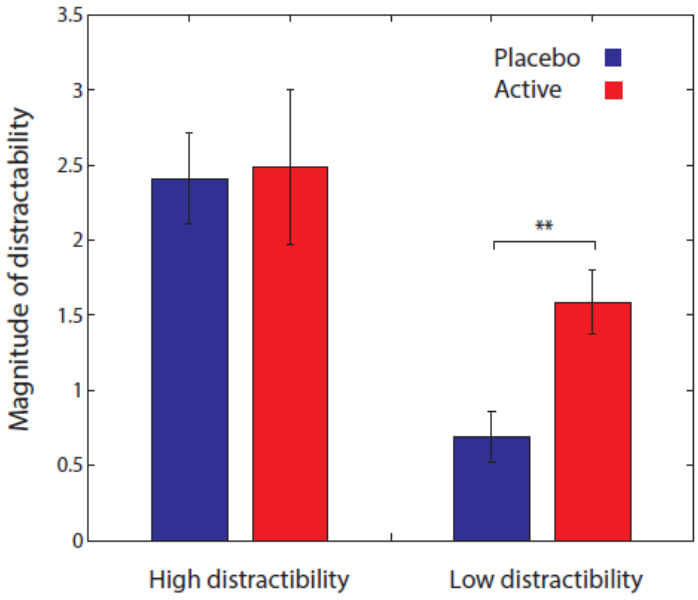


Figure 6. 7: Magnitude of distractibility in both individuals with high and low baseline distractibility. There is a significant increase in distractibility from last item in the sequence in those with low baseline on Cabergoline (within subject error bars).

These findings are in line with results from the pre-cueing condition, showing that in high performers Cabergoline impairs performance specifically increasing the magnitude of distractibility; whether it is from non-target distractors in the pre-cueing condition or the last item in the sequence in the working memory condition.

6. 4 General Discussion

Studies on the role of dopaminergic medication on cognitive performance point to an inverted U-shape relationship between performance and dopamine (for review see Cools and D'Esposito, 2011). The results from the present chapter extend previous studies, demonstrating that the direction of change in performance on a pre-cueing, working memory task on Cabergoline depends on individuals' baseline performance. Moreover, the effects were specific to the magnitude of distractibility, highlighting potentially different roles of dopaminergic medications on different processes within memory. There was no evidence that Cabergoline affected overall precision of recall when pre-cueing was not used.

Filtering abilities are influenced by Cabergoline

In the pre-cueing (filtering) study reported in this chapter, participants were asked to perform a working memory task for a pre-cued item embedded within non-targets in a sequence of 4 items. Results illustrated that Cabergoline influenced precision of memory for the target item differentially for individuals with high and low average performance. Performance of individuals with high baseline precision was subsequently impaired on Cabergoline while low-baseline performers improved on this drug. This pattern of results was observed in overall performance as well as performance at different serial positions of the target (Fig. 6.4). The effect was larger in high performers, also observed in the distribution of responses around the target orientation in this group of participants; high performers on Cabergoline responded less to the target. Probabilistic modelling of error in response further confirmed the findings that memory for the target orientation was more variable in high performers on Cabergoline compared to placebo (Fig. 6.6).

These are in line with previous studies arguing for an inverted U-shape relationship between cognitive processes and dopamine (Cools and D'Esposito, 2011). Overdosing the dopaminergic system in individuals with optimal dopamine levels (i.e., potentially our high performer group) resulted in impairment in maintenance of a pre-cued item in working memory in the presence of disctractors; i.e., resulted in higher distractibility. Since no modulation by Cabergoline was observed in a condition where no distractors

were present (1 item working memory task), one can argue that the effects of Cabergoline are specific to magnitude of distractibility in working memory, although it is not possible to conclude whether this effect was at encoding (or visual attention), maintenance, retrieval - or all of these.

Dopamine is believed to increase the efficiency of processing by augmenting signal-to-noise ratio (Sawaguchi, 1987, 2000; Lewis and O'Donnell, 2000; Meyer-Lindenberg et al., 2005). In relation to working memory, dopamine has been shown to influence task-related activity, i.e., "signal" (Williams and Goldman-Rakic, 1995; Sawaguchi, 2001; Vijayraghavan et al., 2007). At higher dopamine levels however, signal-to-noise ratio has been reported to degrade due to an overall suppression of both signal and noise (Vijayraghavan et al., 2007). Considering the increase in noise of representation on Cabergoline in high performers, one can argue that Cabergoline modulated signal-to-noise ratio only when irrelevant information was present, presumably as a consequence of this information not being fully ignored. However such a suggestion remains speculative.

Interference from last item in sequence is modulated by Cabergoline

Cabergoline did not influence performance on the 4-item sequential working memory even when baseline performance was considered. In this condition, participants were asked to maintain all four items in memory and were later probed to recall one of the items.

Our findings in the pre-cueing condition suggested that the effects of Cabergoline may be limited to filtering abilities. Since items were presented sequentially in the 4-item working memory task, it was possible to investigate the effects of Cabergoline on ability to protect earlier items from interference from the last item, i.e., to filter out information from last item when earlier items were probed as target.

The results showed that indeed similar to the pre-cueing condition, there was a baseline-dependency on the direction of effect of Cabergoine on filtering the last item from interfering with previous items. Average memory precision of items presented earlier in the sequence relative to the last item was modulated by Cabergoline in a manner that those who were good at protecting previous items were impaired on this drug.

Therefore, Cabergoline appears to have influenced a specific process within working memory, namely to modulate individual's ability to filter irrelevant information, whether in the context of a pre-cueing task where non-targets are highlighted prior to presentation of items or in a multiple item working memory task where last item in the sequence has to be filtered at recall to ensure successful performance for earlier items in a sequence.

Role of dopamine in distractability

Previous studies have highlighted the role of D2 agonists on performance in working memory processes. Specifically, in line with the findings presented in this chapter, Frank and colleagueas (2006) showed Cabergoline impaired working memory performance in a condition where distractors were presented amongst target items. Other studies using D2 agonists however have shown overall influence of dopamine on working memory performance (Kimberg et al., 1997b; Mehta et al., 1999, 2004; Luciana et al., 2004), though the tasks employed in these studies do not allow for deconstruction of components within working memory. For example, in the study by Mehta and colleagues (2001) performance in a self-ordered spatial working memory task was modulated by D2 agonist. In this task successful performance depended heavily on constant updating and maintaining information while ignoring distractors. It was not however possible to decompose performance for each of these different processes and isolate the locus of influence of D2 agonist. Therefore, the present study firstly confirms the findings of Frank et al. (2006) on modulation of distractibility by Cabergoline but also highlights the importance of investigating different aspects and mechanisms within working memory.

Chapter 7

Working memory impairments in Gaucher's disease patients and carriers

7. 1 Introduction

One of the key priorities in PD research is to detect the disease at its earliest stage so that neuroprotective therapies might potentially be used before the onset of widespread neurodegeneration (Schapira and Tolosa, 2010; Berg et al., 2012). Studies suggest that some PD patients might suffer from non-motor impairments, including cognitive

deficits, long before the onset of motor symptoms (Verbaan et al., 2007; Savica et al., 2010; Schapira and Tolosa, 2010). Such impairments potentially provide a means of prosecuting early detection. However, although screening programmes are currently being investigated, detection of deficits on a population-wide basis would be a challenging undertaking (Berg et al., 2012a).

An alternative strategy would be to target individuals who are at particularly high risk of developing PD, due for example to genetic factors. Several genes have now been associated with PD, including those that affect the lysosomal enzyme glucocerebrosidase (GBA) (Klein and Westenberger, 2012). GBA mutations represent the highest known genetic risk for developing PD (Clark et al., 2009; Neumann et al., 2009) .Classically, these mutations have been associated with Gaucher's disease (GD), a condition that results from homozygosity or compound heterozygosity for mutations in the GBA gene (Pastores and Hughes, 2011). Overall, the lifetime risk of developing PD is 21-fold greater in GD patients compared to controls (Bultron et al., 2010).

GD has been subdivided into different types based on absence (Type I) or presence (Type II and III) of neuropathology, but recent studies have shown clinical and pathological findings that point to involvement of the central nervous system even in patients classified as Type I (Sidransky, 2004; Capablo et al., 2008). In fact, several studies have now identified Type I GD as a risk factor for developing both Parkinson's disease (PD) (Sidransky et al., 2009a; Bultron et al., 2010; Rosenbloom et al., 2011) and dementia with Lewy bodies (Clark et al., 2009). Lewy bodies are considered to be the pathological hallmark of PD (Mazzulli et al., 2011). High penetrance of PD has also been reported in heterozygous carriers of the GBA mutation (Goker-Alpan et al., 2004), pointing to GBA as a PD causal dominant gene (Anheim et al., 2012). Moreover, Type I GD patients with Parkinsonism demonstrate Lewy body pathology (Wong et al., 2004).

Individuals with GBA mutations are therefore a potentially important group of people to screen for impairments that might be the earliest signs of PD. Here, we focused on cognitive deficits, which have long been associated with established PD (Bradley et al., 1989; Owen et al., 1992, 1993, 1997a; Owen, 2004). Cognitive dysfunction reported in *early* PD include poor planning, sequencing, cognitive flexibility and problem solving, and most prominently impairments in working memory and attention (Cooper et al., 1991; Owen et al., 1992; Dujardin et al., 1999; Muslimovic et al., 2005). Recently,

cognitive deficits have also been identified in individuals with GBA mutation. In fact, impairments in those *PD patients with GD* appear to be more frequent and severe compared to sporadic PD patients without GD, as measured by the Montreal Cognitive assessment (MoCA) (Brockmann et al., 2011).

GD patients and mutation heterozygous carriers *without PD* have also been shown to be impaired on the MoCA as well as a test of olfaction, both considered to be putative markers of increased risk of neurodegeneration (McNeill et al., 2012). However, based on these findings alone, one cannot conclude whether such deficits are related to GD pathology or are manifestations of early stages of PD. Indeed, since one would *not* predict that all individuals with GBA mutations would develop PD, it is quite possible that cognitive deficits identified on a population basis in GD are quite separate from those in PD.

To make a more compelling argument, it would be important to demonstrate that the *pattern* of cognitive impairment in some individuals with GBA mutation resembles that in early PD patients without a family history of GD. In this study, we examine visual working memory and any observed deficits in this cognitive process in individuals with GBA mutation.

Several early studies reported that non-medicated, newly-diagnosed PD patients show impairments on visual working memory tasks (Morris et al., 1988; Owen et al., 1992). Subsequently, large population-based samples of recently-diagnosed PD patients have confirmed this view (Foltynie et al., 2004b; Muslimovic et al., 2005). Our findings, reported in Chapter 5, also confirm that de novo PD patients suffer from deficits in visual working memory precision as measured by 4-item working memory adjustment task. This substantial body of evidence (reviewed in detain in Chapter 5) leads to the conclusion that visual working memory deficits are one of the most prominent observed in early PD.

Intriguingly, a recent report has also shown that visual working memory performance is impaired in GBA mutation carriers *with PD* (Alcalay et al., 2012). In that study, GBA mutation carriers with early-onset PD were severely and prominently impaired in visual memory tests compared to non-carrier PD patients, highlighting the possibility that there might actually be some differences in performance between the two patient groups.

Based on these findings, the authors suggested that GBA mutation might be an independent risk factor for development of *cognitive impairments in PD patients*.

However, if visual working memory deficits are a consistent abnormality in PD patients with GBA mutation, the question also arises whether one might be able to identify individuals with GBA mutations at risk of *developing PD* long before manifestation of any motor signs, using visual working memory as an index. To be able to test this hypothesis in the future, we first need to establish whether GD patients and carriers of GBA mutation *without PD* exhibit visual working memory deficits. Although cognitive dysfunction has now been shown in GBA carrier as well as full-blown GD patients without PD (McNeill et al., 2012), no previous research has been conducted specifically on detecting visual working memory impairments in such individuals.

In the present study, we employed the more sensitive measures of working memory performance, measured using the adjustment task (as employed in previous Chapters). Part of the rationale for using such a paradigm is that a continuous response measure might be a more sensitive index of working memory. Importantly, such working memory precision tasks also provide a means to dissect out sources of error contributing to the pattern of performance. By applying a recent analytical technique (Bays, Catalao and Husain, 2009) we were able to deconstruct the proportion of responses arising from each of different sources of error and to investigate whether any working memory impairments in GBA mutation cases resembles the *pattern* of working memory deficit in *de novo* untreated, recently-diagnosed PD patients. Ideally, we would seek to find cases with GBA mutation that show the same pattern of working memory impairment as in early PD.

7. 2 Methods

7. 2. 1 Participants

In total, twenty individuals with GBA mutation were tested: 9 patients with type I GD (homozygous for GBA mutation) and 11 GBA mutation carriers (without GD). None of them had a prior diagnosis of PD or dementia. Individuals who could carry

heterozygous GBA mutations were identified from relatives of those with homozygous GBA mutation by considering the family history of each proband (Table 7.1). Further carriers were recruited from the UK Gaucher's Disease Association. For comparison, fourteen recently-diagnosed, un-medicated PD patients with no family history of GD or personal history of mental illness, matched for age and years of education, were also recruited (UPDRS scores in Table 7.2). In addition, 18 healthy control participants matched to GD patients and carriers as well as PD patients for age and years of education were tested (Table 7.1). Control participants had no neurological disease or any history of GD in their family.

GBA mutation status was confirmed by sequencing exons 1 to 11 of the GBA gene using a published protocol (Neumann et al., 2009) with polymerase chain reaction (PCR) primers designed for regions of the GBA gene not found in the pseudogene. After amplification by PCR the product was run on a 1% agarose gel with ethidium bromide and size-checked to ensure it was not the pseudogene. Sanger sequencing was performed for each exon and flanking intronic sequences using the Dye Terminator Sequencing Kit (Applied Biosystems) on an ABI 3700xl genetic analyser. Demographics of GD patients and carriers are presented in Table 1 (See Table 7.3 genetic characteristics of patients and carriers). GD patients and carriers were assessed by a movement disorders-trained physician (Dr. McNeill) using the Unified Parkinson's Disease Rating Scare (UPDRS) subscales II and III (relating to daily activities and motor subscales). All patients and carriers except one patient (excluded from the rest of the analysis) scored zero on these subscales. None of the GD patients were on substrate reduction therapy.

All participants had normal or corrected to normal vision and normal colour vision. GD patients and carriers, PD patients and age-matched controls provided written informed consent to the procedure of the experiment. This study was approved by the local ethics committee. All participants scored 30/30 on the Mini Mental Status Examination (MMSE) (Folstein et al., 1975b). The rest of the protocol was carried out identically in both patients and age-matched control groups.

Table 7. 1: Demographic information on GD patients and carriers, PD patients and controls.

	Age (years) Mean (SD)	Gender Male	Female	Years of Education Mean (SD)
GD patients (N= 9)	60.5 (9)	5	4	15 (2)
Carriers (N= 11)	62 (10)	6	5	13.5 (5)
PD patients (N= 14)	65 (5)	2	8	14.5 (3)
Controls (N= 18)	60.5 (10)	9	9	15(3)

Table 7. 2: Unified Parkinson's Rating Scale scores for different subscales and overall score for all PD patients. Subscales: I: Mental, Behaviour and Mood, II: Activities of Daily Living, III: Motor Examination, IV: Complications of Therapy, V: Modified Hoehn and Yahr Staging and VI: Schwab and England Activities of Daily living Scale.

	Unified Parkinson's Rating Scale Sub-scales						
PD patients	**I**	**II**	**III**	**IV**	**V**	**VI**	**Overall**
01	3	6	17	0	1	1	28
02	1	10	9	0	1	2	23
03	1	1	4	5	0	0	11
04	3	8	14	6	1.5	1	33.5
05	1	7	6	0	1	1	16
06	3	2	4	0	1	1	11
07	4	2	4	0	1	1	11
08	1	5	10	0	1	0	16
09	5	6	9	0	1	0	21
10	5	12	15	1	1.5	2	36.5
11	1	8	11	0	1.5	1	22.5
12	3	6	6	1	1	1	18
13	2	9	10	1	1	1	25
14	4	6	11	1	1	1	24

Table 7. 3: Age, sex and genotypes of GD patients and carriers.

	Age, Sex	Genotype
GD patients		
01	69, F	N370S/L444P
02	67, M	N370S/L444P
03	44, M	N370S/Rec*Nci*I
04	59, M	N370S/L444P
05	58, M	N370S/203insC
06	57, F	N370S/L444P
07	63, M	N370S/second mutation not identified
08	55, F	N370S/V447E
09	72, M	N370S/N370S
Carriers		
10	70, M	R463C
11	66, F	N370S
12	66, M	L444P
13	65, F	N370S
14	67, M	Rec*Nci*I
15	73, M	L444P
16	73, F	V394L
17	43, F	L444P
18	42, F	N370S
19	57, M	N370S
20	61, M	N370S

7. 2. 2 Tasks

Both patient groups and healthy controls completed similar tasks as those explained in Chapter 5. Everyone completed forwards and backwards digit and spatial spans as well as sensorimotor control, 1-item working memory, pre-cueing and 4-item working memory conditions (see Chapter 5, Section 5.2.2). All GD patients and carriers, 9 PD patients and 8 of the aged-matched controls completed 20 trials of the sensorimotor task. GD patients and carriers completed 50-100 trials depending on their ability; PD

patients completed 100-200 trials and all age-matched controls performed 200 trials of the 1-item working memory, pre-cueing and 4-item working memory conditions

7. 2. 3 Analysis

For each trial, a measure of raw error was obtained by calculating the angular deviation between the orientation reported by participants and the orientation of the target item. These values were averaged for overall performance and separately for the different serial positions of the target. Unlike previous chapters, working memory precision wasn't calculated; this was due to small number of trials completed by patients.

7. 3 Results

There was no significant difference in performance between GD patients and carriers in any of the experimental or control tasks. Therefore, for the remaining analyses we collapsed the data from both groups and treated them as one group of individuals with GBA mutations (N=19).

7. 3. 1 Working memory impairments in individuals with GBA mutation and PD patients

In order to compare performance in the experimental working memory task across groups, we first calculated the difference between response angle and the correct value of the target orientation at each serial position, i.e., *when* the target was presented in the sequence. There was a significant effect of serial order on recall error (Fig. 7.1A; two-way ANOVA, main effect of serial order, $F(3, 192)= 26.03$, $p< 0.001$). All participants performed better for items presented last in the sequence compared to earlier items, demonstrating a strong recency effect which is well established for visual stimuli (Phillips and Christie, 1977; Nairne, 1988; Hay et al., 2007; Botvinick et al., 2009;

Blalock and Clegg, 2010). In addition, there was a main effect of group on memory recall ($F(2, 192)=12.4$, $p< 0.001$).

Recall error was significantly worse in individuals with GBA mutation compared to controls for the first item, penultimate one and last item (respectively $t(35)= 2.51$, $p= 0.017$; $t(35)= 2.62$, $p= 0.012$ and $t(35)= 2.76$, $p= 0.009$; Fig. 7.1A). Comparison of PD patients with controls revealed a significant impairment in performance for the penultimate and last items in the sequence ($t(30)= 3.42$, $p= 0.002$ and $t(30)= 3.33$, $p= 0.002$ respectively, Fig. 7.1A). Overall performance (collapsing across all serial positions) was also significantly worse in both individuals with GBA mutation and PD patients compared to healthy controls (respectively $t(35)= 2.8$, $p= 0.008$, 95% confidence interval of difference: 1.4-8.8 and $t(30)= 2.95$, $p= 0.006$, 95% confidence interval of difference: 1.5-8.3) (Fig. 7.1B). Thus both groups were impaired in their precision of recall on the working memory task. However, there was no significant difference in performance between individuals with GBA mutation and PD patients, either in *overall performance* or at any serial position.

Examination of the distribution of errors in relation to the target orientation also revealed that both GBA mutation and PD groups were different to controls. The proportion of responses falling close to the target orientation was lower in individuals with GBA mutation and PD compared to healthy age-matched people (Fig. 7.1C). This is illustrated by a decrease in the peak of the response distribution around the target value in both patient groups. At the peak of the distribution, there was a significant decrease in proportion of responses compared to controls in both individuals with GBA mutation ($t(35)= 2.4$, $p= 0.021$) and PD patients ($t(30)= 2.58$, $p= 0.015$).

In summary, our experimental working memory task was able to show significant impairments in both individuals with GBA mutations and unmedicated PD when conventional clinical working memory tasks (forward and backward digit and spatial span) did not reveal any differences.

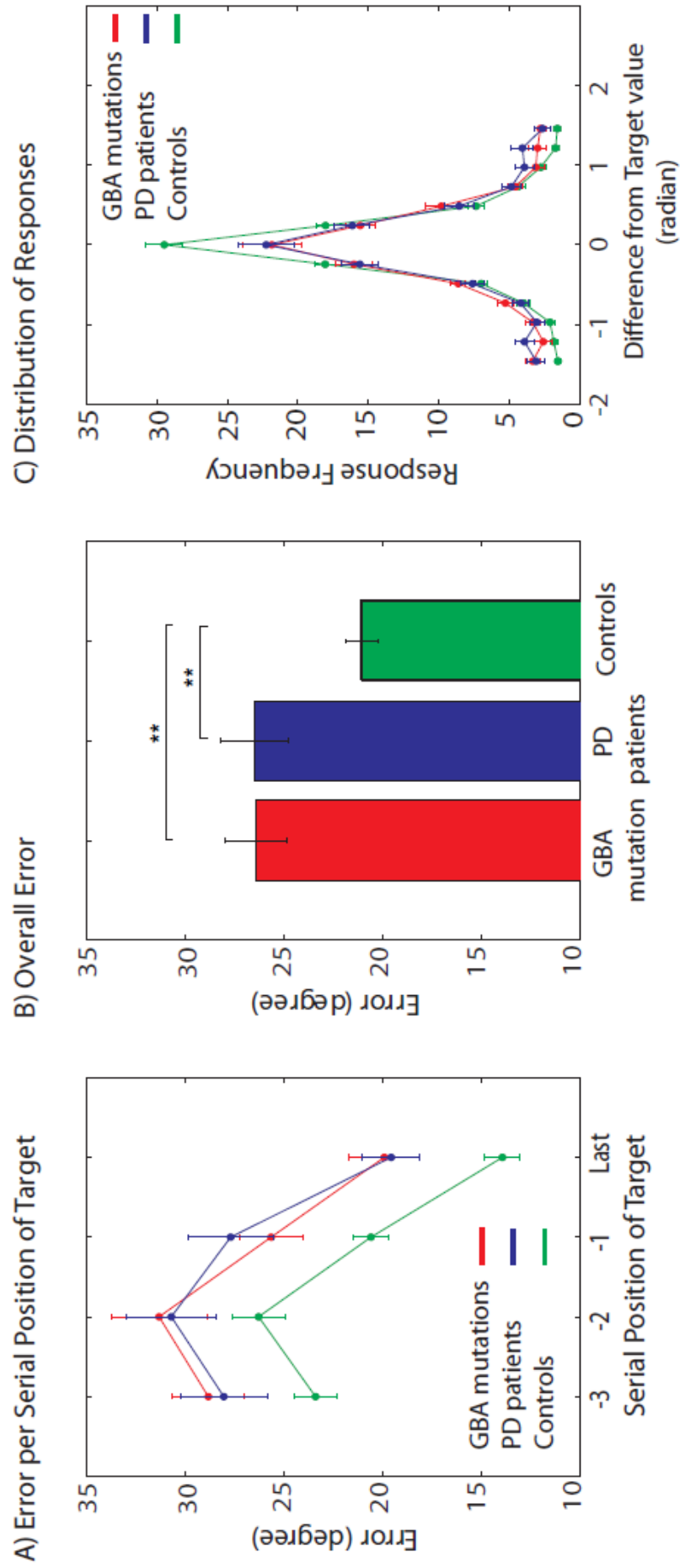


Figure 7. 1: Performance of all participants in 4-item working memory task.
A) Error at each serial position of the target, for both individuals with GBA mutation and PD patients compared to controls. Error bars represent standard error of the mean. B) Overall error in performance. Both patients with PD and those with GBA mutation make significantly more errors compared to controls. C) Distribution of responses around the target orientation for PD patients, individuals with GBA mutation and controls. Proportion of responses around the target value decreased both in PD patients and those with GBA mutation.

7. 3. 2 Sources of error in working memory impairments

Although the analysis above reveals that both GBA mutation and PD groups are impaired on the working memory task, and indistinguishable on the basis of *overall performance*, we would not anticipate that all individuals with GBA mutation would eventually develop PD. So it is also important to examine whether the *pattern of errors* made by our participants with GBA mutation are the same as those in PD patients, or whether in fact only some individuals with GBA mutation show the 'signature' of working memory impairment that characterizes PD.

In order to examine the sources of error resulting in deficits of working memory, we applied a three-component model of response error to our data that was first introduced by Bays et al., (2009, see Chapter 2). After model fitting, any individual with outlier parameter values (defined as values 2.5 SD from the mean of each parameter) were excluded. Two individuals with GBA mutation and one healthy control were excluded.

Comparison of model estimates between individuals with *GBA mutation* and healthy controls, showed no significant change in the concentration parameter between the two groups. Therefore, decrease in resolution of information in working memory cannot explain working memory deficits in our sample of people with GBA mutations (Fig. 7.2A). In line with the pattern of distribution of responses around the target orientation (Fig. 7.1C), individuals with GBA mutation responded significantly less to the *target* orientation compared to controls ($t(32)= 2.46$, $p= 0.02$; Fig. 7.2B). This decrease in probability of target responses in the GBA mutation group was accompanied by a significant increase in probability of responding to *non-target* orientations compared to controls ($t(32)= 2.34$, $p= 0.026$; Fig. 7.2C). However, there was no significant difference in the proportion of *random* responses between cases with GBA and controls (Fig. 7.2D).

Comparison of model estimates between *PD patients* and healthy controls, revealed that the proportion of responses to the *target* orientation was also significantly lower in PD patients compared to controls ($t(29)= 2.5$, $p= 0.019$; Fig. 7.2B). But, unlike the overall pattern for the GBA mutation group, this decrease in proportion of target responses was accompanied by a significant increase in proportion of *random* responses in PD patients compared to controls ($t(29)= 3.35$, $p= 0.002$- Fig. 7.2D). Furthermore – and again

unlike the GBA mutation group –there was no significant change in proportion of responses on *non-target* values in this group of patients compared to controls. Variability in memory for the target orientation, i.e., the concentration parameter, was comparable between PD patients and healthy controls. Therefore, decrease in resolution of information in memory cannot be used to explain working memory deficits in our sample of PD patients (Fig. 7.2A).

Together, these findings point to different sources of error that result in working memory impairments in PD patients and those with GBA mutation. Individuals with GBA mutation were more prone to making binding failures, that is failure to bind features within objects (here colour and orientation). Thus, their memory is corrupted by features belonging to *non-targets* (other items in the array). In contrast, information maintained in working memory in our un-medicated PD patients were more prone to *random* errors or guessing, rather than being systematically biased towards features that belong to other items in the sequence.

A direct comparison of model estimates between the GBA mutation and PD groups showed a significant increase in proportion of responses to non-target orientations in those with GBA mutation compared to those with PD ($t(29)= 3.4$, $p= 0.002$). On the other hand, the proportion of random responses was higher in PD patients compared to individuals with GBA mutation ($t(29)= 2.97$, $p= 0.006$). Thus, although both groups are impaired on our working memory task and indistinguishable in overall error, the *pattern of errors* they made is actually very different.

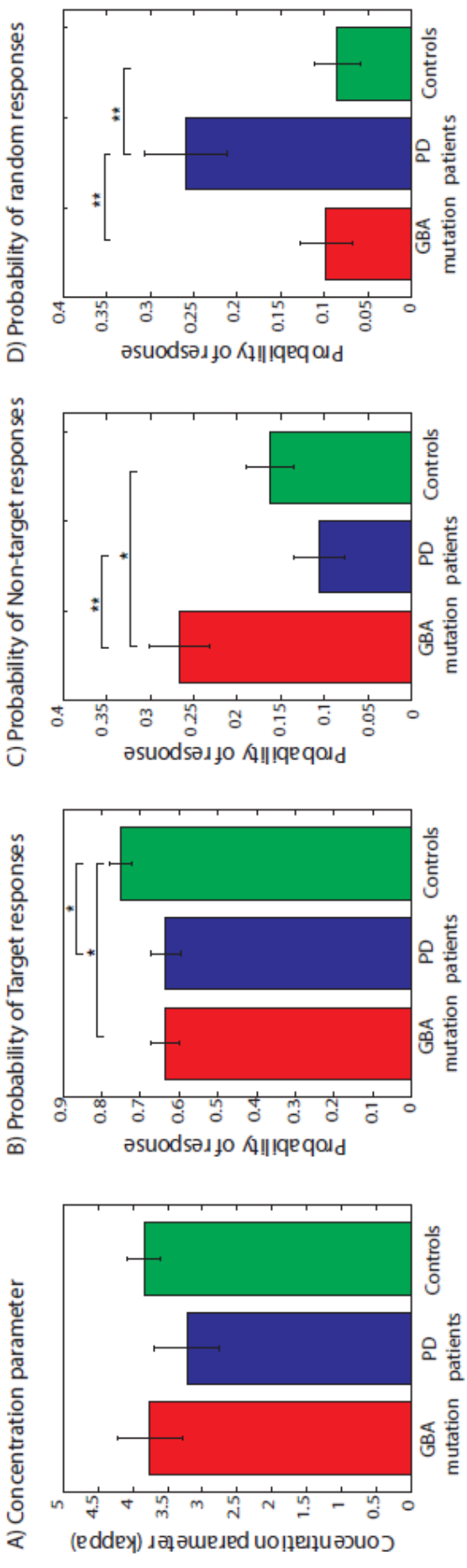


Figure 7. 2: Model estimates for different sources of error in the 4-item working memory task.
A) Concentration parameter did not differ significantly between individuals with GBA mutation and controls but was significantly lower in PD patients. B) Probability of target responses (p(T)) was significantly lower in both patient groups compared to controls. C) Probability of non-target responses (p(NT) was significantly higher in those with GBA mutation compared to both PD patients and controls. D) Probability of random responses (p(U)) was significantly higher in PD patients compared to controls (* $p<0.05$, ** $p<0.01$).

Up to now, we have considered our findings at the group level. Several studies have shown that people with GBA mutations are at a higher risk of developing PD (Goker-Alpan et al., 2004; Sidransky et al., 2009a; Bultron et al., 2010; Rosenbloom et al., 2011). But most individuals with GBA mutation do not eventually develop PD, so are there individuals within our GBA group who show the same pattern of error as unmedicated PD patients? To examine this issue we plotted the frequency of random responses for each GBA mutation and PD participant against the 95% confidence intervals of healthy controls (Fig. 7.3).

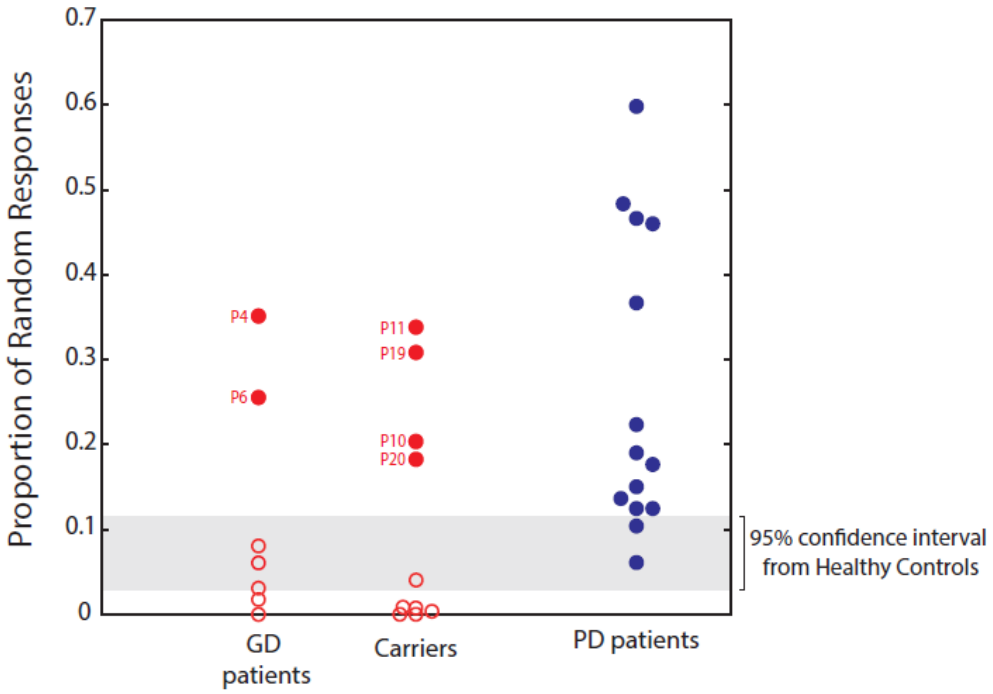


Figure 7. 3: Probability of random responses in both individuals with GD and carriers as well as PD patients.
95% confidence-intervals for normal controls are presented in grey. Highlighted patients with GBA mutation (filled red) are example of individuals with GBA mutation who show overlapping pattern of responses to those with PD, i.e., high proportion of random responses.

Although most individuals with GBA mutation make very few random responses (denoted by unfilled red circles in Fig. 7.3), there are clearly some whose pattern of error overlaps that of PD patients. Filled red circles indicate those GD patients or GBA carriers who show increased random responses outside the normal range, but in the range of PD patients. In our sample, individuals with GBA mutation labeled P4, 6, 10,

11, 19 and 20 make high frequency random responses. These people show the pattern of impairment observed overall in the GBA mutation group in responding to non-targets, but importantly they also demonstrate show the same 'signature' of error as PD patients, that is a large proportion of random responses. Using this form of analysis it is possible, therefore, to demonstrate that there is a sub-group of individuals with GBA mutation whose performance on a working memory task resembles that of untreated PD patients.

7. 3. 3 Working memory deficits cannot be explained by impairments in attentional filtering, temporal decay or sensorimotor performance

To examine whether the differences in performance on our working memory task were caused by impairments in factors other than in working memory, we analysed their performance on our three control tasks (Fig. 5.1). There was no significant difference in the attentional filtering, pre-cueing condition between the GBA mutation, PD or healthy control groups. Thus, any difference in performance between groups is unlikely to be due to difficulties in attending to items presented in a sequence. Similarly, overall performance in the 1-item working memory task at different delay intervals did not differ between the groups. Therefore, we conclude that impairments on our experimental 4-item working memory task cannot be attributed simply to *differences* between the groups in how information decays over time for single item (although, of course, this does not mean that there is no influence of maintenance duration on precision of memory). Finally, there was also no significant difference in performance between groups on the sensorimotor control task where a target bar remained on the screen and participants simply had to move a dial to rotate a probe bar to match the orientation of the target. This result is particularly important in the context of testing PD patients who might have difficulties with dexterity in using the dial. Our findings show that this is not a confounding factor in interpreting the data.

7. 3. 4 Performance in standard measures of working memory

We then examined whether impairments in working memory in individuals with GBA mutation and PD are picked up by standard measures of working memory performance,

i.e., digit and spatial spans. There was no difference in performance between individuals with GBA mutation and controls in forwards ($t(35)= 0.5$, $p= 0.6$) and backwards ($t(35)= 0.5$, $p= 0.65$) digit span. PD patients performed similar to healthy controls; no deficit was observed in both forwards ($t(30)= 0.39$, $p= 0.57$) and backwards ($t(30)= 0.96$, $p= 0.34$) digit span in PD patients compared to controls. PD patients also performed comparably to individuals with GBA mutation in forwards ($t(31)= 0.88$, $p= 0.38$) and backwards ($t(31)= 0.07$, $p= 0.9$) digit span.

Similar pattern of results was obtained for spatial span. There was no difference in performance between patients with PD and individuals with GBA compared to controls in both forwards ($t(30)= 0.3$, $p= 0.8$ for PD patients; $t(35)= 1.2$, $p= 0.23$ for those with GBA mutation) and backwards ($t(30)= 1.3$, $p= 0.2$ for PD patients; $t(35)= 0.14$, $p= 0.88$ for those with GBA mutation) spatial span. Patients with PD performed similarly to those with GBA mutation in forwards ($t(31)= 1.2$, $p= 0.26$) and backwards ($t(31)= 1.3$, $p= 0.2$) spatial span.

7. 4 Discussion

The findings presented here, to the best of our knowledge, demonstrate for the first time that individuals with GBA mutation but *without PD* show deficits compared to healthy controls in visual working memory. Performance in the GBA mutation group was comparable to that observed in the PD group. Crucially however, the pattern of error in working memory associated with GBA mutation was different to that observed in PD patients. Therefore, although both individuals with PD and GBA mutations have working memory deficits, there was a dissociation between the sources of error that resulted in such deficit.

Working memory impairments in individuals with GBA mutation and PD

Individuals with GBA mutation without PD show impairments in visual working memory, similar to that observed in de novo, un-medicated PD patients compared to

aged-matched healthy controls. Performance did not appear to depend upon gene mutation "dosage" as the impairments were indistinguishable between patients with GD and asymptomatic, heterozygous GBA mutation carriers in our sample. Importantly, deficits in working memory were not detectable on conventional clinical working memory tasks (forward or backward digit or spatial span). Recently-diagnosed, unmedicated PD patients were also impaired, again without showing any deficit on the conventional clinical working memory tasks we used. The performance in both groups could not be explained by difficulties in attending to different serial positions of a sequence, differences in temporal decay of information or sensorimotor control.

Overall, performance in the GBA mutation group was comparable to that observed in the PD group (Fig. 7.1). Crucially, however, the *pattern of errors* in working memory associated with GBA mutations was different to that observed in PD patients. As a group, those with GBA mutations made significantly greater responses to *non-targets*, demonstrating they were more prone to making binding failures, that is failures to correctly bind features (colour and orientation) of the visual items they encoded in memory (Fig. 7.2C). In contrast, un-medicated PD patients were more prone to making *random* errors or guesses, rather than being systematically biased towards orientations that belonged to other coloured bars in the sequence (Fig. 7.2D).

Working memory impairments as a marker for neurodegeneration?

These analyses revealed similarities (impaired visual working memory) as well as differences in cognitive dysfunction (pattern of working memory errors) associated with these two disorders. But there was also overlap in patterns of error. Importantly, a few individuals with GBA mutation made a high frequency of *random* responses, well above the range of healthy controls but similar to those of PD patients (Fig. 7.3). Analysis of the pattern of errors therefore demonstrates that there is a sub-group of individuals with GBA mutation whose performance on a working memory task resembles that of untreated PD patients with respect to the proportion of random responses. This deeper analysis of working memory impairments potentially provides a more nuanced perspective of working memory deficits that might be associated with GBA mutation versus those associated with PD. It points to the possibility that some individuals with

GBA mutation might be at risk of developing PD and hence demonstrate a high frequency of random responses.

Binding failures as a marker for MTL disorders?

Recently, it has been suggested that mutations in the GBA gene may be an independent risk factor for developing cognitive impairments in PD (Alcalay et al., 2012). Our findings clearly demonstrate working memory impairments in individuals with GBA gene mutation prior to manifestation of any Parkinsonian motor signs. In this group, the observed deficit arose as a result of systematic corruption/biasing of the target orientation by *non-target* items in memory. Performance in tasks similar to the one we employed in this study (Bays et al., 2009a; Gorgoraptis et al., 2011) relies on remembering both target features (i.e., orientation and colour) as well as correctly binding those features (i.e., which orientation with which colour). In individuals with GBA mutation, there was a decrease in correct maintenance of binding of features compared to controls. Hence non-target features interfered with target memory, resulting in significantly increased responses towards non-target orientations (Fig. 7.2C). This pattern of error in working memory appears to be associated with GBA mutation and is distinctly different to the increased random responses associated with PD.

Human post-mortem specimens and mouse models of GD provide some support for possible distinct memory impairments in those with GBA mutation compared to PD patients. Mutated mice carrying heterozygous mutation in the GBA gene have progressive accumulation of α-synuclein (the primary structural component of Lewy body fibrils) in hippocampal neurons (Sardi et al., 2011). In humans, Type I GD patients with dementia and PD have pathological changes in hippocampal regions CA2-3 (Wong et al., 2004). The medial temporal lobe and hippocampus appears to play a critical role in binding of information in working memory (Olson and Marshuetz, 2005; Parra et al., 2009a, 2010a; Della Sala et al., 2012). Together these findings suggest that there might be specific visual working memory *binding* deficits that occur in individuals with pathology in medial temporal lobe (MTL), including perhaps individuals with GBA mutation. We suggest that indeed these types of error (i.e., misbinding) might be a marker for detecting MTL dysfunction in different patient populations. By contrast our early PD cases displayed a different pattern of corruption of their memory,

demonstrating increased random responses, analogous to injection of noise in a neural network, which might not necessarily be specific to any particular brain region but perhaps be associated with cholinergic deficits in PD (Kehagia et al., 2010) .

Future research

Important issues remain to be determined in future investigations. Firstly, future research should focus on the nature of visual working memory deficits in PD patients with GBA mutation, comparing their performance to both those with GBA mutation without PD and non-carrier PD patients. This would help establish cognitive impairments that are purely associated with the GBA mutation and those arising as a result of neurodegenerative disorders such as PD. Prospective longitudinal studies including individuals with GBA mutation with or without PD will help establish cognitive impairments that can be used as a risk factor for developing PD.

Conclusion

To date, most studies on the nature of cognitive impairments in individuals with GBA mutation have mainly focused on individuals who have already developed PD (Brockmann et al., 2011; Alcalay et al., 2012). Here, we provide evidence for cognitive impairments that are purely associated with GBA mutation in the absence of overt Parkinsonism. We argue that visual working memory impairments can be a useful tool in order to have a better understanding of both GD/GBA mutation and its relationship with PD.

Chapter 8

General Discussion

8. 1 Introduction

The principal aim of this thesis has been to explore some of the functions of visual working memory and modulation of its mechanisms by attentional manipulation and the neurotransmitter dopamine. The research reported was divided into two sections. In the first three experimental chapters, I examined the predictions of different models of

working memory and the role of attention in these models in healthy controls. Furthermore, I attempted to investigate the relationship between attention and working memory and the role of early visual areas in working memory processes. In the last three experimental chapters I investigated the role of dopamine in working memory precision in both patients with neurodegenerative disorders and a psychopharmacological study in healthy controls.

8. 2 Summary of findings

8. 2. 1 Evidence for resource model of working memory

" The moment one has offered an original explanation for a phenomenon which seems satisfactory, that moment affection for [one's] intellectual child springs into existence, and as the explanation grows into a definite theory [one's] parental affections cluster about [the] offspring and it grows more and more dear…There springs up also unwittingly a pressing of the theory to make it fit the facts and a pressing of the facts to make them fit the theory…"

Thomas Chamberlain

For more than two decades the field of visual working memory has been dominated by a single theory, arguing for a limited capacity of 3-4 independent memory "slots", each storing information regarding an *integrated* visual object (Pashler, 1988; Luck and Vogel, 1997; Cowan, 2001; Anderson et al., 2011; Luria and Vogel, 2011). More recently however, resource models of memory have been introduced suggesting that the resolution with which an item is stored in memory is proportional to the fraction of memory resource allocated to each item. According to such models, as the number of items in memory increases, the fraction of memory allocated to each item decreases and each item is stored with less precision (e.g., Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009).

Establishment of a model requires replication of its predictions across a variety of visual features and modes of presentations. Therefore, in Chapter 2, I examined the predictions of the 'slot' and resource models of working memory for motion sequences. The findings provide evidence for the dynamic allocation of resources in working memory for sequences of items, extending the resource model to motion directions. Together with studies of memory for location, colour and orientation (e.g., Bays et al., 2009, 2011; Gorgoraptis et al., 2011; Pertzov et al., 2012), it can be argued that the resource model can be used as a general conceptual framework for understanding visual working memory across a range of visual features.

Furthermore, in Chapter 2, two current computational models of the sources of error in working memory (Zhang and Luck, 2008; Bays et al., 2009) were compared head to head. Both models include terms for variability of memory around the target (probed) item and random errors (guessing). However, the model proposed by Bays et al. (2009) accounts for an important additional source of error: the proportion of misbinding errors in working memory. In other words, errors that arise as a result of systematic biasing of target by non-target items retained in memory. The findings demonstrated that Bays et al.'s (2009) model provides a significantly better fit for our data, providing evidence for the existence of a source of error that was not accounted for by a previous computational model of error in working memory (Zhang and Luck, 2008). Moreover, I showed that items presented earlier in a sequence are more prone to this additional source of error. Thus the re-distribution of memory resource for earlier items, when novel items are introduced in memory, comes with a cost, specifically making these items more susceptible to misbinding errors.

The resource model, although a good starting point, is far from a complete model of working memory. Recently, a later version of the resource model was put forward proposing that the resource is not only continuous but also variable across items and trials, resulting in random fluctuations in encoding precision(Berg et al., 2012). According to this model, memory limitations should be conceptualized by considering the quality of encoding; items are not discarded but their fidelity of encoding could by chance be very low resulting in an apparent capacity of about four items. Notwithstanding these considerations, the experimental evidence and new models of working memory pose a serious challenge to the notion of discrete slots in visual working memory.

8. 2. 2 Role attention in resource model of working memory

Attention and working memory are intimately connected constructs, both in terms of behaviour and neural substrate (e.g., Awh & Jonides, 2001; Chun, 2011; Chun, Golomb, & Turk-Browne, 2011; Lavie, 2005; Rensink, 2000; Wheeler & Treisman, 2002b). It has been illustrated that attention plays an important role in different stages of working memory processes, from influences during the preparatory period (Schmidt et al., 2002; Bollinger et al., 2010) through to selection and encoding (Vogel and Machizawa, 2004; Vogel et al., 2005) as well as maintenance of information in working memory (Awh et al., 1998; Jha, 2002; Postle et al., 2004).

Behavioural findings on the role of attention in maintenance of bound information

Different models of working memory agree on the highlighted role of selective attention in selection and encoding of information in working memory. In Chapter 2, I demonstrated that selective attention enhances working memory precision, specifically memory for correct binding of visual features in memory. Furthermore, in Chapter 4, findings from dual-task experiments (requiring participants to perform attention-demanding tasks while they maintained information in working memory) point to a cross-modal attention resource that is essential for maintenance of bound representations in working memory. Taxing this resource while participants retained visual information resulted primarily in a specific type of error: *feature binding failures*. Therefore, attention appears to be a crucial process for both successful encoding and retention of bound representations in visual working memory.

These findings are in line with current advances in resource models of working memory. Recently it has been shown that errors in recalling the colour and orientation of an object can be quite uncorrelated (Bays et al., 2011), suggesting independent storage of each feature category. It was thus suggested a further mechanism is needed to maintain the bound information of independently stored features (Bays, Wu, & Husain, 2011). Considering the findings in Chapter 4, I suggested that maintenance of integrated objects depends heavily on available resources that are also deployed in attention-demanding tasks such as visual search. Further, selective attention at the time of encoding protects items in working memory from biding failures (Chapter 2).

Neural correlate of items in working memory

Recent conceptual models of working memory suggest different states of items within working memory (e.g., Oberauer, 2002, 2006): items that are in the focus of attention (FOA) and all other items held in working memory. Items can gain the status of being in FOA by either being the item most relevant to the task in hand or presented last in a series of relevant items. It has further been suggested that the items in FOA are the only items maintained in early sensory areas (Olivers et al., 2011). In Chapter 3, I demonstrated, for the first time, a causal role of an early visual area important for perception of motion (MT+) in retention of memory representation in a theoretical FOA. This special state was achieved either by prioritizing one item in memory for the next cognitive operation (Chapter 2, section 3.2, Experiment 1) or by manipulating the temporal context of items (Chapter 2, section 3.3, Experiment 2). Thus, the memory for motion directions in this conceptual state, regardless of how they achieved this *special* state, can be disrupted with TMS applied to MT+.

These findings have important theoretical application, firstly highlighting the close relationship between attention and working memory and also the need to dissociate items with different "states" in working memory. The results challenge the notion that all items are retained in working memory with equal fidelity (as stated by object-limit models), instead providing evidence to support recent theoretical concepts suggesting that items in working memory are represented in different states (i.e., in and out of FOA).

Together these findings illustrate the close relationship between attention and working memory in different stages of memory processes as well as the importance of understanding these relationships specifically for current neural and conceptual models of working memory.

8. 2. 3 Role of dopamine in working memory processes

In the second part of this thesis I focused on understanding the role of dopamine on different working memory processes in both individuals with dopamine dysfunction (i.e., PD patients) and in healthy participants.

Dopamine improves working memory in PD patients

The results from Chapter 5 point to working memory impairments in *de novo* untreated PD patients that are known to have dopaminergic dysfunction. Precision of working memory was significantly improved such that it was not significantly different to normal following 3 months of dopaminergic medication. Further, 12 hour withdrawal from regular dopaminergic medication impaired working memory precision to levels comparable to untreated PD patients, again highlighting a key role of dopamine in working memory function. These findings extend previous literature on temporal progression of PD and the influences of dopaminergic medication, designed to target motor symptoms, on cognitive function (Verbaan et al., 2007; Schapira and Tolosa, 2010).

In this study, we employed a more sensitive measure of working memory; calculating precision of recall. This method allowed us to detect small changes in performance as well as understanding the nature of sources of error modulated by dopaminergic medication. Recently, studies have highlighted the importance of employing more sensitive measures of working memory performance using tasks similar to the one used in the present chapter (Bays et al., 2009; Gorgoraptis et al., 2011). Future studies examining working memory performance in different groups might profitably employ these measures because it is possible that classical methods (such as change detection or span measures) might not be as sensitive nor as informative about the mechanisms underlying working memory impairments.

Cabergoline increases distractibility in working memory in healthy controls

As demonstrated in Chapter 5, dopaminergic medication can improve working memory precision in patients who are otherwise seemingly unimpaired (for example on span

measures). A question that rises naturally is whether dopaminergic medication can also be used to improve working memory function in healthy participants. We aimed to address this issue in Chapter 6, investigating the role of Cabergoline (a predominantly D2 receptor agonist) on different processes within working memory. The results would be consistent with an inverted U-shaped relationship between distractibility and dopamine, suggesting that effectively 'overdosing' the dopaminergic system in individuals with high baseline performance results in impaired performance.

Precision of memory recall of an item embedded within distractors (pre-cueing condition- Chapter 5, Fig. 5.1B**)** was significantly impaired on Cabergoline in individuals with high baseline performance. The inverted U-shaped principle applied to these findings is illustrated in Figure 8.1. In individuals with low baseline distractibility (i.e., those with high precision of memory for the target item), Cabergoline impaired performance (illustrated in green). However, those with relatively high baseline distractability, improved on this medication (blue line). It is important to note, however, that the improvement in these individuals failed to reach significance presumably because these individuals were in the lower half of the normal range rather than being pathologically impaired.

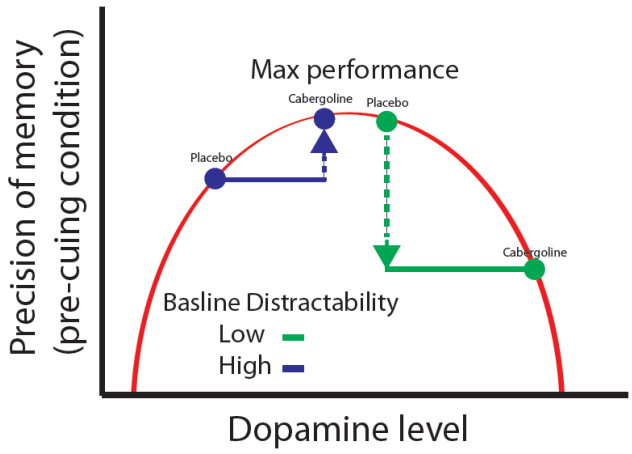


Figure 8. 1: Inverted U-shaped model describing the effects of Cabergoline on participants with low and high distractibility on placebo.

An important finding of Chapter 6 was the specific effect of Cabergoline within working memory processes, influencing only distractibility (as indexed by the pre-cueing method and also the recency effect in the 4-item working memory task I used). The effects were observed in conditions where distractors were presented during the encoding phase or whether the representation of the last item in working memory had to be filtered out when recalling earlier items in a sequence. Such a specific influence of Cabergoline is in line with previous research demonstrating modulation of distractibility by Cabergoline (Frank and O'Reilly, 2006).

The majority of human psychopharmacology studies, however, have failed to distinguish different mechanisms within working memory that are influenced by different medication (e.g., Kimberg, D'Esposito and Farah, 1997; Mehta et al., 1999, 2004; Luciana et al., 2004). The results of Chapter 6 demonstrate the importance of investigating various aspects and mechanisms within working memory in isolation since dopaminergic medication can have differential effects on these mechanisms. This is essential to provide a clear comprehensive understanding on the relationship between neurotransmitter functions and working memory.

8. 2. 4 Working memory as a candidate marker for neurodegenration

One of the key priorities of research with different neurological disorders is to detect the disease at earliest stage to improve diagnosis and treatment monitoring in patients. Studies suggest that PD patients suffer from deficits in working memory, detectable at early stages of this disease (e.g., Morris et al., 1988; Owen et al., 1992; Foltynie et al., 2004; Muslimovic et al., 2005; Owen et al., 1997; Postle et al., 1997; Chapter 5). Such impairments potentially provide a means of prosecuting early detection. However, screening for deficits on a population-wide basis would be a challenging undertaking (Berg et al., 2012). An alternative strategy would be to focus on individuals who are at high risk of developing PD, due to genetic factors for example.

In Chapter 7, I investigated whether individuals with GBA mutation who are known to be at significantly higher risk of developing PD, also show impairments in working memory like PD patients. I provided evidence for a pattern of working memory impairment that is associated with GBA mutation and a different pattern of deficit

associated with early stages of PD. However, I also found that the pattern of cognitive impairment in some individuals with GBA mutation resembles that in early PD patients, possibly pointing to early stages of neurodegeneration in these patients.

These findings serve several important purposes. First, they contributed to our understanding of the genetic basis of a key cognitive process. Second, these findings aid in establishing working memory deficits as a potential marker for neurodegeneration. The final purpose of this research concerns treatment of individuals with GBA mutations as currently the therapies employed focus on non-neuronopathic impairments in these individuals (Weinreb et al., 2002). If there are cognitive deficits (as illustrated in Chapter 7) associated with GBA mutation cases, it might be important to determine whether such treatment might protect against deterioration in these cases, regardless of their risk of developing PD.

Misbinding errors- marker for medial temporal disorder?

As the results of Chapter 8 indicate, individuals with GBA mutation make significantly more *misbinding errors* compared to both PD patients and age-matched healthy controls. Their recall is corrupted by features belonging to other items in the memory array than the object that was probed. I speculate that this specific impairment might be related to possible dysfunction of the medial temporal lobe (MTL). Human post-mortem and mouse models of Gaucher's disease and individuals with GBA mutation have demonstrated pathological changes in MTL (Wong et al., 2004; Sardi et al., 2011). Moreover, studies have demonstrated a role of MTL in binding of information in working memory (e.g., Olson et al., 2006), a process that is impaired in individuals with Alzheimer's disease (Parra et al., 2009b, 2010b) who are considered to have MTL dysfunction. Together, these findings suggest that there might be specific visual working memory binding deficits that occur in those with MTL pathology, including, perhaps those with GBA mutation.

Consistent with these suggestions, similar findings have been detected in individuals with MTL damage associated with voltage-gated potassium channel antibody in tasks in which participants were required to remember the identity and location of objects (Pertzov and Husain, 2012). These individuals showed increased proportion of

misbinding errors compared to healthy participants; supporting the role of MTL in binding features in working memory. Considering the evidence, I would suggest that such misbinding errors might be a candidate marker for detecting MTL dysfunction in different patient populations. This is not to say that misbinding errors might not also result from damage elsewhere in the brain, e.g., misbinding at encoding occurring from parietal damage (Friedman-Hill et al., 1995).

8. 3 Future research

8. 3. 1 Role of oscillatory activity in working memory

In the studies reported in this thesis, I aimed firstly to examine current models of working memory and the role of attention in these processes, behaviourally and using pharmacological and TMS modulation. However, the exact neural mechanisms underlying these cognitive abilities remain to be fully established. There are currently a variety of hypothesis on neural substrates supporting working memory mechanisms. These include theories of sustained activity (e.g., Smith and Jonides, 1997; Bisley et al., 2001, 2004; Postle et al., 2003; Ranganath et al., 2004; Serences et al., 2009), neural oscillations (e.g., Jensen, 2006; Sauseng et al., 2009, 2010; Axmacher et al., 2010), functional connectivity (e.g., Zanto et al., 2011) or through temporary weight changes in hidden states of neuronal populations (Mongillo et al., 2008; Buonomano and Maass, 2009).

There is converging evidence demonstrating that persistent firing of neurons, known to support working memory processes, has an oscillatory character. More specifically, the frequencies involved are in the theta and gamma (4-8Hz and 30-100Hz respectively) ranges (e.g., Jensen et al., 2002; Jensen, 2006; Düzel et al., 2010; Jafarpour et al., 2012). Recently, the theta-gamma coding scheme of working memory has been proposed, arguing that different memory items are represented by different groups of active cells that fire in different gamma cycles of a theta cycle (e.g., Jensen and Lisman, 2005; Lisman, 2010). According to this view, each item in memory is associated with a different theta phase and in cases where multiple items are retained in memory, the full

pattern of oscillations, repeat on subsequent theta cycles. In other words, groups of neurons that represent a single item in memory, may fire on each theta cycle, but do so only in a given gamma subcycle.

The replay of information during maintenance has recently been investigated using multivariate pattern classifier (MVPC) decoding of Magnetoencephalography (MEG) signals (Fuentemilla et al., 2010). In that study, MVPC analysis demonstrated replay of stimulus features during memory retention. The periodicity of replay events was phase-coupled to theta oscillations and importantly correlated with the ability to identify the images. These findings, together with studies showing that neuronal spiking tends to be phase-locked to specific phases of theta and gamma oscillations (Jacobs et al., 2007), would indeed be compatible with a role of oscillations in active maintenance of information (Jensen and Lisman, 2005; Siegel et al., 2009). Further, it has been hypothesized that during maintenance of sequential items, retained information is active also in sequential gamma subcycles, thereby encoding order of items (e.g., Jensen and Lisman, 2005; Lisman, 2010; Jafarpour et al., 2012). However, the extent to which this is the case remains to be tested.

It is possible that the theta-gamma scheme might be able to explain the capacity limits observed in studies of working memory. There might be a limit on the number of gamma oscillations that can be represented within a theta cycle. If fidelity/resolution of retained information is represented in the qualities of gamma cycles (that is, if more precise items are represented at a lower range of gamma frequencies) fewer items can be represented with higher precision. Tasks that measure working memory precision in conjunction with MVPC techniques and MEG, might profitably be used to test whether the qualities of gamma oscillations also represent precision with which items are stored in memory.

What about items represented at different "states" within working memory? Can oscillatory activity provide insight into how this is accomplished? Activity within the alpha range is known to correlate with inhibition. That is, at the peak of alpha cycle, inhibition is strongest (Klimesch et al., 2007; Jensen and Mazaheri, 2010). Interestingly, the brain state prior to presentation of highly distractable items demonstrates an increase in alpha power (Bonnefond and Jensen, 2013). Posterior alpha oscillations, as suggested more recently, can be a mechanism for prioritizing and ordering visual information

according to their relevance (e.g., Jensen and Mazaheri, 2010; Jensen et al., 2012). If one considers a similar role of alpha for items in working memory, the phase coupling of gamma-alpha cycles might provide a mechanisms for "sorting" items in memory according to relevance/state. In other words, prioritizing and sorting items in memory can occur through nesting information on alpha activity; low priority items are nested at peaks of a cycle while high priority items are presented at troughs of alpha cycle.

One way to test such a hypothesis is to conduct Electroencephalography in conjunction with TMS. In a task similar to the one presented in Chapter 3, Experiment 3.1; TMS after the presentation of retro-cue can be applied at different phases of alpha, testing whether the cued items is nested at trough of this cycle or not. Although our understanding of the role of oscillatory mechanisms underlying working memory processes has advanced considerably, there remains many unresolved issues (as demonstrated by the few examples mentioned here) that have yet to be unravelled.

8. 3. 2 Working memory as a cognitive marker for brain disorders

Increased random responses – a cognitive marker for PD?

One critical finding from the work presented here was the possibility of identifying a cognitive marker for PD. Working memory precision was impaired in PD patients pre-medication and this was specifically due to an increased proportion of random responses. To identify and establish these errors as a cognitive marker for early stages of neurodegeneration, further research is essential. One possible step might be to screen for these specific impairments on a population-wide basis- using adjustment tasks of measuring working memory precision. However, this would be a massive undertaking and, of course, although working memory impairments might be a sensitive marker of PD, I would not expect them to be specific to only individuals at risk of developing this condition.

Perhaps a better strategy would be to focus on individuals already at higher risk of developing PD such as individuals with genetic risk factors other than GBA mutation. Such cases would provide a great opportunity to test and establish whether increased proportion of random response can indeed distinguish those who will develop PD. In addition, it would be important to follow-up the GBA mutation cases that I have

identified to be potentially at risk of developing PD to determine if this really is the case over time. Moreover, it is important to test those with GBA mutation who already suffer from PD to see whether they exhibit the pattern of impairments associated with both disorders (increased misbinding as well as random responses, respectively). In the future, I aim to examine pattern of impairments in individuals with GBA mutation with PD, on and off domapminergic medication, to further our understanding of the progression of working memory deficits in PD.

Increased misbinding error – a cognitive marker for MTL pathology?

A common pathology associated with individuals with GBA mutation is pathological changes in MTL (Wong et al., 2004; Sardi et al., 2011). The MTL is crucial for maintenance of bound features in memory with MTL dysfunction resulting in an increased proportion of such errors (e.g., Olson et al., 2006; Parra et al., 2009, 2010). The data from individuals with GBA mutation in Chapter 7 and recent work from our group showing increased "swap" or misbinding errors with MTL pathology (Pertzov and Husain, 2012) demonstrates that increased misbinding errors might be used as a marker for MTL pathology.

To establish whether these errors can be put forward for detecting such pathology, we need to test patient groups with MTL pathology on a variety of working memory tasks. Importantly, the nature of these types of errors needs to be better understood. Do they arise due to failure to bind features of objects at encoding and a further confusion of participants at the time of recall, which is exaggerated in MTL patients? Or alternatively do participants actually misbind information, *maintaining* the incorrect feature conjunctions? Furthermore, are there specific oscillatory characteristics of misbinding errors?

The nature of these errors may be better understood by examining participants' subjective confidence ratings on the quality of their memories. If these errors are a result of actual misbinding of features, individuals' confidence ratings of their memories should be high. The role of oscillations and phase synchronization in binding and maintenance of features and the nature of impaired mechanisms in individuals with MTL pathology is still unknown.

8. 4 Conclusion

In this thesis, I have attempted to examine a few aspects of working memory in healthy people and patients. In so doing it has become clear how much we do not know – as well as how much we have learnt – about this fundamental cognitive process. This is an exciting time for research in this area and its application to clinical problems. Perhaps, over the coming years, studies of higher cognitive functions such as working memory might profit from the application of emerging behavioural and computational methods to imaging and intervention techniques such as TMS to produce a more detailed understanding of the nature of cognitive mechanisms. Importantly, the interaction between working memory and other psychological processes – such as attention, novelty and reward – is not sufficiently understood and is a potentially rich area for investigation.

Finally, I would like to emphasize the application of this type of research on the lives of patients with neurological disorders. The benefits of understanding the cognitive abnormalities in individuals with brain pathology is twofold. It firstly advances our knowledge of brain structures that support various cognitive functions. Secondly, and of great importance, are the implications of such research on various aspects of patient's lives: early detection, diagnosis and even treatment.

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