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Visual Working Memory

in Health and Disease

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Abstract

The ability of the nervous system to retain, manipulate and use visual information which is no longer present in the external environment contributes to intelligent behaviour. A new approach to studying visual working memory has led to re-evaluation of the nature of its limitations in keeping with a finite memory resource which is flexibly distributed across space according to attentional priority.

Using a novel behavioural paradigm to study visual working memory precision for sequentially presented items, I demonstrate how the resolution with which healthy subjects recall simple objects changes dynamically with each new item in the sequence. Stochastic modelling of the distribution of responses suggested that memory for earlier objects in the sequence was especially prone to failure in integration of visual features, such as orientation and colour, into complete objects.

Next, I examined how memory precision was affected by attentional selection according to the relative behavioural relevance of objects in a sequence, and explored the limitations in this filtering process and their relationship with performance on standard measures of memory and intelligence.

The role of updating of non-spatial visual working memory across time was then examined in patients with visual neglect following right hemisphere stroke, revealing a profound non-spatial impairment in WM and its voluntary attentional control in neglect, when compared to stroke patients without neglect and healthy control subjects. Lesion analysis identified separable neural correlates of these deficits.

Dopaminergic activity in the prefrontal cortex and basal ganglia has a pivotal and complex role in mediating and controlling working memory and attentional processes. In a randomised, double-blind, placebo controlled study, employing a replicated ABA N-of-1 randomised design, I tested the hypothesis that the dopamine agonist rotigotine improves visual neglect following right-

hemisphere stroke. Rotigotine was associated with significant improvement in visual search, an effect that appears to have been mediated by an enhancement of selective, goal-directed attention.

The medial temporal lobe (MTL) has an established role in supporting long-term memory processes, but its involvement in working memory has been debated recently. I studied visual working memory for sequentially presentated objects in four patients with MTL lesions and found that short-term memory can be compromised in such individuals.

Overall, this thesis explores how visual working memory is updated dynamically across time according to attentional priority in health, how these processes are affected in patients with visual neglect following right hemisphere stroke and in those with medial temporal lesions, and how a dopamine agonist might ameliorate visual neglect by modulating selective attention. The thesis concludes with a brief discussion suggesting further research directions.

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Publications related to this thesis

Chapter 2 and parts of Chapter 3 have been published in *The Journal of Neuroscience* (Gorgoraptis et al., 2011).

Chapter 5 has been published in *Brain* (Gorgoraptis et al., 2012). Further analysis of patient data acquired off medication produced a methodological article by Dr Bjoern Machner in the *Journal of Neurology, Neurosurgery & Psychiatry* (Machner et al., 2012).

Data from Voltage-Gated Potassium Channel Antibody-associated encephalitis patients presented in Chapter 6 have been included in a publication by Dr Yoni Pertzov, currently in press in *Brain* (Pertzov et al., 2013).

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List of Abbreviations

AB	Attentional Blink
AMIPB	Adult Memory and Information Processing Battery
Ang	Angular Gyrus
ANOVA	Analysis Of Variance
COMT	Catechol-O-Methyltransferase
CT	Computed Tomography
DTI	Diffusion Tensor Imaging
EEG	Electro-Encephalography
FEF	Frontal Eye Fields
FIT	Feature Integration Theory
fMRI	Functional Magnetic Resonance Imaging
HSV	Herpes Simplex Virus
IFG	Inferior Frontal Gyrus
IPL	Inferior Parietal Lobule
ISI	Inter-Stimulus Interval
IVIg	Intravenous Immunoglobulins
LTM	Long-Term Memory
MCA	Middle Cerebral Artery
MEG	Magneto-Encephalography
MHRA	Medicines and Healthcare products Regulatory Authority
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
NRES	National Research Ethics Service
PCA	Posterior Cerebral Artery
PD	Parkinson's Disease
PET	Positron Emission Tomography
RMT	Recognition Memory Test
ROI	Region Of Interest
RT	Reaction Time

SD	Standard Deviation
SEM	Standard Error of the Mean
SLF	Superior Longitudinal Fasciculus
SPM	Statistical Parametric Mapping
STM	Short-Term Memory
VGKC	Voltage-Gated Potassium Channels
VLSM	Voxel-based Lesion-Symptom Mapping
VOI	Volume Of Interest
VOSP	Visual Object and Space Perception Battery
VSTM	Visual Short-Term Memory
VWM	Visual Working Memory
WAIS-III	Wechsler Adult Intelligence Scale, Third Edition
WM	Working Memory

Chapter 1

General Introduction

> Once, in his first term, Cartwright had been bold enough to ask him why he was clever, what exercises he did to keep his brain fit. Healey had laughed.
> "It's memory, Cartwright, old dear. Memory, the mother of the Muses... at least that's what thingummy said."
> "Who?"
> "You know, what's his name, Greek poet chap. Wrote the Theogony... what was he called? Begins with an 'H'."
> "Homer?"
> "No, dear. Not Homer, the other one. No, it's gone. Anyway. Memory, that's the key."
>
> *The Liar,* Stephen Fry

1.1 The concept of visual working memory

In Hesiod's Theogony, Mnemosyne, the embodiment of memory, gives birth to the Muses; a poetic symbolism on the significance of memory for human creativity (Athanassakis, 2004). We can appreciate intuitively the importance of memory in the behaviour of humans and other animals: perception, action, and, indeed, survival, often depend on the ability of the nervous system to store information which no longer exists in the external environment. However, understanding the cognitive mechanisms and neural substrate of memory has proved less intuitive, and remains a central question in cognitive neuroscience

since the emergence of the field (Milner et al., 1998).

Inspired by studies on focal lesion patients showing selective memory impairments (Scoville and Milner, 1957; Baddeley and Warrington, 1970; Shallice and Warrington, 1970) and also taking into account findings from behavioural experiments on healthy subjects (Sperling, 1960, 1963; Phillips, 1974), early cognitive models attempted to parcellate memory into dissociable components. In an influential model, Atkinson and Shiffrin (1968), suggested memory consists of multiple stores: sensory memory, a passive, high-fidelity system which keeps information for up to a few hundred milliseconds, short-term memory (STM), which can hold a strictly limited amount of information for up to a few seconds, and long-term memory (LTM), in which an immeasurably large quantity of data can be stored, sometimes for a lifetime.

Working memory (WM) refers to the temporary retention of information when it is no longer present as sensory experience and to its manipulation and use in guiding behaviour (Postle, 2006; Baddeley, 2007; D'Esposito, 2007). The term was introduced to emphasise that information within short-term memory is actively maintained, and used to inform goal-directed action (Miller et al., 1960; Baddeley, 2003, 2007). Baddeley and Hitch (1974) proposed a tripartite model that has dominated the concept of WM. According to these authors, WM is a distinct cognitive system, consisting of three components: the central executive, the phonological loop, and the visuo-spatial sketchpad. The latter two components are considered as subsidiary systems under the control of the central executive. A further component, the episodic buffer, was added more recently (Baddeley, 2000). The need for a system with multiple parts was based on experiments where concurrent tasks disrupted WM within the same component, for example, repeating a word during a verbal WM task impaired performance (Baddeley et al., 1975), while two tasks from different domains did not interfere with each other (Repovš and Baddeley, 2006).

In contrast to this modular view of WM, other authors emphasised the close relationship of WM with attention and LTM (Cowan, 1999; Awh and Jonides, 2001; Awh et al., 2006). Cowan (1988, 1999) put forward an embedded

processes model, according to which WM is organised in multiple embedded levels. The first level consists of LTM representations that are activated; there is no limit to the number of representations at this level. The second level is called the focus of attention, and this is regarded as capacity limited and able to hold approximately up to four representations (Cowan, 1999).

The present thesis focuses on visual working memory (VWM), i.e. WM for visually perceived, non-verbal material, without necessarily considering it as an independent, self-contained system, but adopting the view that the cognitive and neural overlap between memory systems and their relationship with attention and executive control are empirical questions. VWM refers to the retention of visual information for a few seconds, so that it can be used in the service of ongoing cognitive tasks (Luck, 2008). VWM is maintained across eye movements and blinks, and it may have an important role in preserving continuity across these interruptions (Bays and Husain, 2007; Luck and Hollingworth, 2008). The term visual short-term memory (VSTM) has been used by some authors to describe the visual storage component of WM (Alvarez and Cavanagh, 2004; Todd and Marois, 2004; Luck, 2008). VSTM and VWM will be used interchangeably in this thesis, with preference to the latter term.

In this chapter I will attempt to delineate the concept of VWM by considering some key questions that stimulate ongoing research. First, how do the contents of VWM constrain its capacity limits? Second, does binding of visual features, such as colour and shape, into integrated objects, place any constraints on VWM? Third, how does goal-directed attentional control modulate VWM? Fourth, how is VWM maintained and updated across time? Finally, I will review selected neural data which have been crucial in shaping current understanding of VWM, and are pertinent to the empirical work on focal lesion patients presented in Chapters 4 to 6 of this thesis.

1.2 Capacity and resolution limits in visual working memory

Perhaps the most characteristic property of VWM is its limited capacity (Baddeley, 2003; Cowan, 2005). Defining these capacity limits is important in order to understand the cognitive mechanisms of VWM and the constraints that these place on neural models of VWM. This line of research has wider implications, given the strong correlation of VWM capacity measures with general fluid intelligence (Conway et al., 2003; Jaeggi et al., 2008), and its role in many neurological and psychiatric disorders (Park et al., 2003; Silver et al., 2003; Mehta et al., 2004a; Malhotra et al., 2005). The nature of VWM capacity limits has been an area of intense debate recently (Bays and Husain, 2008; Zhang and Luck, 2008; Bays et al., 2009). In the following paragraphs, I will review the key evidence that has informed this debate.

1.2.1 Item-limit theory of VWM

Early studies on the capacity of short-term memory used brief displays containing alphanumeric characters, which subjects had to report back from memory (Sperling, 1960). These studies showed a typical capacity limit of 4 to 5 characters, but it is not clear whether these were stored visually or verbally. Phillips (1974) examined memory across brief presentations using purely visual, non-verbal stimuli: matrices of varying complexity, consisting of different numbers of randomly arranged filled and unfilled squares were briefly displayed, subjects were asked to memorise them, and report whether the memorised matrix was the same or different to a probe one. These experiments provided evidence for two distinct visual memory processes: a fragile, high-fidelity system of sensory memory, which is disturbed by visual masking, now known as iconic memory (Di Lollo, 1977; Coltheart, 1980), and VWM, a more durable system, the limited capacity of which was demonstrated by a decrement in performance for matrices larger than 4x4 squares (Phillips, 1974).

The sequential comparison procedure introduced by Phillips evolved into the standard way of studying VWM subsequently (Pashler, 1988; Luck and Vogel, 1997; Vogel et al., 2001; Luck, 2008). Luck and Vogel (1997) used a similar design, known as change detection task (**Figure 1.1A**): an array with a varying number of coloured squares was briefly displayed, followed by a probe array, which could either be the same, or contain a change in the colour of one of the squares. Subjects were asked to make a simple judgement from memory on whether the test and probe arrays were the same or different. Detection remained close to 100% for arrays of few (1-3) items, and it declined sharply when set size exceeded 4 items. Critically, the same item limit was observed not only in memory for single features, including colour and orientation, but also for items consisting of conjunctions of two features, i.e. orientation + colour in arrays of coloured bars, and colour + colour in arrays of composite, two-colour squares. Therefore, these authors suggested, VWM is limited by the number of objects that it can hold, but not necessarily by the number of features of these objects (Luck and Vogel, 1997; Vogel et al., 2001).

A widely used empirical calculation of VWM capacity based on change detection tasks was introduced by Pashler (1988) and further developed by Cowan (2001). This approach assumes that if a subject can hold K items in memory from an array of S items, then the item that changed should be remembered on K/S trials, leading to correct performance on K/S of the trials on which an item changed. To correct for guessing, this calculation takes into account the false alarm rate. Therefore, this estimate of the object limit in VWM, known as Cowan's K, is calculated as follows:

$$K = S(H - F),$$

where K is the memory capacity, S is the set size of the array, H is the observed hit rate and F is the false alarm rate (Cowan, 2001). Alternative approaches of measuring VWM have been proposed more recently (Wilken and Ma, 2004; Bays and Husain, 2008; Morey, 2011).

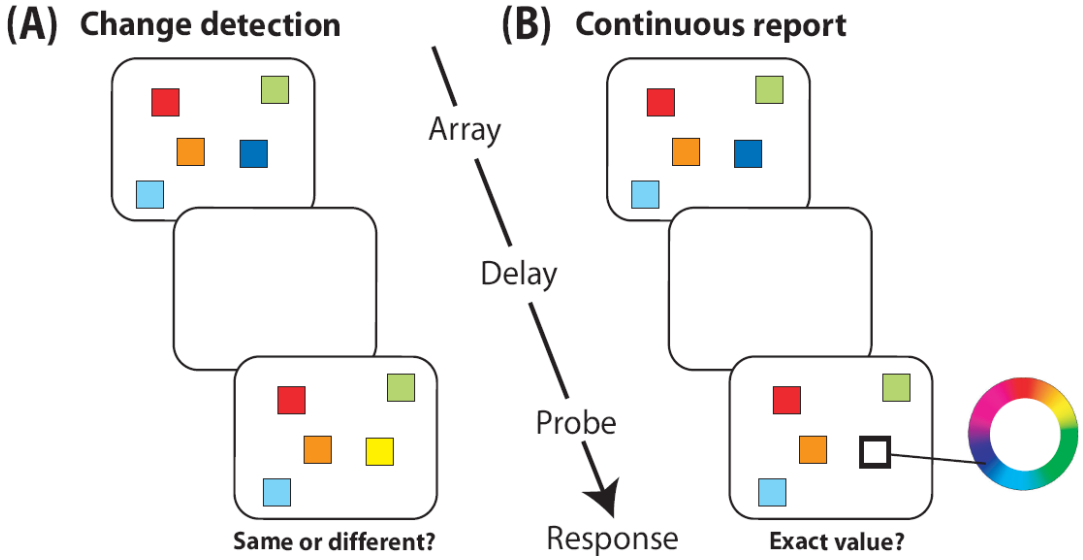


Figure 1.1: Different approaches in examining VWM: a change detection task (A) and a continuous report task (B).

In an example of a typical change-detection task **(A)**, an array with a varying number of coloured squares is briefly displayed, followed by a probe array. Subjects are required to make a judgement from memory on whether the test and probe arrays were the same or different. Adapted from Luck and Vogel (1997).

In this example of a continuous report task **(B)**, during testing subjects are required to choose from memory the precise colour of one of the items from the test array from a continuous colour space Adapted from Bays et al. (2009).

Alvarez and Cavanagh (2004) used Cowan's K on change detection tasks to determine VWM capacity for different objects of varying complexity (coloured squares, line drawings, Chinese letters, random polygons, shaded cubes). They estimated VWM capacity to about 4 items for simple objects but, interestingly, capacity was reduced to about two items for more complex figures. Accordingly, these authors suggested that VWM is limited both by the number of objects and their complexity (Alvarez and Cavanagh, 2004). In contrast, Awh et al. (2007) saw this conclusion as an interpretational pitfall rather than a true reflection of VWM limits. These authors argued that increasing complexity does not pose a limit on VWM, but it enhances the similarity of target items to distractors, therefore making the comparison between memorised and presented items more difficult. They observed that even within complex objects, a cross-category change (for example, from Chinese letters to random polygons; both complex but dissimilar objects) could be as easily detected as within simple objects. This was interpreted as evidence that VWM is solely limited by number of objects, regardless of their complexity (Awh et al., 2007).

In conclusion, several authors consider VWM as being limited by the maximum number of objects that can be remembered. This school of thought sees VWM as containing a fixed number of quantized 'slots' (Zhang and Luck, 2008) or 'chunks' (Cowan, 2005) which accommodate a finite, small, number of objects, usually estimated around 4 (Cowan, 2001). Two important predictions stem from this theory: first, once this capacity limit is reached, no information on any additional objects can be kept in VWM, and second, all objects within WM are expected to be remembered with equal, and perfect, resolution.

1.2.2 VWM as a flexibly shared resource

In change detection tasks, subjects are asked to make a binary decision; that is, to detect a change that either is or is not present in the probe array. An alternative approach in studying VWM was put forward by Wilken and Ma (2004), and further elaborated by Bays and Husain (2008). These authors used discrimination or continuous report tasks, in which subjects memorised arrays

of items, just as in a change detection task. Crucially however, on responding, these tasks provided an estimate of *how accurately* items were remembered, either by comparing the correct feature value with the subject's selection from a continuous feature space (continuous report), for example a colour wheel (Wilken and Ma, 2004; Bays et al., 2009; **Figure 1.1B**), or by asking subjects to make a two-alternative forced choice on the direction in which the probe item had been displaced or rotated in comparison to a memorised item, while the magnitude of this change varied probabilistically according to responses (discrimination; Bays and Husain, 2008). This approach enabled the measurement of VWM *resolution*, or *precision*, determined by the reciprocal of the standard deviation (1/σ) of responses (Bays and Husain 2008). In other words, precision is a measure of the degree to which responses cluster around the correct feature value (Bays et al., 2011b). Therefore, rather than estimating *whether* an object is remembered or not, this technique provided for the first time an estimate on *how precisely* it is remembered.

The results from these experiments were in stark contrast to the predictions of the item-limit model of VWM. Bays and Husain (2008) demonstrated that the precision with which visual items were remembered decreased with increasing numbers even at the smallest set sizes, (from one to two items). However, if VWM was limited by number of items, discrimination performance would be expected to decline only once the limiting number of items had been exceeded. Bays and Husain (2008) did not find a discontinuity beyond the supposed 4-item limit; instead, the relationship between precision and set size was well described by a power law: $P \propto R^k$, where R is resources available to encode an item, P the precision with which it is remembered, and k a constant. These authors also showed that targets of eye movements, or covert shifts of attention, were recalled with enhanced precision, at the expense of precision for other items. These results were incompatible with an item-limit in VWM; they were more in keeping with a limited VWM resource, shared across items flexibly, with attended items being allocated the lion's share (Bays and Husain, 2008).

Proponents of the 'slot' model of VWM offered a revised version of the item-limit theory of VWM to take results from such recall tasks into consideration. Zhang and Luck (2008) proposed a 'slot + averaging model' whereby VWM has a small number of discrete, fixed-resolution representations, which however, when operating below capacity limits, can 'double-up' to store a small number of items with enhanced precision (Zhang and Luck, 2008). In other words, this model suggests that VWM resources are discrete, quantized, but if needed they can be pooled together to store, for example, an attended item with higher resolution. This model is virtually indistinguishable from a pure flexible resources one when operating below maximum capacity, but when the maximum number of slots is reached, the predictions of the two models are expected to diverge.

Zhang and Luck (2008a) applied a mixture model to subjects' responses, consisting of two components: the probability that an item was present in memory, with a Gaussian component around the target value, plus a uniform (random) component, corresponding to the cases when the item was not in memory, and subjects were responding randomly. Results from this model analysis showed a steep decrease in the probability that an item was present in memory beyond 4 items, which was interpreted as indicating that the object-limit of 4 items had been breached.

Bays et al. (2009) replicated the same colour VWM task, but used VWM precision for their analysis, a direct measure of VWM which does not make assumptions on the distribution of responses. In contrast to Zhang and Luck, these authors found no such discontinuity for up to 6 items (Bays et al., 2009). Instead, the relationship of precision and number of items was well described by a power law, as demonstrated previously in Bays and Husain (2008).

Further evidence informing this debate will be examined in the following section, in the context of feature binding and its role in VWM.

1.3 The binding problem in visual working memory

In the early stages of visual processing, basic visual features are extracted and processed in parallel. For example orientation and colour are coded by discrete channels at the level of the primary visual cortex (Hubel and Wiesel, 1959; Livingstone and Hubel, 1984, 1988; Zeki, 1993). Logically, the inverse problem arises: how are simple visual features, such as orientation and colour, combined, bound together, to form objects in visual perception (Zeki, 1993)? Furthermore, what constraints does this integration of features place on VWM?

1.3.1 Feature integration theory

Treisman and Gelade (1980) proposed an influential model of such a binding process in visual perception, known as feature integration theory (FIT). According to this theory, analysis of the visual world into basic features occurs at a pre-attentive stage, early during visual perception. This is followed by a second, focused attention stage, in which individual features of objects are combined to create integrated objects. This stage requires cognitive resources that subserve selection of some items at a cost to others, and such selection was proposed to occur within a 'master map' of all the locations in which features have been detected, with each location in the master map having access to the multiple feature maps (Treisman and Gelade, 1980). Support to this theory was offered by several lines of experimental evidence (for a review, see: Treisman, 1999), including the observation of illusory conjunctions when focused attention is prevented (Treisman and Schmidt, 1982; Treisman and Paterson, 1984; Wolfe and Cave, 1999), an illusory conjunction being a binding error in which a feature of one object is seen as characterizing another - for example, the presentation of a green X and a red O might yield the illusory percept of a red X or green O (Treisman, 1996).

Single case studies on patients with focal lesions provided important insights in the neural substrate of such binding processes. Illusory conjuctions were

much more common on the affected (right) side of space in a patient with a left sided posterior parietal lesion (Cohen and Rafal, 1991). Another patient with bilateral posterior parietal lesions manifested a striking inability in correctly binding shapes with their colours (Robertson and Treisman, 1995). In keeping with these results, fMRI experiments in healthy subjects showed that posterior parietal regions involved in spatial attention were active in response to feature conjunctions when multiple objects were present simultaneously in the scene (Shafritz et al., 2002).

In contrast, other studies suggested that successful feature binding need not engage the posterior parietal cortex. For example, in a fMRI study, Nobre et al. (2003) manipulated the requirement to integrate visual features in a visual search task, and found that while there was a close correlation between visual search efficiency and fMRI signal in the intraparietal sulcus and the superior parietal lobule, feature binding during efficient search did not engage parietal regions. Data from patients with right parietal lesions also suggested that this brain region is not necessary for effective feature binding during visual search, but instead it might contribute to shifting attention effectively to new locations in such tasks (Ashbridge et al., 1999).

Regardless of the controversies on the localisation of the brain correlates of feature integration at the mesoscopic level, a pervasive hypothesis suggests that, at the cellular level, feature integration is mediated by temporally correlated activity in neurons coding different visual features (Singer and Gray, 1995). It has been suggested that feature integration might be mediated by such phase synchrony among neuronal oscillations within, but also between brain regions (Usher and Donnelly, 1998; Rodriguez et al., 1999; Palanca and DeAngelis, 2005). For example, it can be plausibly hypothesised that oscillatory phase synchronisation between occipital, posterior parietal, and temporal cortical areas might mediate conjunction of an object's location with other visual features (Tallon-Baudry and Bertrand, 1999).

1.3.2 Feature integration within VWM

FIT was proposed for visual perception, but an analogous problem arises also for VWM. Specifically, from a cognitive perspective, a critical question is whether maintaining bound representations in VWM requires the same or a different amount of memory and / or attentional resources as memory for individual features.

As already mentioned, Luck and Vogel (1997) found no difference in terms of VWM capacity in arrays of simple coloured squares and in arrays of squares containing feature combinations, suggesting there was no added cost for remembering objects with multiple features. In contrast, Wheeler and Treisman (2002) came to different conclusions in a series of similar change-detection experiments. They found that VWM capacity for three composite two-coloured objects (i.e., six colours for three objects) was identical to that for six objects with one feature each, and that memory capacity for three objects with one feature each was higher than in both of the previous conditions. This suggests a cost in VWM resources for maintaining bound representations (Wheeler and Treisman, 2002).

These authors examined the binding costs further by comparing feature binding across different dimensions with memory for single features. In the critical binding trials, participants had to remember specific combinations of features in order to make a correct selection. Performance in the binding condition was lower than in the single feature condition, but, interestingly, this effect was modulated by the way memory was tested. If at test the whole display with all objects was shown, VWM performance in the binding condition was lower than in the single feature condition. However, when only one object was presented as test stimulus, memory for the correct feature combination was as good as memory for the single feature that had the lowest memory performance. VWM for single features was not influenced by this manipulation (Wheeler and Treisman, 2002).

Furthermore, Treisman and Zhang (2006) found that, even when location was task irrelevant, memory for bound features was strongly impaired if an object

changed its (irrelevant) location, whereas single feature memory was influenced only minimally by location changes. Woodman and Vogel (2008), however, proposed that binding within VWM is not generally obligatory but depends on task requirements, as they found it was possible to store voluntarily a single attribute of an object without necessarily keeping all of its remaining features in VWM.

1.3.3 Attentional requirements of feature binding within VWM

Based on these results, Wheeler and Treisman proposed a framework which assumed that feature values from different dimensions are stored in parallel, each in its own dimension-specific space. They suggested that there is competition for a limited VWM resource within each of those dimensions, but not between dimensions. Binding information is additionally maintained if required by the task, and these authors proposed that this incurs no cost in terms of memory resources, but it depends on other limited attentional resources, and anything that competes for these would interfere with binding memory performance (Wheeler and Treisman, 2002).

Subsequent studies examining these proposals further present us with a complex picture. Allen et al. (2006b, 2009) found that attention-demanding secondary tasks, such as backward counting, did not influence memory for colour-shape conjunctions more than for individual features, as long as the items were simultaneously presented. Gajewski and Brockmole (2006) came to a similar conclusion by applying an exogenous cue during maintenance of bound features that should distract attention; although the cue was efficient, as it enhanced memory at target locations, it did not selectively impair conjunctions.

In contrast, multiple object tracking, another attention-demanding task, disrupted VWM for colour-shape conjunctions above and beyond any impairment to VWM for object features, and this impairment was larger when stimuli were presented at different locations (Fougnie and Marois, 2009). Other

studies also demonstrated selective impairment of feature binding in WM when attention was engaged (Elsley and Parmentier, 2009; Brown and Brockmole, 2010). Furthermore, although as mentioned, Allen et al. (2006b) did not find attentional distraction impaired binding for simultaneously presented items, interestingly, they showed that binding was selectively impaired in a task using sequential presentation (Allen et al., 2006b).

Therefore, the problem of attentional requirements in feature integration within VWM remains unresolved. Some aspects of this question are examined further in the empirical chapters of this thesis.

1.3.4 VWM precision taking into account feature integration

As discussed earlier (Paragraph 1.2.2), Zhang and Luck (2008) proposed a 'slot + averaging' item-limit model of VWM based on a colour report task. In their paradigm, following a brief display containing a variable number of coloured squares at random locations, subjects were asked to indicate the colour value (on a circular colour space) of one of one of the squares (specified by location) from memory. In their analysis, they used a mixture model which considered two possible sources of error on each trial: Gaussian variability in memory for the target colour, and a fixed probability of uniformly distributed responses due to guessing at random. This model can be described as follows:

$$p(\hat{\theta}) = (1-\gamma)\phi_{\sigma}(\hat{\theta}-\theta) + \gamma\frac{1}{2\pi},$$

where θ is the true colour value of the target item, $\hat{\theta}$ the colour reported by the subject, φ_{σ} is the circular analogue of the Gaussian distribution with mean zero and standard deviation σ, and γ is the proportion of the trials where the subject responds at random (Zhang and Luck, 2008; as replicated in: Bays et al., 2009).

As mentioned, this model analysis conflicted with a more direct analysis on the same task by Bays et al. (2009) based on VWM precision. Bays et al. (2009) also

re-examined the problem but also taking feature binding into consideration. According to these authors, one important parameter had been overlooked in the previous model by Zhang and Luck: error in the dimension that was cued, in this case, location. Therefore, in addition to Gaussian variability in memory for the target colour and a probability of responding randomly, there was additional uncertainty in the cued dimension, or a probability that subjects might mistakenly bind the colour of a non-target with the target location. Therefore, they proposed an additional term, describing this probability of misbinding, to the model by Zhang and Luck (2008), as follows:

$$p(\hat{\theta}) = (1-\gamma-\beta)\phi_\sigma(\hat{\theta}-\theta) + \gamma\frac{1}{2\pi} + \beta\frac{1}{m}\sum_{i}^{m}\phi_\sigma(\hat{\theta}-\theta_i^*),$$

where, as before, θ is the true colour value of the target item, $\hat{\theta}$ the colour reported by the subject, φ_σ is the circular analogue of the Gaussian distribution with mean zero and standard deviation σ, and γ is the proportion of the trials where the subject responds at random. The probability of mistakenly reporting a non-target item is given by β, and $\{\theta^*_1, \theta^*_2, ..., \theta^*_m\}$ are the colour values of the m non-target items (Bays et al., 2009).

This analysis revealed that misbinding errors accounted for a significant proportion of the loss of precision, higher as the number of non-target items increased - about 10% of responses for 4 item arrays, and as high as 30% of responses for 6 items (Bays et al., 2009). As orientations of non-targets were selected randomly, these non-target responses would simply have been (mis)classified under the uniform (random) component by the model proposed by Zhang and Luck (2008), thereby overestimating random responses. Therefore, the steep increase in random responses found by Zhang and Luck (2008) was largely accounted for by uncertainty in the cued dimension, or misbinding, by Bays et al., (2009).

Taking this approach a step further, Bays et al. (2011b) introduced a task in which two visual dimensions were probed at the same time. On each trial,

subjects were asked to memorise an array of coloured bars, each with a random colour and orientation. A single probe item was then presented at one of the locations from the preceding memory array, and subjects were asked to adjust *both* its orientation and its colour to match the features of the target item that had been presented at the same location in the memory array. As previously (Bays et al., 2009), these authors identified a significant proportion of misbinding in both dimensions, as the number of items increased (Bays et al., 2011b).

Crucially, this design gave the possibility to test whether errors in one feature dimension were independent to errors in the other tested dimension or whether errors between feature dimensions were correlated. Interestingly, the results revealed that VWM errors were strongly independent across dimensions. This is incompatible with an integrated-object hypothesis (Luck and Vogel, 1997), as in that case an object's features would always be remembered together, and therefore errors between feature dimensions sould be strongly correlated. The absence of such a correlation in Bays et al. (2011b) leaves two possibilities: either selection of a limited number of features for storage occurred independently in each feature dimension, or all the features in each array were stored in memory, albeit with less than perfect precision. The first hypothesis, however, seemed inconsistent with current models of attentional selection (Treisman and Gelade, 1980; Posner et al., 1982; Desimone and Duncan, 1995), therefore Bays et al. (2011b) concluded that all perceived visual features were stored, but as memory load increased, the fidelity with which they were represented declined, while, in parallel, the frequency with which independently stored features were incorrectly combined, increased (Bays et al., 2011b).

1.4 Goal-directed attentional modulation of VWM

As we saw in section 1.2, the amount of information that can be kept in VWM is very limited. In a world inundated by visual information, attentional selection of the stimuli that might be behaviourally important for storage in VWM, and suppression of less important ones, becomes therefore immediately relevant (Desimone and Duncan, 1995). Behavioural priority is often determined by the visual salience of the stimuli, for example a large, bright object against a dark background might attract more attention than a smaller, darker object. This stimulus-driven process is commonly referred to as bottom-up attention. Attention is often also goal-directed, selecting visual stimuli that are relevant to the task at hand, as for example when searching for a familiar face in a crowd; this mode of attention is known as top-down (Driver, 2001; Corbetta and Shulman, 2002; Theeuwes, 2010; Chun et al., 2011). Attention and VWM are closely interrelated, or even, according to some authors, overlapping processes, cognitively, as well as neurally (LaBar et al., 1999; Awh and Jonides, 2001; Corbetta et al., 2002; Awh et al., 2006; Chun and Turk-Browne, 2007; Mayer et al., 2007). The rapport between attention and VWM is bidirectional: attention can determine the contents of VWM, and in turn, the contents of VWM can bias attentional selection (Desimone, 1996; De Fockert et al., 2001; Lavie and De Fockert, 2005; Soto et al., 2005, 2007, 2008; Olivers et al., 2011).

In the following paragraphs I will focus on how goal-directed attention can guide VWM, and this question will be addressed further in the experimental part of this thesis.

1.4.1 Selective attentional filtering into and within VWM

In an influential and widely replicated experiment, Posner et al. (1978) demonstrated that directing attention to a location by using a predictive cue – an arrow indicating that location– shortened reaction time (RT) for stimuli

which appeared subsequently in these cued locations. Conversely, RT was prolonged for items displayed in contralateral, 'uncued' locations, away from the focus of attention (Posner et al., 1978; Posner, 1980). It has been repeatedly demonstrated since that stimuli in attended locations are processed more rapidly and more accurately than those in unattended locations (Prinzmetal et al., 1986; Henderson, 1996; Cheal and Gregory, 1997).

Spatial cues not only enhance perceptual performance, but also VWM. Schmidt et al. (2002) found that both involuntary –bottom-up– and voluntary –top-down– orienting of attention to spatial locations enhanced VWM accuracy for items appearing in these locations subsequently. Converging evidence comes from several studies showing that memory for location in a variety of VWM tasks was adversely affected by shifts of spatial attention (Smyth and Scholey, 1994; Smyth, 1996; Awh et al., 1998, 2006; Awh and Jonides, 2001).

Griffin and Nobre (2003) took the concept of cueing a step further. They demonstrated that VWM was enhanced to a similar magnitude by predictive spatial cues which appeared *retrospectively*, after the stimuli had been encoded in WM and were no longer visible. Therefore, spatial attention is not only important in selecting items which will be subsequently encoded in VWM, but also influences processing of already encoded, internal representations within VWM (Griffin and Nobre, 2003). Such retro-cues have been shown to enhance VWM accuracy in several subsequent change detection experiments (Lepsien and Nobre, 2007; Makovski and Jiang, 2007; Makovski et al., 2008; Astle et al., 2009, 2012; Sligte et al., 2010; Lepsien et al., 2011).

Pertzov et al. (2012a) studied the temporal dynamics of attention directed to internal VWM representations using retrospective cues in a continuous report task, which allows measurement of VWM precision. They found that, while in the absence of selective attention VWM precision decreased with time, retro-cues protected memory for attended items from temporal degradation, but with a corresponding cost for the precision of the remaining, uncued items, which were more rapidly forgotten (Pertzov et al., 2012a). These results suggest that,

remarkably, dynamic redistribution of VWM resources according to attentional priority continues long after perceptual processing and encoding are completed.

1.4.2 Non-spatial goal-directed attentional selection in VWM

Selective attention can also operate in a non-spatial manner. In a classic study, Rock and Gutman (1981) displayed spatially overlapping abstract shapes of different colours, and asked subjects to attend to only one of the colours. Memory was significantly worse for shapes of the non-attended colour, even though they were at the same location as the attended objects (Rock and Gutman, 1981). Several subsequent studies confirmed that goal-directed attention to object features or categories, irrespective of spatial location, can enhance VWM. For example, Rutman et al. (2010) displayed faces and scenes, overlaid at the same location and asked subjects to either remember one of these stimulus categories, or to view passively. VWM performance was predicted well by an electro-encephalographic (EEG) measure of the efficiency of top-down attentional modulation (Rutman et al., 2010). Similarly, VWM performance depended on effective goal-directed attentional selection of a visual feature (colour or motion direction) by suppressing successfully the irrelevant feature (Zanto and Gazzaley, 2009).

Non-spatial attention can also be allocated retrospectively: cueing previously presented faces or scenes led to improved memory for the cued category (Lepsien and Nobre, 2007). Non-spatial (colour) retro-cues were just as advantageous as spatial ones in maintaining the accuracy of VWM representations across time (Pertzov et al., 2012a).

1.4.3 Attentional filtering ability determines VWM performance

Selective, goal-directed attention can therefore modulate the distribution of VWM resources flexibly and dynamically. However, the contents of VWM are not entirely under volitional control; for example, in a series of cueing tasks,

distracting items 'intruded' upon the contents of VWM even when they were task-irrelevant (Olson et al., 2008). Individual and developmental differences in attentional control have been shown to determine VWM performance (Astle and Scerif, 2011). Vogel et al. (2005) used contralateral delay activity as an EEG measure of top-down attentional filtering to examine how individual limits in the ability to exclude distracting information from memory determine VWM capacity. They found that high capacity individuals are much more efficient at selecting and maintaining only the task-relevant items in VWM. In contrast, low capacity individuals unselectively encoded and maintained information about both relevant and irrelevant items (Vogel et al., 2005).

An important question is whether enhancement of task-relevant information and suppression of distracting, irrelevant stimuli, are dissociable processes. Gazzaley et al. (2005a) attempted to establish the neural signatures of both processes by comparing active selection or active suppression of stimulus categories (faces or scenes), with a neutral, passive viewing condition, using both EEG and fMRI. Using these measures to compare attentional filtering between young subjects and healthy older individuals with lower VWM performance, these authors found that the ability to suppress irrelevant information decreases with normal aging, while the ability to enhance task-relevant memories remains unaffected (Gazzaley et al., 2005b, 2008), suggesting that top-down enhancement and suppression in VWM might be dissociable.

In conclusion, the distribution of both spatial and non-spatial VWM resources is determined by goal-directed attention. This process seems to be highly dynamic, and can influence the contents of VWM even after encoding is completed. Neural measures of top-down attentional selection suggest that VWM capacity and accuracy might be primarily determined by the ability to filter irrelevant information out of VWM, rather than by enhancing relevant information.

1.5 Visual working memory across time

Most of the studies reviewed so far, and indeed, most of the previous work on VWM, examined memory for static displays. However, the visual environment is dynamic, constantly changing across time: through body and eye movements and alterations in the environment, information is often presented to the visual system in sequence. Therefore, VWM has to be constantly updated to accommodate old and new information according to behavioural priority. In this section, I will review previous studies on serial order effects in VWM, as well as relevant experimental work on the temporal properties of VWM.

1.5.1 Serial order effects in VWM

Considerable experimental and theoretical effort has been made to characterise memory for lists of words, non-words, syllables or letters (e.g. Baddeley et al., 1975; Lee and Estes, 1977; Hartley and Houghton, 1996; Burgess and Hitch, 1999, 2006; Logie et al., 2000; Henson et al., 2003). However serial WM has been much less well studied in the visual domain and observations from verbal WM do not automatically extend to VWM (Baddeley, 2007). The effects of recency –memory being more accurate for more recent items– and primacy –memory being more accurate for the first few items in a list– are typically observed in the verbal domain, producing a characteristic U-shaped curve when accuracy of recall is plotted against serial order (Henson et al., 2003).

These effects have been also examined in serial VWM, with variable outcomes. Phillips and Christie (1977) presented sequences of patterns of filled and unfilled squares, and then tested WM for each of the patterns in the sequence in reverse order (last pattern displayed was tested first) using a change detection task. They found that memory for the last item shown was much more accurate than for previous items, which were all remembered with

similar accuracy. This one-item recency effect was dissimilar to the recency effect observed in verbal WM, where it typically extends to several items before the last (Henson et al., 2003). No primacy effect was observed. Furthermore, Phillips and Christie (1977) found that WM accuracy for the last item was adversely affected by 3s of mental arithmetic, or unfilled delays of at least 10s, while WM for previous items was unaffected by these manipulations – however, performance for the previous items was already very low (accuracy close to 60%), therefore this might represent a floor effect, and this observation was not replicated subsequently (Broadbent and Broadbent, 1981; Avons, 1998). Based on these results, Phillips & Christie (1977), proposed a model which postulates two distinct forms of visual memory representation. Previously viewed items generate an internal representation which Phillips and Christie termed stable long-term visual memory. In contrast, the most recent item is held in a fragile, but more accurate, short-term visual memory store with a capacity limited to a single item.

Later work suggested that serial order effects might depend on the mode of testing. Avons (1998) followed a very similar experimental procedure to that of Phillips and Christie (1977) to examine whether different modes of probing had an impact on serial order effects. When a two-alternative forced choice paradigm was used to test WM for each item in the sequence, but in a forward, rather than backward order, no primacy or recency effects were noted (Avons, 1998). In another variant, participants were presented on testing with all the items that had been displayed in the sequence and they were asked to indicate each item's serial order starting from the first one. This mode of testing produced yet another pattern of results: a primacy effect which extended further than a single item, and a recency effect which was confined to a single item (Avons, 1998). This was replicated in a subsequent study on sequences of faces using the same mode of testing. Smyth et al. (2005) displayed pictures of unfamiliar faces one at a time, then presented the complete set at test and asked for serial reconstruction of the order of presentation. Again, multiple-item primacy and one-item recency was observed (Smyth et al., 2005).

Therefore, serial order effects in VWM seem to depend upon the mode of testing, rather than the type of stimuli used.

The temporal properties of sequentially presented stimuli might also determine recency and primacy in VWM. Wright et al. (1985) tested recognition memory for sequences of pictures in humans, macaque monkeys, and pigeons. Both recency and primacy effects were observed in all three species, but the magnitude of each effect depended on the length of the retention time interval between the last item and the probe. When the probe appeared shortly after the last item, there was a significant multiple-item recency effect, with no primacy effect observed. As the retention interval became longer, the recency effect attenuated gradually and gave its place to a primacy effect; following a 30s retention interval, WM accuracy was characterised by significant multiple-item primacy, but no recency effect (Wright et al., 1985).

These findings were replicated in a subsequent study that tested VWM of sequentially presented abstract figures in humans (Neath, 1993). Neath (1993) introduced the concept of distinctiveness to explain serial order effects, initially based solely on the temporal relationships between items, and proposed that more recent items in a sequence are temporally more distinct. This model accounted well for the author's results, as well as for those of Wright et al. (1985), however subsequent data did not fit well (Kerr et al., 1999). The concept of distinctiveness was later refined in a proposed model –Scale Invariant Memory, Perception and Learning (SIMPLE)– which took into account both temporal distinctiveness and visual similarity between items to explain serial order functions (Brown et al., 2002; Neath and Brown, 2006; Neath et al., 2006; Hay et al., 2007).

Other studies examined the role of spatial overlap between serially presented items. Broadbent and Broadbent (1981) studied VWM for serially presented complex figures consisting of random combinations of abstract shapes (lines, dots, arrows). VWM was tested at the end of each sequence with a two-alternative forced choice between one of the items that had appeared in the sequence and one that had not. A clear recency effect, with no primacy, was

observed in a condition where all the figures were presented serially at the same location. Unlike Phillips and Christie (1977) recency was not confined to the last item, but it extended to previous items, an observation which was replicated in a further study using a similar mode of testing (Johnson and Miles, 2009). Critically, Broadbent and Broadbent (1981) observed that when items were presented serially, but each at a different location, there was no significant recency effect, and overall WM accuracy improved in comparison to presentation at the same location (Broadbent and Broadbent, 1981). Note that eye movements were not controlled in this study and subjects were free to fixate items. Therefore spatial overlap in this case concerned an external (spatiotopic), rather than retinotopic, frame of reference.

It has been proposed that spatial organisation, configuration of stimuli in space, is critical in explaining improved memory for items presented at different locations (Jiang et al., 2000; Blalock and Clegg, 2010). Subsequent studies explored the observation that memory for the same number of items is more accurate when they are presented simultaneously, rather than sequentially (Allen et al., 2006b; Alvarez and Thompson, 2009; Blalock and Clegg, 2010). Blalock and Clegg (2010) compared simultaneous presentation with the same number of items presented sequentially in different locations, and still found a disadvantage in sequential presentation in WM accuracy, even though items did not overlap spatially. These authors suggested that information for spatial organisation –the relationship between items' spatial coordinates– is incompletely encoded in sequential presentation (Blalock and Clegg, 2010).

An alternative, but not necessarily contradictory, explanation was offered by Allen et al. (2006b). These authors found that although VWM for integrated objects with multiple features was worse in sequential presentation, this was not the case for memory for single features. They suggested that binding between visual features, especially for items early in the sequence, is fragile and susceptible to overwriting from subsequent visual information (Allen et al., 2006b).The difficulty in maintaining integrated representations of objects long enough to form a global representation might explain the lower WM

performance for sequential versus simultaneous presentations in Blalock and Clegg (2010).

Finally, an important common observation in several studies using different display and probing techniques, is that the dominant error patterns were transpositions of items adjacent in serial order (e.g. Smyth and Scholey, 1996; Henson et al., 2003; Smyth et al., 2005). If we consider serial order as one of the features of an object, to which other visual features can be associated, in order to form a spatiotemporal continuity in VWM, then these transposition errors might be considered as a specific case of misbinding. Clearly, the maintenance and updating of feature integration across time is a complex issue which warrants further investigation.

1.5.2 Temporal properties of VWM

Several studies have examined the time course of visual information transfer from multiple item displays into VWM. In these experiments, a number of objects were simultaneously displayed for a set time interval, after which encoding into VWM was halted by visual masking (Breitmeyer, 1984). Using change detection paradigms to probe VWM as a function of time, it was found that encoding became slower with increasing number of items (Shibuya and Bundesen, 1988; Duncan et al., 1994; Vogel et al., 2006). According to one hypothesis, this finding might represent a serial process, whereby items are encoded one at a time (Hoffman, 1979; Wolfe, 1994; Chun and Potter, 1995). Alternatively, it could reflect a parallel process during which multiple items are encoded into WM simultaneously at a rate determined by total stimulus load (Shibuya and Bundesen, 1988; Bays et al., 2011a).

In contrast to previous change detection experiments which adopted a binary approach whereby each object was considered to be either perfectly encoded in memory or not remembered at all, Bays et al. (2011a) quantified *how precisely* items were encoded as a function of time. These authors investigated the temporal evolution of VWM precision, based on observers' ability to reproduce

the orientations of a varying number objects presented for varying durations. They found that VWM resolution increased with time of exposure for all items, in parallel, until it reached a maximum precision. Precision as a function of exposure time, $P(t)$, was well described by an exponential equation, similar to the one governing the charge of a resistor-capacitor circuit in electronics:

$$P(t) = P_{max}(1-e^{-t/\tau}),$$

where P_{max}, the maximum precision which will be attained after a sufficient amount of time, and τ, the rate of encoding, are both determined by the number of items to be encoded. Furthermore, cuing individual items within the array revealed flexible reallocation of VWM resources, increasing the resolution of recall for visually salient or behaviourally important items at the cost of reduced precision for lower priority items (Bays et al., 2011a).

Once encoded, information can maintained within VWM only for a limited amount of time (Posner and Keele, 1967). Forgetting is the opposite side of the temporal characteristics of VWM, and recent studies have examined the properties and potential mechanisms of this process. Zhang and Luck (2009) used a continuous report task, introduced in a previous study by the same authors (Zhang and Luck, 2008; reviewed in Paragraph 1.2.2), to examine the effects of variable retention intervals on VWM. They concluded that loss of information in VWM with time is not gradual, but sudden; VWM representations may be retained for several seconds with little or no loss of precision, but that they may terminate suddenly and completely during this period (Zhang and Luck, 2009). As in their previous work (Zhang and Luck, 2008), this result was based on model estimates of two parameters: the probability that an item was stored in memory, and the precision with which it was remembered.

Using a similar report task, (Pertzov et al., 2012b) examined forgetting in VWM taking also into account the probability of misbinding between visual features of different objects, across variable time intervals. These authors found that while single items could be maintained in memory with high

fidelity, additional objects degraded each other's representation with time. Crucially, this was explained to a significant extent by failures in binding, as evidenced by increasing report of features of non-probed items. In keeping with the results of Allen et al. (2006b), these authors found that single features were robustly maintained across time, but the association between different features belonging to an object was fragile and increasingly vulnerable to degradation and forgetting (Pertzov et al., 2012b). This failure in feature integration with time might offer a potential mechanism for the 'sudden death' in VWM described by Zhang and Luck (2009).

1.6 Neural correlates of VWM

There is great wealth of data on the brain correlates of VWM from human and animal neuroimaging, electrophysiology, neuropharmacology and lesion studies (Goldman-Rakic, 1995; Smith and Jonides, 1997; Ellis and Nathan, 2001; Postle, 2006; D'Esposito, 2007). An exhaustive review is beyond the scope of this chapter. Rather, I will focus on selected studies which are particularly relevant to the experimental parts of this thesis.

1.6.1 VWM at the systems level

Lateral prefrontal cortex

A widely replicated finding from single neurone recordings in behaving non-human primates is that cells within the lateral prefrontal cortex show sustained activation during the retention period in tasks that require the animal to keep information in memory over a brief interval (Kubota and Niki, 1971; Kojima and Goldman-Rakic, 1982; Funahashi et al., 1989, 1990; Funahashi and Kubota, 1994; Miller et al., 1996). Many of these experiments employed oculomotor delayed response tasks, where the animal was presented with a visual stimulus on a screen, and then, following a brief delay period, it was required to make a voluntary saccade from memory (Joseph and Barone, 1987; Compte et al., 2003).

Functional imaging studies in humans using similar delayed response tasks have produced converging evidence: they consistently demonstrated sustained prefrontal cortical activity during the memory period, bridging the stimulus cue with its contingent response (D'Esposito et al., 2000; Postle et al., 2000; Curtis and D'Esposito, 2003; Curtis et al., 2004). Further evidence for the necessity of the prefrontal cortex in maintaining task relevant representations in WM has been provided by selective lesion studies in monkeys, which revealed spatially selective impairment on delayed response tasks, in keeping with 'mnemonic scotomas' when parts of the dorsolateral prefrontal cortex were

lesioned (Bauer and Fuster, 1976; Funahashi et al., 1993). A recent lesion study in stroke patients with lateral prefrontal lesions has demonstrated similar spatially selective VWM deficits (Voytek and Knight, 2010).

While there is ample evidence for a role of the lateral prefrontal cortex in VWM, there is also active debate on the specific contributions of its anatomic subdivisions in different components of WM tasks. Some authors proposed a dorsal-ventral dichotomy within the prefrontal cortex, with the dorsolateral prefrontal cortex being responsible for processing spatial information, while the ventrolateral prefrontal cortex is involved in mnemonic representation of object identity (Wilson et al., 1993; Courtney et al., 1996; Rao et al., 1997; Sala et al., 2003; Ventre-Dominey et al., 2005). Other researchers suggested that different anatomical subdivisions of the prefrontal cortex are involved in different cognitive processes related to WM (D'Esposito et al., 1999a; Petrides et al., 2002; Petrides, 2005). More specifically, enhanced activity in the dorsolateral prefrontal cortex may be related to active monitoring, manipulation and restructuring of mnemonic information: updating of information, reordering, and resolving interference within WM have all been associated with activity in that area (D'Esposito et al., 1999b; Rypma and D'Esposito, 1999; Jonides et al., 2002; Curtis and D'Esposito, 2003; Leung and Zhang, 2004). Interestingly, activity in the dorsolateral prefrontal cortex was particularly related to processing serial order information (Ninokura et al., 2004; Amiez and Petrides, 2007). Activity in the ventrolateral prefrontal cortex, on the other hand, has been more closely associated with retrieval and goal-directed attentional selection in VWM (Owen and Evans, 1996; Jonides et al., 2002; Badre and Wagner, 2007; Cadoret and Petrides, 2007; Champod and Petrides, 2007; Dove et al., 2008).

The prefrontal cortex has therefore an essential and multifaceted role in supporting cognitive operations related to VWM. However it is in no way sufficient or independent in doing so. Rather, there is increasing evidence for a widespread network of areas implicated in WM functions, including prefrontal, posterior parietal, medial and inferior temporal, early sensory, and subcortical areas (Awh and Jonides, 2001; Pasternak and Greenlee, 2005; Ranganath and

D'Esposito, 2005; Postle, 2006; D'Esposito, 2007; Simons and Mayes, 2008). In the following paragraphs, I will review some of the key evidence on the involvement of these brain regions in VWM, and on proposed interactions between them.

A very influential model of visual perception posits the existence of two distinct but interacting systems in the brain: a dorsal stream, extending from primary visual to posterior parietal areas, which is proposed to subserve encoding of spatial location or to support visually guided action, and a ventral stream from early visual areas to the inferior temporal lobe, which is suggested to have a role in object identification (Mishkin et al., 1983; Goodale and Milner, 1992). Perhaps reflecting the close link of WM with perception and action, the role of the posterior parietal and temporal cortices in VWM has been considered by many authors in the context of an analogous dorsal - ventral dichotomy (e.g. Courtney et al., 1996). While this framework has stimulated extensive experimental work, the parietal and inferior / medial temporal cortices appear to have a complex involvement in VWM, extending beyond a dorsal - ventral dichotomy.

Posterior parietal areas

Single unit recordings from the macaque posterior parietal cortex have shown delay activity during a memory saccade task on the lateral bank of the intraparietal sulcus (area LIP) (Gnadt and Andersen, 1988). Neuronal activity in areas 7a and LIP has been associated with memory of location (Constantinidis and Steinmetz, 1996; Pesaran et al., 2002) and motion direction (Ferrera et al., 1994) over brief delays. Interestingly, the pattern of this delay activity in the posterior parietal cortex matched almost exactly the pattern of neuronal firing in the lateral prefrontal cortex during the same task (Chafee and Goldman-Rakic, 1998), and in turn, inactivation of each of these areas with cooling greatly diminished memory delay activity in the other (Chafee and Goldman-Rakic, 2000). These results suggest a close relationship between posterior parietal and lateral prefrontal areas during VWM maintenance.

Functional imaging in humans also provided evidence for enhanced posterior parietal activity during VWM maintenance of spatial information (Courtney et al., 1996; Pessoa et al., 2002). Furthermore, Todd and Marois found that fMRI signal change in the posterior parietal cortex during a spatial memory task correlated strongly with the number of items accurately maintained in VWM and predicted individual differences in memory capacity (Todd and Marois, 2004, 2005). Xu and Chun (2006) took these observations further, by proposing a functional segregation in the way anatomical subsets of the posterior parietal cortex support VWM. Based on fMRI signal within the posterior parietal cortex during a series of VWM tasks in which they manipulated both the number of objects to be remembered and their complexity, they suggested that activity in the inferior intraparietal sulcus was related to maintaining spatial attention over a fixed number of objects at different spatial locations, whereas the superior intraparietal sulcus and the lateral occipital complex encoded and maintained a variable subset of the attended objects, depending on their complexity (Xu and Chun, 2006).

Posterior parietal activation was also noted during non-spatial WM tasks. For example, enhanced activity in the supramarginal gyrus was reported in fMRI studies using the *n*-back task, where a sequence of stimuli is presented at fixation and subjects are required to respond when an item matches one that was presented *n* items before (Cohen et al., 1997; Owen et al., 2005). Such studies also illustrate the interplay between frontal and parietal areas which tend to follow closely each other's pattern of activity (Cohen et al., 1997).

Visual neglect and VWM

A complex picture on the role of the posterior parietal cortex in VWM emerges from focal lesion patient studies. Patients with right posterior parietal damage often manifest visual neglect, a striking difficulty to acknowledge or respond to people or objects to the left even in the absence of a primary sensory deficit (Heilman and Valenstein, 1979; Mesulam, 1981, 1999; Stone and Greenwood, 1991; Driver and Mattingley, 1998; Parton et al., 2004). Neglect is typically caused by extensive cerebral damage due to right hemisphere stroke affecting the right posterior and inferior parietal lobe, including the angular gyrus

(Heilman et al., 1983; Vallar and Perani, 1986; Vallar, 2001; Mort et al., 2003; Gillebert et al., 2011; Vandenberghe et al., 2012). However, there is no simple association between neglect and a single brain region, and the syndrome can also result from focal lesions which do not involve the posterior parietal cortex – for example from strokes affecting the right inferior frontal lobe (Husain and Kennard, 1996), subcortical structures such as the basal ganglia and thalamus (Damasio et al., 1980; Cambier et al., 1982; Karnath et al., 2002), or the medial temporal lobe (Mort et al., 2003).

Rather than being a unitary disorder, neglect consists of several component deficits, which are not necessarily specific to the syndrome, but in combination contribute to exacerbate its severity (Stone et al., 1998; Parton et al., 2004; Bartolomeo, 2007). Neglect can cause spatial biases at the personal, peri-personal, and extra-personal frame of reference, and even in representational space during mental imagery (Bisiach and Luzzatti, 1978; Pouget and Driver, 2000). Independently of sensory awareness, it can result in a directional motor bias away from the contralesional side, causing difficulty in initiating leftward eye or hand movements (Laplane and Degos, 1983; Mattingley et al., 1998; Husain et al., 2000).

Deficits in VWM have been recognised as important components of visual neglect (Husain and Rorden, 2003). Pioneering work by De Renzi et al. (1977) demonstrated impaired performance in patients with right-sided posterior lesions on the Corsi blocks task, a spatial WM test. Subsequent studies have revealed multiple deficits in VWM in neglect patients, including impairments in transaccadic memory (Husain et al., 2001), spatial memory (Mannan et al., 2005; Parton et al., 2006) and non-lateralised spatial memory (Malhotra et al., 2005). VWM for spatial information, but not for object identity, was found to be impaired in patients with right posterior parietal damage and neglect (Pisella et al., 2004). In contrast, in two separate patient groups with right-sided (Berryhill and Olson, 2008a) and bilateral posterior parietal lesions (Berryhill and Olson, 2008b), without clinically detectable visual neglect, profound impairments were found on several tasks involving VWM for location, object identity (including a sequential task), and object/spatial conjunctions.

VWM deficits in visual neglect, including impairment in updating of VWM across time, will be examined further in the empirical part of this thesis (Chapters 4 and 5).

Inferior and medial temporal areas

The role of the temporal neocortex in LTM processes is supported by a vast amount of human and animal data (for a review, see: Simons and Spiers, 2003). However, electrophysiology studies in non-human primates have shown that neurones in the inferior and medial temporal lobe also show persistent delay activity in tasks requiring VWM (Miyashita and Chang, 1988; Miller et al., 1991, 1993; Nakamura and Kubota, 1995; Chelazzi et al., 1998; Petrides, 2000). In addition to delay activity, inferior temporal neurones exhibit match enhancement, an interesting phenomenon whereby neuronal activity is enhanced when the identity of an external visual stimulus matches that of a memorised object (Miller and Desimone, 1994).

Human neuroimaging studies have also provided evidence for VWM related activity in the inferior temporal cortex (Courtney et al., 1997; Sala et al., 2003; Rämä and Courtney, 2005). Furthermore, in keeping with electrophysiology studies demonstrating object-selective activity in temporal neurones (Miyashita and Chang, 1988; Miller et al., 1993; Nakamura and Kubota, 1995), human fMRI studies report VWM-related activity in category-selective areas, such the fusiform face area for faces and the parahippocampal place area for scenes or buildings (Druzgal and D'Esposito, 2003; Ranganath et al., 2004a, 2004b).

It has been suggested that medial temporal (MTL) structures, including the perirhinal, parahippocampal, entorhinal areas and hippocampus, are vital for LTM, but not involved in WM (Squire and Zola-Morgan, 1991; Squire, 1992; Alvarez et al., 1994). However, this view of the medial temporal cortex and related structures is conflicting with evidence from lesion studies in monkeys and humans, which suggest that intact function in these areas is necessary in order to maintain representations of novel or complex objects even across short delays (Murray and Mishkin, 1986; Meunier et al., 1993; Eacott et al., 1994;

Hannula et al., 2006; Olson et al., 2006a, 2006b; Ezzyat and Olson, 2008; Finke et al., 2008). In keeping with these findings, functional imaging studies in humans and other primates have shown increased activity in the MTL during WM tasks with novel visual stimuli (Elliott and Dolan, 1999; Elliott et al., 2000; Sybirska et al., 2000; Ranganath and D'Esposito, 2001; Stern et al., 2001). This activity, specific to novel objects, was enhanced for items that were subsequently remembered successfully after a long delay (Schon et al., 2004; Ranganath et al., 2005a).

It has long been recognised that MTL structures, and particularly the hippocampus, are important in associating separate pieces of information to form an relational representation in episodic and long-term memory (Eichenbaum, 1999, 2006). In patients with selective hippocampal damage, unimodal recognition of words, non-words, and faces, is relatively spared, as is memory for paired associations within modality (e.g. pairs of two non-words or two faces). This comes to stark contrast with a profound impairment in cross-modal association in these patients, for example object-place and voice-face associations (Vargha-Khadem et al., 1997). This specific role of the hippocampus in relational memory has also been corroborated by animal studies (Aggleton and Brown, 1999). What is more, hippocampal lesions resulted to deficits in object location memory, even across short delays, when objects were considered from an external viewpoint, but not when they were seen from ones own perspective (Holdstock et al., 2000; King et al., 2002). This dissociation might relate to the role of the hippocampus in forming cross-modal associations, which are essential in the case of allocentric memory, but less so in the case of egocentric spatial memory.

More recent studies have proposed that MTL has also an important role in binding within VWM. A specific impairment in remembering associations between objects and their locations over brief delays was found in patients with extensive lesions, affecting the MTL (Olson et al., 2006b). Accordingly, fMRI studies in healthy volunteers have shown MTL activation in relation to successful maintenance of object to location binding information in VWM (Piekema et al., 2006; Hannula and Ranganath, 2008). A further fMRI study

examined the role of MTL in binding objects to locations, but also in binding non-spatial features within objects (shape with colour), as well as in forming associations between different objects. Enhanced activity in the MTL was found in successful object-location binding, as well as in associations between different objects, but not in binding between non-spatial features within objects (Piekema et al., 2010).

Early visual areas

It has been proposed that high resolution representations in VWM are maintained through activation of early visual areas (Pasternak and Greenlee, 2005). Direct recording from early sensory cortices showed memory-related activity in motion selective area MT in a task requiring VWM for motion (Bisley et al., 2004), although this signal had remarkably different temporal characteristics to the prolonged sustained delay activity in lateral prefrontal, posterior parietal, and inferior temporal areas (Bisley et al., 2004; Zaksas and Pasternak, 2006; Offen et al., 2009). Furthermore, an fMRI study employing a decoding analysis (Kamitani and Tong, 2005) of individual time points throughout the working memory delay period, found that activity in human visual areas V1-V4 predicted VWM for orientation (Harrison and Tong, 2009).

Basal ganglia and attentional selection

The control of access to VWM by selective goal-directed attention was discussed from a behavioural perspective in Section 1.4. McNab and Klingberg (2007) examined the neural correlates of this process using fMRI. They found that activity in the globus pallidus predicted the extent to which only relevant information was remembered. This filtering activity in the globus pallidus showed a strong positive correlation with VWM capacity, in keeping with previous results (Vogel et al., 2005), and it correlated negatively with posterior parietal activation, which the authors suggested might reflect unnecessary storage of distractors (McNab and Klingberg, 2007).

Further evidence on the role of the basal ganglia in WM comes from patients with unilateral focal lesions in the basal ganglia, manifesting bilateral VWM impairments (Voytek and Knight, 2010). The role of dopaminergic striatal

projections to the prefrontal cortex, as well as of dopaminergic systems within the basal ganglia, in supporting WM processes, including attentional selection, will be examined in more detail in section 1.6.3, in the context of the action of dopamine on WM.

VWM as a network property

VWM therefore engages a complex network of widely distributed brain areas. Recent studies have attempted to characterise the functional connectivity between nodes of this network using EEG, Magneto-encephalography (MEG), and fMRI in healthy subjects (Babiloni et al., 2004; Gazzaley et al., 2004; Ranganath et al., 2005b; Hampson et al., 2006; Palva et al., 2010; Ginestet and Simmons, 2011; Zanto et al., 2011) and in patients, in a variety of clinical conditions where breakdown of connectivity has been associated with VWM deficits (Grady et al., 2001; Meyer-Lindenberg et al., 2001; Glahn et al., 2005; Koshino et al., 2005; My-Van Au Duong et al., 2005; Micheloyannis et al., 2006; He et al., 2007; Vasic et al., 2009; Salvadore et al., 2010).

In parallel, specific EEG and MEG signal properties which constrain interactions within this network, are increasingly characterised. For example, recent studies suggest that coherence of neuronal oscillations in different frequency ranges, including theta and gamma bands, are instrumental in determining interactions between the prefrontal cortex and early visual, posterior parietal and subcortical structures during VWM (Lee et al., 2005; Raghavachari et al., 2006; Palva et al., 2010; Engel and Fries, 2010; Benchenane et al., 2011).

Therefore, VWM can be viewed as an emergent property of a complex, distributed, and highly adaptable network (Postle, 2006; D'Esposito, 2007), the characteristics of which are becoming increasingly understood. In the next section, I will focus on the role of the neurotransmitter dopamine in VWM, including insights gained from its pharmacological modulation.

1.6.2 Dopaminergic actions on VWM

Several neurotransmitters, including acetylcholine, noradrenaline, glutamate and dopamine, have been implicated in WM processes (Lisman et al., 1998; Aultman and Moghaddam, 2001; Ellis and Nathan, 2001; Williams et al., 2002; Bentley et al., 2004; Hasselmo, 2006; Cools and D'Esposito, 2011; Husain and Mehta, 2011). Dopamine is of particular interest in this context, as its complex role in VWM in health and disease is becoming increasingly understood, and as it is emerging as a promising target for treatment of VWM deficits in several clinical conditions (Cools and Robbins, 2004; Husain and Mehta, 2011).

The monoamine neurotransmitter dopamine is the endogenous ligand for five known types of dopamine receptors (D_1 to D_5). These are often subdivided in two families: D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) (Girault and Greengard, 2004). These are not uniformly distributed: there is a much higher concentration of D_1 receptors in the prefrontal cortex, while D_2 receptors are predominantly located in the striatum (Lidow et al., 1991; Hersch et al., 1995). The level of extracellular dopamine is modulated by two mechanisms: phasic and tonic dopamine release. Phasic dopamine release results from the activity of the dopamine-containing cells, characterized by irregular single spikes, as well as rapid bursts of several spikes in quick succession (Grace and Bunney, 1984a, 1984b; Dreyer et al., 2010). Bursts of activity result in higher synaptic concentration of dopamine (Gonon, 1988). Tonic activity refers to the continuous background release of small amounts of dopamine, largely regulated by the activity of other neurones and by neurotransmitter reuptake (Dreyer et al., 2010). Effects of dopamine on post-synaptic neuronal activity are variable and depend on the type of receptor and the interplay between the modes of release (tonic or phasic) (Dreyer et al., 2010). Generally speaking, D_1-like receptors have various effects, while D_2-like receptors tend to have mainly inhibitory effects on post-synaptic neuronal activity (Girault and Greengard, 2004).

Dopamine determines VWM performance

Dopamine receptors, especially D_1, are abundant in the prefrontal cortex (Lidow et al., 1991). This area receives diffuse ascending inputs from dopaminergic neurones in the ventral tegmental area of the midbrain, and these projections are known as the mesocortical pathway (Bannon and Roth, 1983; Goldman-Rakic, 1992, 1995; Goldman-Rakic et al., 2000; Fuster, 2008). Given the well-recognised involvement of the prefrontal cortex in VWM processes, one can hypothesise that modulation of its dopaminergic environment might affect VWM performance. Indeed, a seminal study over forty years ago demonstrated that dopamine depletion in the prefrontal cortex of monkeys caused impairment in VWM, which was as severe as the VWM deficit in animals with complete ablation of the prefrontal cortex (Brozoski et al., 1979). Moreover, the VWM deficit in these animals with prefrontal dopamine depletion was reversed following treatment with a dopamine agonist (Brozoski et al., 1979; Arnsten et al., 1994).

Several subsequent studies provided extensive evidence for the role of dopamine in WM, both in humans and in other animals. For example, administration of dopamine agonists, such as pergolide or bromocryptine led to improved WM performance in healthy volunteers (Luciana et al., 1992; Kimberg et al., 1997; Luciana and Collins, 1997; Mehta et al., 2001; Kimberg and D'Esposito, 2003). In turn, dopamine antagonists caused highly specific impairments on WM tasks (Sawaguchi et al., 1990; Mehta et al., 2004b). It is important to note that these effects were selective to WM function, and could not be attributed to non-specific changes in alertness or motor effects.

However, it is becoming increasingly clear that the role of dopamine in VWM is highly complex, for several reasons (Cools and D'Esposito, 2011). First, dopaminergic effects on VWM are dose-dependent, and can range from impairment to improvement, according to dose. Second, there is great variability between individuals, often with opposing actions of dopamine on VWM in different individuals. Third, D_1 and D_2 receptor activity in the prefrontal cortex and striatum, respectively, have discrete and sometimes even

opposing roles in VWM. In the next paragraphs, I will review the evidence describing this complex relationship.

Dose-dependent effects: an inverted-U shaped function

Several animal studies suggested that optimal performance in WM tasks depends on optimal dopaminergic activity: either too little or too much D_1 receptor activity impaired WM performance (Sawaguchi et al., 1990; Arnsten et al., 1994; Cai and Arnsten, 1997; Zahrt et al., 1997; Seamans et al., 1998). Interestingly, it has been suggested that deficits resulting from excessive dopaminergic stimulation are qualitatively distinct from those due to insufficient stimulation: too little D_1 activity has been associated with an increase in random responses, while too much might result to errors due to perseverative behaviour (Zahrt et al., 1997; Seamans et al., 1998; Floresco and Phillips, 2001).

Dose-dependent effects of dopamine on the prefrontal cortex have been examined at the cellular level. In a pioneering study, Williams and Goldman-Rakic (1995) used iontophoretic application of a D_1 receptor antagonist to single neurones in the behaving monkeys, and demonstrated that the highly selective effect of the drug on delay period activity in the prefrontal cortex was remarkably dose-dependent. Combined evidence from this and further studies determined that there is an optimal range of dopamine function in the prefrontal cortex that is governed by an inverted-U shaped relationship between dopaminergic activity and of WM function (Cools and Robbins, 2004; Williams and Castner, 2006). A schematic representation of this relationship is given in **Figure 1.2.** Such inverted-U functions have also been observed *in vivo,* in neurophysiological data from alert behaving monkeys (Vijayraghavan et al., 2007) and in neuropharmacological studies in humans (Apud et al., 2006; Roussos et al., 2009).

Individual differences, baseline performance and baseline dopamine

Several neuropharmacological studies have shown that the effects of dopaminergic drugs on WM are highly variable between individuals (Kimberg et al., 1997, 2001; Mattay et al., 2000; Kimberg and D'Esposito, 2003; Gibbs

and D'Esposito, 2005). Critically, this variability depends on individuals' baseline WM performance. Dopamine agonists generally improve WM performance in individuals with low capacity at baseline, but tend to worsen performance in individuals who already perform optimally off dopaminergic medication (Kimberg et al., 1997, 2001; Mattay et al., 2000; Kimberg and D'Esposito, 2003; Gibbs and D'Esposito, 2005; Frank and O'Reilly, 2006; Cools et al., 2007). This dependence on baseline performance has been observed for multiple WM processes, including retrieval (Gibbs and D'Esposito, 2005), updating (Frank and O'Reilly, 2006), and set shifting (Frank and O'Reilly, 2006; Cools et al., 2007).

What might be the mechanism behind these individual differences depending on baseline performance? There is evidence suggesting that baseline levels of dopamine might determine dopaminergic drug effects. For example, administration of a D_1 antagonist impaired WM performance in young monkeys, but not in elderly monkeys with presumed D_1 depletion. Accordingly, a D_1 agonist improved performance in aged, but not in young monkeys (Arnsten et al., 1994). Similar baseline dependent effects have also been

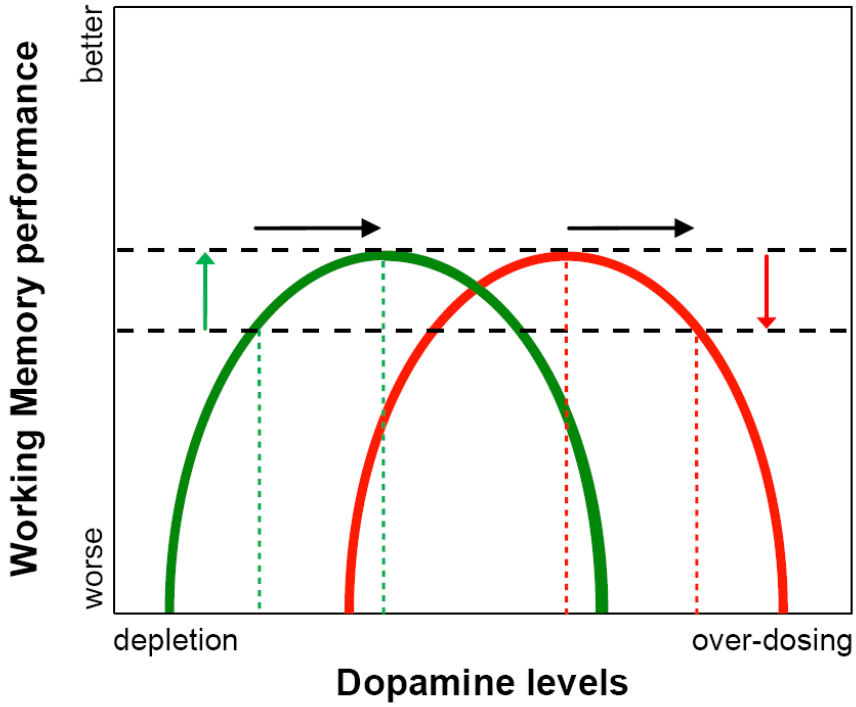


Figure 1.2: Dose-dependency of dopaminergic effects on WM.

The relationship between WM performance and dopamine levels follows an inverted U-shaped function, where both too little and too much dopamine impairs performance. Optimal dopamine concentrations –determining optimal performance– may differ between individuals according to baseline dopamine levels. Therefore, equal doses of a supposed dopamine agonist (black arrows) may be beneficial for one individual's performance (in green) but detrimental for another's (in red). Modified from Cools and Robbins (2004).

observed in rodents (Floresco and Phillips, 2001; Chudasama and Robbins, 2004; Phillips et al., 2004).

Another line of evidence comes from human studies taking into account genetic factors that influence the metabolism of dopamine, such as polymorphisms in the Catechol-O-Methyltransferase (COMT) gene. COMT is an enzyme that breaks down dopamine in the synaptic cleft. Its activity is thought to have a greater impact on dopamine levels in the prefrontal cortex than in the striatum. This is because dopamine transporters, which are responsible for dopamine reuptake, are abundant in the striatum, but less prevalent in the prefrontal cortex, which relies more on COMT to remove dopamine from the synapse (Yavich et al., 2007). There are two recognised polymorphisms in the COMT gene: individuals with the Val polymorphism have high COMT activity and therefore are presumed to have relatively low baseline dopamine levels, and individuals with the Met polymorphism, have low COMT activity, and supposedly relatively high baseline dopamine (Chen et al., 2004).

Individuals homozygous for the Met polymorphism were found to have less pronounced prefrontal fMRI activation during WM tasks than those homozygous for the Val polymorphism (Mattay et al., 2000; Mier et al., 2009). This decreased prefrontal activation is seen by some as representing optimisation of WM processing in the prefrontal cortex (Mattay et al., 2000, 2003; Mehta et al., 2000; Cools et al., 2002; Cools and D'Esposito, 2011), and it is also observed in neurophysiological recordings (Vijayraghavan et al., 2007). Interestingly, when both groups were given dextroamphetamine or tolcapone, both of which increase dopamine levels, WM performance improved in Val, but not in Met participants, and prefrontal cortical activation increased in individuals with the Met polymorphism (Mattay et al., 2000; Apud et al., 2006; Roussos et al., 2009).

More evidence on the role of baseline dopamine in determining drug response comes from studies using Positron Emission Tomography (PET), which enables quantification of dopamine synthesis in midbrain neurones. Individuals with low WM capacity had significantly lower dopamine synthesis capacity (as

quantified by PET) than those with high WM capacity (Cools et al., 2008). Furthemore, in elderly individuals, dopamine synthesis capacity predicted both WM performance and prefrontal activation during a WM task (Landau et al., 2009). Cools et al. (2009) characterised this relationship between dopamine synthesis capacity and response to dopamine agonists more directly: they found that individuals with low striatal dopamine synthetic capacity, and low WM capacity, had a beneficial effect from the dopamine agonist bromocriptine, while WM performance was impaired by the same agent in those with high dopamine synthetic (and high WM) capacity.

D_1 versus D_2 and prefrontal versus striatal activity

As already discussed, the anatomical distribution of different types of dopamine receptors is not uniform: density of D_1 receptors is up to 10-fold higher than that of D_2 in the prefrontal cortex (Lidow et al., 1991), while D_2 receptors are predominantly located in the striatum (Hersch et al., 1995). An important observation, coming both from animal and human neuropharmacology studies, is that D_1 and D_2 receptor stimulation have disparate, at times even opposite, effects on WM (Sawaguchi et al., 1990; Schneider et al., 1994; Müller et al., 1998).

For example, Müller et al. (1998) studied the effects of pergolide, a mixed D_1/D_2 receptor agonist, and bromocriptine, a selective D_2 receptor agonist, on a delayed response task, and found that pergolide, but not bromocriptine, facilitated VWM performance. Accordingly, several animal studies have demonstrated that modulation of D_1, but not D_2 receptor activity influences the delay period of WM tasks (Sawaguchi et al., 1990; Schneider et al., 1994; Castner et al., 2000; Castner and Goldman-Rakic, 2004).

However, modulation of D_2 receptor activity has also been shown to influence VWM (Luciana et al., 1992; Kimberg et al., 1997, 2001; Glickstein et al., 2002; Mehta et al., 2004b, 2005). Furthermore, there is evidence that D_2 receptor activity affects VWM in a highly specific way. Examining the action of the D_2 receptor antagonist on VWM in a delayed response task, Mehta et al. (2004b) found that in addition to (and perhaps underlying) VWM impairment due to

the drug there was impaired set-shifting – the ability to flexibly disengage from an irrelevant task and engage with a task-relevant one. In contrast, the drug had also a protective effect against task-irrelevant distraction (Mehta et al., 2004b). Cools et al. (2007) investigated how the D_2 receptor agonist bromocriptine in a VWM task where subjects had to remember either faces or scenes over a brief delay, while ignoring congruent and incongruent distracting images. They found that bromocriptine improved flexible set-shifting between stimulus categories in individuals with low WM span but impaired flexible updating in high-span subjects. Furthermore, in low WM span subjects, bromocriptine significantly potentiated fMRI activation in the striatum (Cools et al., 2007).

Another line of evidence on the role of dopaminergic activity, especially D_2, in WM comes from patients with Parkinson's disease (PD). Neurodegeneration in the dopaminergic nigrostriatal pathway in PD is characterised by selective cognitive impairments, including deficits in WM and set-shifting, even in early stages of the disease (Owen et al., 1992, 1995; Fournet et al., 1996; Cools et al., 2001; Gurvich et al., 2007). Impaired set-shifting ability in PD has been noted in a variety of tasks (Lees and Smith, 1983; Cools et al., 1984; Taylor et al., 1986; Hayes et al., 1998). These deficits in PD may be qualitatively distinct from those noted in prefrontal focal lesions: for example, patients with frontal lobe damage were found to be impaired in their ability to shift attention *from* a previously relevant stimulus dimension, medicated PD patients had difficulty shifting *to* a previously irrelevant dimension, and non-medicated PD patients were impaired in both conditions (Owen et al., 1993).

Based on these observations, some authors have proposed that D_1 receptor activity in the prefrontal cortex and D_2 receptor activity in the striatum might have qualitatively different, even opposing, but complementary actions (Cools and D'Esposito, 2011). According to this view, the prefrontal cortex is responsible for maintaining stable WM representations, while the striatum has a role in flexible updating of information in WM. In other words, while dopaminergic activity in the prefrontal cortex is important in *maintaining* WM representations across brief delays, striatal dopaminergic activity, modulated

principally by D_2, rather than D_1 receptor stimulation, might be important in *updating* these representations with new information. This model, therefore suggests a dynamic balance between stability and flexibility: high levels of D_1 activity in the prefrontal cortex would result to excessive stabilisation, which would lead to perseveration, while excessive D_2 activity in the striatum would result to extreme flexibility, manifesting itself as distractibility (Cools and D'Esposito, 2011).

In conclusion, dopaminergic activity plays an instrumental role in WM processes. Dopaminergic systems might therefore present good potential targets for new treatments aiming to improve cognition in clinical conditions characterised by deficits in WM and associated functions. However, as we saw, there are multiple levels of complexity in the way prefrontal and striatal dopaminergic systems determine WM processes, and in the way they are modulated by pharmacologic manipulation. Careful consideration of these factors should inform the design of future studies on neuropharmacological modulation of VWM.

1.7 Outline of the thesis

This thesis consists of two interconnected parts, the first examining VWM in health and the second in focal lesion patients.

Chapters 2 and 3 study how VWM is distributed and dynamically updated across time and according to attentional priority in healthy volunteers. In Chapter 2, I examine how a finite memory resource is distributed between objects over time, using a novel task which permits calculation of VWM precision for visual objects presented in sequence. I describe how memory resources are redistributed as new items are added in the sequence, and how different sources of error, including failures in feature binding, contribute to loss of precision. The role of goal-directed attention in redistributing VWM resources over time to task-relevant items is examined in Chapter 3, where individual differences in this filtering ability are also considered.

In Chapters 4 and 5, I investigate how these processes might be affected by focal brain lesions associated with visual neglect following right hemisphere stroke, and how dopaminergic modulation can ameliorate component cognitive deficits of this syndrome. Chapter 4 studies VWM updating using a sequential task in patients with right hemisphere stroke, with or without visual neglect, and examines the lesional correlates of VWM precision and attentional filtering. Chapter 5 is a double-blind randomised trial of the dopamine agonist rotigotine in a group of patients with visual neglect and motor weakness following right hemisphere stroke. Using an innovative design, this study tests the hypothesis that rotigotine can ameliorate neglect by modulating cognitive component deficits of the syndrome, including VWM and attention, and examines whether these effects depend on relative preservation of the right prefrontal cortex. In Chapter 6, the role of the MTL in VWM across time is studied in two patients with highly focal hippocampal lesions due to autoimmune limbic encephalitis, and in further two patients with more widespread temporal lobe damage.

Finally, the general discussion (Chapter 7) draws together the findings from healthy subjects and focal lesion patients, and suggests directions for further research.

Chapter 2

Dynamic Updating in Visual Working Memory

2.1 Introduction

One of the fundamental properties of working memory (WM) is its limited capacity (Cowan, 2001; Baddeley, 2003). For vision, this has been estimated to be 3-4 items, based on the ability of observers to *detect changes* made to a *static* array of objects over a brief delay (Phillips, 1974; Pashler, 1988; Luck and Vogel, 1997; Vogel et al., 2001; Todd and Marois, 2004). But in real-world situations, the visual input to the brain is constantly changing with movements of the body and alterations in the environment, so ecologically important objects are often viewed in sequence. Vital cognitive processes – such as action selection and planning – therefore have to be informed by memory for objects that have been replaced by others. The neural mechanisms involved in maintaining these representations across intervening items and over time have become the focus of intense investigation using neurophysiological and imaging techniques (D'Esposito et al., 1999b; Marshuetz et al., 2000; Xu and Chun, 2006; Siegel et al., 2009; Jenkins and Ranganath, 2010; Takahama et al., 2010; Warden and Miller, 2010).

Like change detection experiments, studies examining visual WM for serially presented items have tested recall in a binary fashion, assuming that each object in a sequence is either perfectly stored or entirely forgotten (Phillips and Christie, 1977; Smyth et al., 2005; Johnson and Miles, 2009). But this approach does not provide any information on the fidelity of stored representations. An

alternative method is to measure the variability of memory estimates around the true value, i.e., the *precision* of recall for object attributes such as location, orientation or colour (Palmer, 1990; Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009, 2011b; Fougnie et al., 2010).

This approach has recently prompted a re-evaluation of the classical view of visual WM as comprising a fixed number of 'slots', each maintaining a single object with high resolution. Instead, such investigations have led to a radically different proposal: that although WM resources are highly limited, they are not quantized, so they can be flexibly distributed to prioritize a few items for high resolution storage or store a larger number with lower fidelity (Alvarez and Cavanagh, 2004; Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009). This is a fundamentally different conceptual framework to the traditional account and has important implications for research that seeks to examine the neural basis of WM. However, previous studies have not examined the *precision* of memory when objects are presented *sequentially*.

In the present Chapter, I examine how a finite memory resource is distributed between objects *over time*. In other words, what happens to the memory of a visual object when newly presented stimuli are memorised, and how does having to keep in memory a certain number of objects affect memory for an additional item, presented subsequently? A new behavioural task was used, in which visual stimuli were presented sequentially, and memory precision was measured for one of the items, which could have any order in the sequence. Memory resolution for objects in sequences was compared with simultaneously presented items, and a probabilistic model was used to account for the distribution of responses. I demonstrate how the precision with which objects are stored in memory changes dynamically in favour of more recent items. Critically, I argue that memory for sequentially presented objects is especially prone to corruption by features belonging to other items in the sequence (misbinding). These observations suggest new cognitive mechanisms on how WM resources are distributed and dynamically reallocated over time, as new visual stimuli are encoded.

2.2 Methods

2.2.1 Participants

A total of 34 healthy volunteers (19 female, 15 male, age: 19-34 years) participated in the study after providing written informed consent to procedures approved by the local Ethics Committee. All participants had normal or corrected-to-normal visual acuity and reported normal colour vision. Nine volunteers (six female, age [mean ± s.d.]: 25.8 ± 5.3 years) took part in Experiment 1, eight volunteers (six female, age: 21.4 ± 3.1) participated in Experiment 2, eight (four female, 24.8 ± 2.5) in Experiment 3.

2.2.2 Experimental procedure

Experiment 1: ***Sequential presentation.*** A schematic representation of the task is shown in **Figure 2.1A**. Each trial consisted of a sequence of 1, 2, 3, 4, or 5 coloured bars (2^o x 0.3^o of visual angle) consecutively presented on a grey background, on a 21-inch CRT monitor at a viewing distance of 60 cm. Each bar had a different colour and orientation and all were presented at fixation, at the centre of the display. The sequence of colours in each trial was produced by permutation of a random selection of five easily distinguishable colours. On each trial, participants did not know in advance how many objects they would have to remember. Stimuli within the same sequence differed by at least 10^o in orientation, which was otherwise random. Each stimulus was shown for 500ms, followed by a 500ms blank screen.

At the end of each sequence, recall for one of the items was probed by redisplaying a bar of the same colour with a random orientation. A circle surrounding this probe item made it easily distinguishable from the to-be-remembered items in the sequence. Subjects were instructed to rotate the probe using a response dial (Logitech Intl. SA) to match the remembered orientation of the item of the same colour in the sequence – henceforth termed

the *target*. Note that I use the term 'target' here simply to distinguish from other objects in the sequence, or *non-target*s, that were not probed. I emphasize that in this experiment, participants did not know which item would be tested or how long each sequence would be from trial-to-trial.

Each subject completed a total of 400 interleaved trials. There were 25 trials for each of the 15 combinations of sequence length (1–5) and serial position of the target item within the sequence (375 trials in total). In addition, there were 25 trials where a single item was followed by a longer blank period of 3500ms (equivalent in duration to a four-item sequence). These trials were presented interleaved with other conditions to examine the pure effects of temporal delay on memory, in the absence of intervening objects.

Experiment 2: ***Simultaneous presentation.*** To compare WM precision for items presented sequentially with objects displayed simultaneously, the task shown in **Figure 2.1B** was used. Each trial started with a central fixation cross displayed on a grey background. Once stable fixation was established, 1, 2, 3, 4, or 5 bars, each of different colour and orientation, were now presented simultaneously. The display settings, dimensions of the stimuli and the selection of colour and orientation were as in Experiment 1. Stimuli were displayed at random positions on an invisible circle of radius 6°, with a minimum centre-to-centre separation of 3° of visual angle. This memory array was shown for 1000ms, followed by a 1000ms blank. Subsequently, one of the items in the array was probed by colour at central fixation, and the participant had to indicate the remembered orientation of the item, as in Experiment 1. Each subject completed 500 trials. Eye position was monitored online at 1000 Hz using a frame-mounted infrared eye tracker (SR Research Ltd, Canada), to ensure subjects maintained central fixation. Trials were repeated if gaze deviated more than 2° from the fixation cross during stimulus presentation.

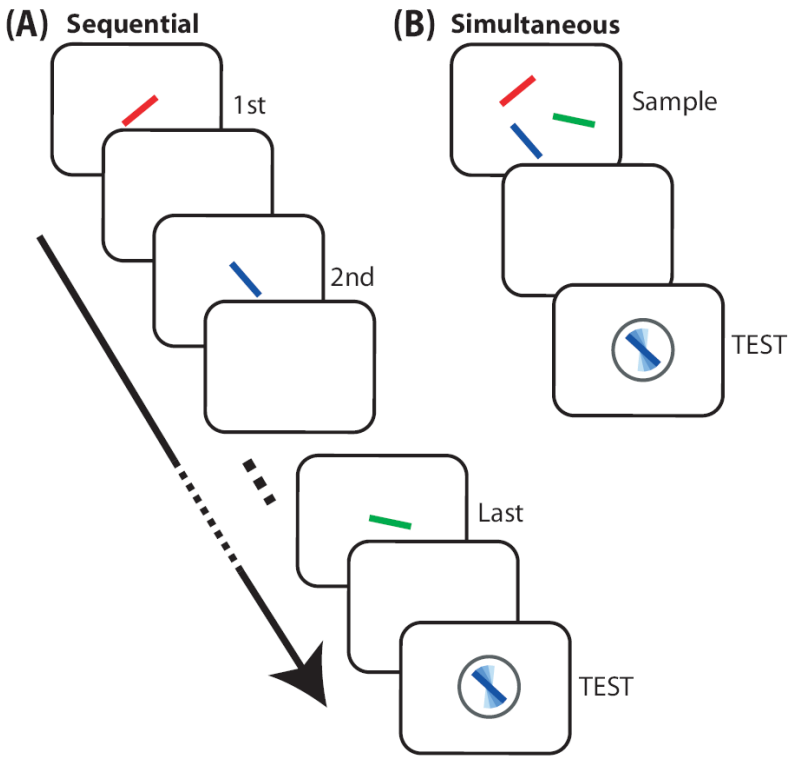


Figure 2.1: Experimental paradigm

(**A**) In Experiment 1, participants were presented with a sequence of coloured bars, each with a different orientation. A probe item of a randomly chosen colour (in this case, blue) was then presented, and subjects adjusted the orientation of the item of the same colour in the sequence (in this case, the 2nd item). (**B**) In Experiment 2, stimuli were shown simultaneously, in an array, following which the orientation of one of the items (in this case, again blue) was probed and had to be reproduced from memory.

Experiment 3: ***Simultaneous versus sequential presentation at different locations.*** In Experiment 1, items were presented at the same spatial location, which may confound the comparison with simultaneous presentation, where each item occupies a different location in space. Therefore, we performed an additional experiment to distinguish the effects of sequential versus simultaneous presentation from the potentially confounding effects of presenting stimuli at the same or at different locations. In Experiment 3, two, four, or six items were presented either simultaneously or sequentially, always at different locations, with a minimum centre-to-centre separation of 3° of visual angle. All stimuli were presented at an eccentricity of 6° for 500ms, followed by a 500ms blank. The dimensions of the stimuli and the selection of colour and orientation were identical to the previous experiments. As in Experiment 2, central fixation was monitored online using infrared eye tracking and trials were repeated if gaze deviated more than 2° from the fixation cross during stimulus presentation. At the end of each trial, one of the items was probed by colour at the centre of the screen, as in the previous experiments. Each subject completed a total of 480 trials consisting of four 60-trial blocks of sequential and four blocks of simultaneous presentation. The order of the eight blocks was randomized.

2.2.3 Analysis

For each trial, a measure of error was obtained by calculating the angular deviation between the orientation reported by the subject and the correct orientation of the target bar in the preceding sequence. Precision was calculated as the reciprocal of the standard deviation of error across trials ($1/\sigma$). As the parameter space for orientation is circular, we used Fisher's definition of standard deviation for circular data, i.e. the square root of minus 2 times the log of the mean resultant length of the circular data vector divided by the number of observations (Fisher, 1993), subtracting the value expected for chance: therefore a precision value of zero corresponds to responding at random. This method of estimating the fidelity of recall of a visual stimulus

based on the distribution of error has previously been described for orientation, location (Bays and Husain, 2008) and colour (Bays et al., 2009), but only for *simultaneous* displays where all objects to-be-remembered were presented together. Precision was calculated separately for each subject, set size and condition. Hypotheses regarding the effects of experimental parameters (number of items, order in sequence, cueing condition) on precision were tested by ANOVA and *t*-tests, as specified in the Results. Where parametric tests were used, assumptions on normality and equal variances were tested using Kolmogorov-Smirnov and Levene tests, respectively.

To quantify the contribution of different *sources of error* to overall precision estimates in each experiment, I applied a probabilistic model introduced previously by Bays et al (Bays et al., 2009). This model, building on an earlier proposal by Zhang and Luck (Zhang and Luck, 2008), attributes errors on the reproduction task to three sources:

- Gaussian variability in memory for the target orientation
- A certain probability on each trial of misreporting one of the other *non-target* orientations in the sequence
- A certain probability of responding with a *random* orientation, *not related* to any of the items in the sequence.

This model is described as follows:

$$p(\hat{\theta}) = \alpha \phi_\kappa(\hat{\theta} - \theta) + \beta \frac{1}{m} \sum_i^m \phi_\kappa(\hat{\theta} - \varphi_i) + \gamma \frac{1}{2\pi}$$

where θ is the true orientation of the target item, $\hat{\theta}$ the orientation reported by the subject, and ϕ_κ is the von Mises distribution (the circular analogue of the Gaussian) with mean zero and concentration parameter κ. The probability of reporting the correct target item is given by α. The probability of mistakenly reporting a non-target item is given by β, and $\{\varphi_1, \varphi_2, \ldots \varphi_n\}$ are the orientations

of the m non-target items. The probability of responding randomly is given by $\gamma = 1 - \alpha - \beta$. A graphical representation of these model components is given in **Figure 2.5**.

Maximum likelihood estimates (Myung, 2003) of the parameters κ, α, β, and γ were obtained separately for each subject and set size in Experiments 1, 2 and 3, using an expectation-maximization algorithm (MATLAB code available at: http://www.sobell.ion.ucl.ac.uk/pbays/code/JV10/).

To investigate how serial order of the target item (when it appeared) in a sequence affected the model parameters, the model was also applied separately for each combination of serial position and sequence length in Experiment 1. As this meant dividing the data from each subject between a large number of conditions, for this analysis data was pooled across subjects, maximizing the data available for each condition. Likelihood ratio tests were used for statistical comparison of parameter values estimated from pooled data.

2.3 Results

2.3.1 Effects of serial order and set size on recall precision

In Experiment 1, subjects were presented with a sequence of randomly oriented coloured bars, and asked to reproduce from memory the orientation of one bar, specified by colour (**Figure 2.1A**). The total number of stimuli varied between 1 and 5, and participants were unaware of how many would be displayed in each trial. All items in the sequence were equally likely to be tested.

Figure 2.2 shows how the precision with which subjects recalled an item's orientation varied as a function of its serial position (i.e. when it appeared in a sequence), for different sequence lengths (denoted by different colours). Serial order had a significant effect on precision, irrespective of the total number of items in the sequence (two-way ANOVA, set size × serial position, main effect of serial position: $F_{(4,120)}=11.2$, $P<0.001$) with the most recent item remembered significantly more accurately than preceding items (two-way ANOVA, simple contrast to last item: $F_{(4,120)}=3.67$, $P=0.007$). Thus there was a clear recency effect. No statistically significant differences in precision were observed for earlier positions in a sequence (main effect of serial position with final item excluded: $F_{(3,80)}=0.57$, $P=0.64$). Performance was significantly better than chance for every combination of serial order and set size ($t_{(8)}>2.9$, $P<0.023$), indicating that some information was stored about every item in a sequence.

How does the *total* number of objects in the sequence affect the fidelity of recall? As shown in **Figure 2.2**, when comparing between sequences of different lengths, for every serial position, precision decreased significantly as the number of items increased (main effect of set size: $F_{(4,120}=11.8$, $P<0.001$; set size × serial position interaction: $F_{(6,120)}=0.23$, $P=0.97$). Remarkably, this effect was present even for the last (and best remembered) item in a sequence: precision for the final item decreased significantly as the number of preceding items increased (main effect of set size, final items only: $F_{(4,40)}=4.7$, $P=0.004$). Therefore, as the total number of items held in memory increases, there is a

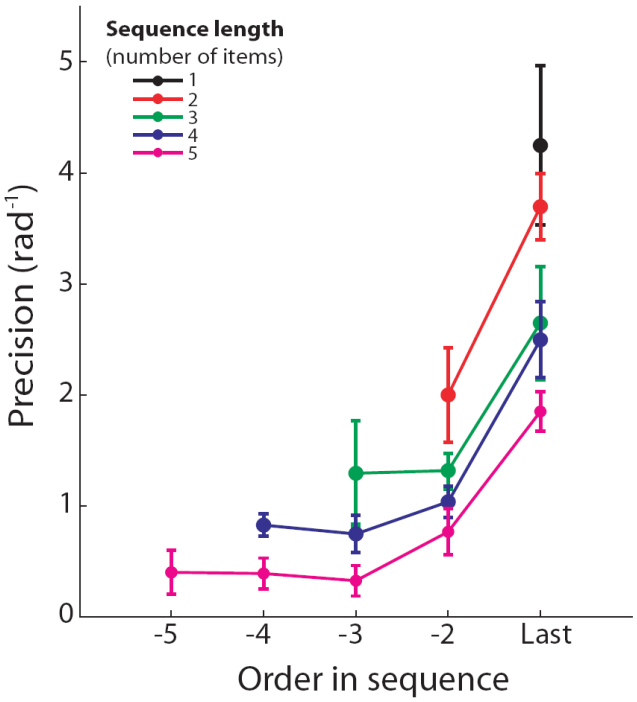


Figure 2.2: Serial order and sequence length modulate memory precision.

Precision is plotted against order in the sequence, i.e., when in a sequence the item probed after the end of the sequence had appeared. Each coloured line represents a different sequence length. The last item was remembered most accurately, while earlier items in the sequence were recalled with similar precision. Error bars represent SEM.

loss of fidelity in recall of items of *any* serial order, including the most recent. Note that many previous studies of serial WM, using for example verbal or visuospatial lists to-be-remembered (Broadbent and Broadbent, 1981; Burgess and Hitch, 1999; Logie et al., 2000), have also shown recency effects but crucially, in those studies, participants were either able to report an item or not, in a binary – all or nothing – fashion. Here I demonstrate that the fidelity with which the last item is recalled is modulated in a graded manner by the number of items that precede it.

2.3.2 Comparison with simultaneous presentation

The results of Experiment 1 also have implications for models of WM because they are consistent with the principles of a *shared resource* model of working memory, which until now has been applied only to simultaneous displays (Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009). Specifically, the findings above show that as the total number of items in memory increases the proportion of resources dedicated to each item declines, degrading the fidelity of storage. A simple 'slot' model limited to three objects (Luck and Vogel, 1997; Cowan, 2005) would not predict such a graded decline in performance for sequences below the capacity limit of 3, since each item should be capable of being stored with equal, high resolution up to that limit. Only after all available slots had been occupied would one expect a rapid decline in precision.

From the perspective of a shared resource model, the recall advantage for the final item in a sequence observed here could result from an uneven distribution of resources, with the largest proportion allocated to the most recently presented item. To investigate this possibility further, I compared the results of sequential displays in Experiment 1 with a second task that differed only in that all items were presented *simultaneously* in a single display (Experiment 2; task shown in **Figure 2.1B**). This provides a direct comparison of how resources are allocated when information is processed sequentially in a temporal stream versus when it is presented all together to the visual system.

In **Figure 2.3**, mean recall precision is presented as a function of the *total number of items* presented for sequential (black symbols) and simultaneous display (red symbols). While precision declined similarly with increasing number of items in both cases, on average, items were recalled with significantly lower precision when presented sequentially ($F_{(1,83)}=22.2$, $P<0.001$). Importantly, however, this cost for sequential presentation was confined to the earlier items in each sequence.

When performance for only the *last* item in each sequence was considered (blue symbols in **Figure 2.3**), it was found to be stored with equivalent resolution to items in a simultaneous display *of the same number of items* ($F_{(1,83)}=0.18$, $P=0.67$), while memory for all previous items in the sequence was significantly less precise ($F_{(1,7)}=47.7$, $P<0.001$). Thus, for example, if the total sequence length was three items, the last item was recalled with precision equivalent to when 3 items were presented simultaneously, but the previous items were recalled with significantly lower precision than the average precision for 3 simultaneously presented objects.

Therefore, every time a new item was added to a sequence, the precision with which it was remembered was limited only by the number of previous items already stored in memory, just as for simultaneous presentation *of the same number of items*. However, crucially, earlier items were remembered significantly less accurately. Thus memory precision for these is not simply determined by the total number of objects that have to be kept in memory, but is also limited by some additional source of error, which I sought to determine.

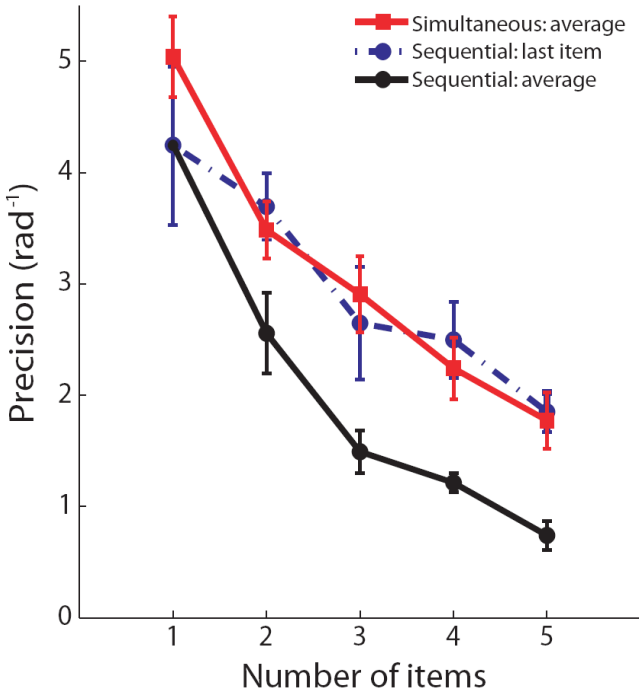


Figure 2.3: Effect of the number of items on memory in sequential and in simultaneous presentation.

Average precision (across all items) decreased with increasing number of items presented in a sequence (black line), or simultaneously (red line). Note that the last object in a sequence (blue dash-dotted line) was remembered with similar precision to an item in an array of the same number of simultaneously presented objects. There was no significant difference for one item in "sequential" compared to "simultaneous" conditions. Error bars are SEM.

2.3.3 Cost of sequential presentation is not due to temporal decay

There is a long-standing controversy as to whether WM recency effects are a result of interference between remembered objects, or whether time-related memory decay also plays a role (Hole, 1996; Berman et al., 2009; Zhang and Luck, 2009; Lewandowsky et al., 2009). To control for the possibility that loss in precision for earlier items is due to time-dependent decay in their memory representation, I compared precision for the first item from a sequence of 4 with a single object followed by a long retention period, equivalent in duration to a sequence of three further items.

Recall was not affected by the longer retention period ($t_{(8)}$=1.1, P=0.32; **Figure 2.4**), but there was a fivefold decrease in memory precision when three consecutive items were presented during the same amount of time ($t_{(8)}$=8.9, P<0.001). Therefore, rather than time-related decay of their memory representation, the loss in accuracy of recall for earlier items in this study is due to the presence of the subsequent items.

2.3.4 A probabilistic model to investigate the sources of error in sequences

The precision measure used thus far to describe performance is a non-parametric statistic reflecting the fidelity of recall of a target feature, independent of any particular model of the underlying response distribution. To investigate further possible mechanisms producing the loss of memory precision for earlier items in sequences, I applied to the data a probabilistic model that assumes three potential *sources of error*: i) Gaussian variability in recall of the target orientation, ii) a certain probability of responding with the remembered orientation of a *non-target*, due to associating incorrectly, or *misbinding* a target's colour with the orientation of a non-target, and iii) a certain probability of producing a random response not related to any of the orientations presented (**Figure 2.5**; for further details, see paragraph 2.2.3). This analysis method has been used in previous studies, but only for simultaneously presented items (Bays et al., 2009, 2011b; Fougnie et al., 2010).

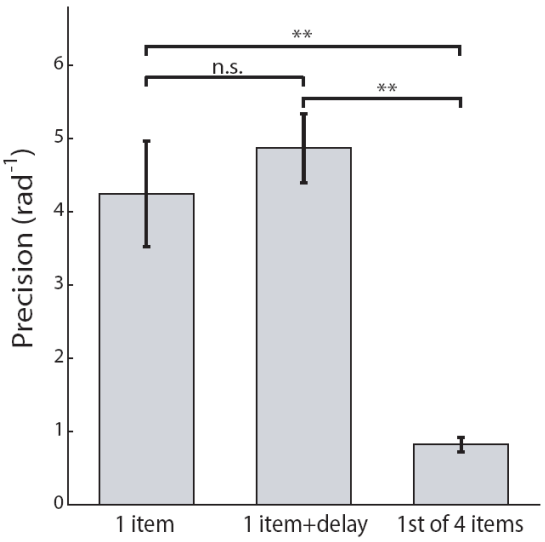


Figure 2.4: Loss of precision for previous items is not time-dependent.

When compared with a single item (left bar), memory precision was not affected by a longer retention time (middle bar), but was significantly lower when three further items were presented in the same retention period (right bar). Error bars are SEM. **P<0.001, n.s: non-significant.

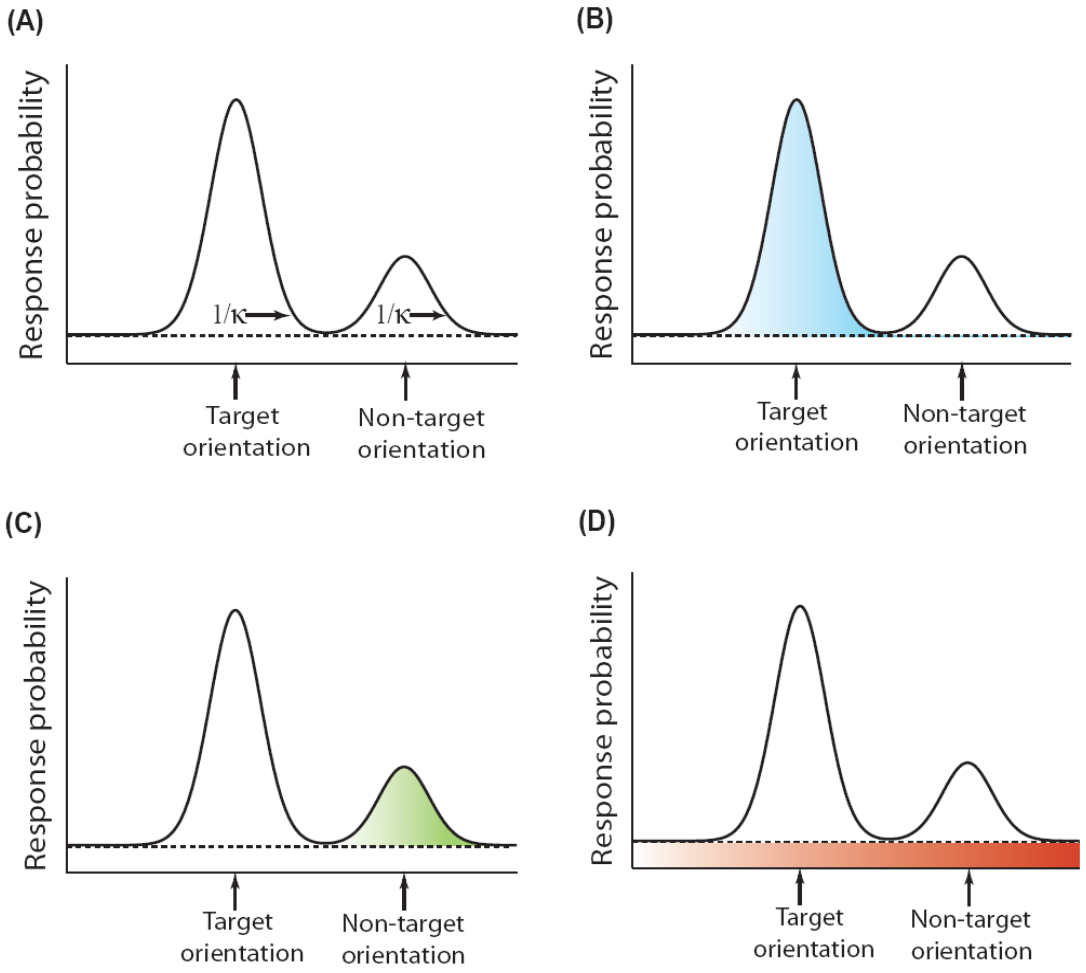


Figure 2.5: A probabilistic model of three sources of error in subjects' responses.

Subject responses on the memory task were decomposed into three separate components, illustrated by the shaded regions in (**B–D**): a circular Gaussian distribution of responses centred on the orientation value of the target (**B**), circular Gaussian distributions with the same width centred on each non-target orientation value, corresponding to *misbinding* errors (**C**), and a uniform distribution, capturing random responses unrelated to any of the sample orientations (**D**). The *variability* in recall of each item's orientation was governed by κ, the concentration parameter of the circular Gaussian (von Mises) distributions (**A**).

First, the model was applied separately for each number of items, presented sequentially or simultaneously. As shown in **Figure 2.6**, for both sequential (in black) and simultaneous presentation (in red), as the number of items increased, responses centred on the target became increasingly variable, as indicated by a significant decrease in the concentration parameter (κ) of their distribution (**Figure 2.6A**; two way ANOVA, set size × presentation mode: main effect of set size: $F_{(4,75)}=15.9$, $P<0.001$, interaction with mode of presentation: $F_{(4,75)}=0.33$, $P=0.86$). Importantly, the variability of subjects' responses for the same number of items was indistinguishable, whether presented sequentially or simultaneously (main effect of presentation mode: $F_{(1,75)}=0.47$, $P=0.50$).

In addition to the increase in variability, the proportion of responses attributed to report of the correct target item (α) declined significantly as set size increased, in both sequences and simultaneous arrays (**Figure 2.6B**, main effect of set size: $F_{(3,60)}=13.7$, $P<0.001$, interaction: $F_{(3,60)}=0.33$, $P=0.05$). Here, however, a significant difference was observed between sequential and simultaneous presentation (main effect of presentation mode: $F_{(1,60)}=61.6$, $P<0.001$), with a substantially smaller probability of responses centred on the target orientation under sequential presentation (mean $\alpha = 74\%$ for sequential vs. mean $\alpha = 93\%$ for simultaneous presentation, for set size ≥ 2).

The decline in the probability of responding with the target orientation with increasing set size coincided with a corresponding increase in both *misreporting* a non-target as a target (β, **Figure 2.6C**, main effect: $F_{(3,60)}=7.7$, $P<0.001$, interaction: $F_{(3,60)}=1.6$, $P=0.21$) and of responding with a *random* orientation (γ, **Figure 2.6D**, main effect: $F_{(3,75)}=2.9$, $P=0.009$, interaction: $F_{(3,75)}=0.84$, $P=0.50$). However, the difference between sequential and simultaneous presentation was primarily accounted for by changes in the rate of misreporting (mean $\beta = 19\%$ for sequential vs. mean $\beta = 4\%$ for simultaneous presentation, for set size ≥ 2; $F_{(1,60)}=46.5$, $P<0.001$).

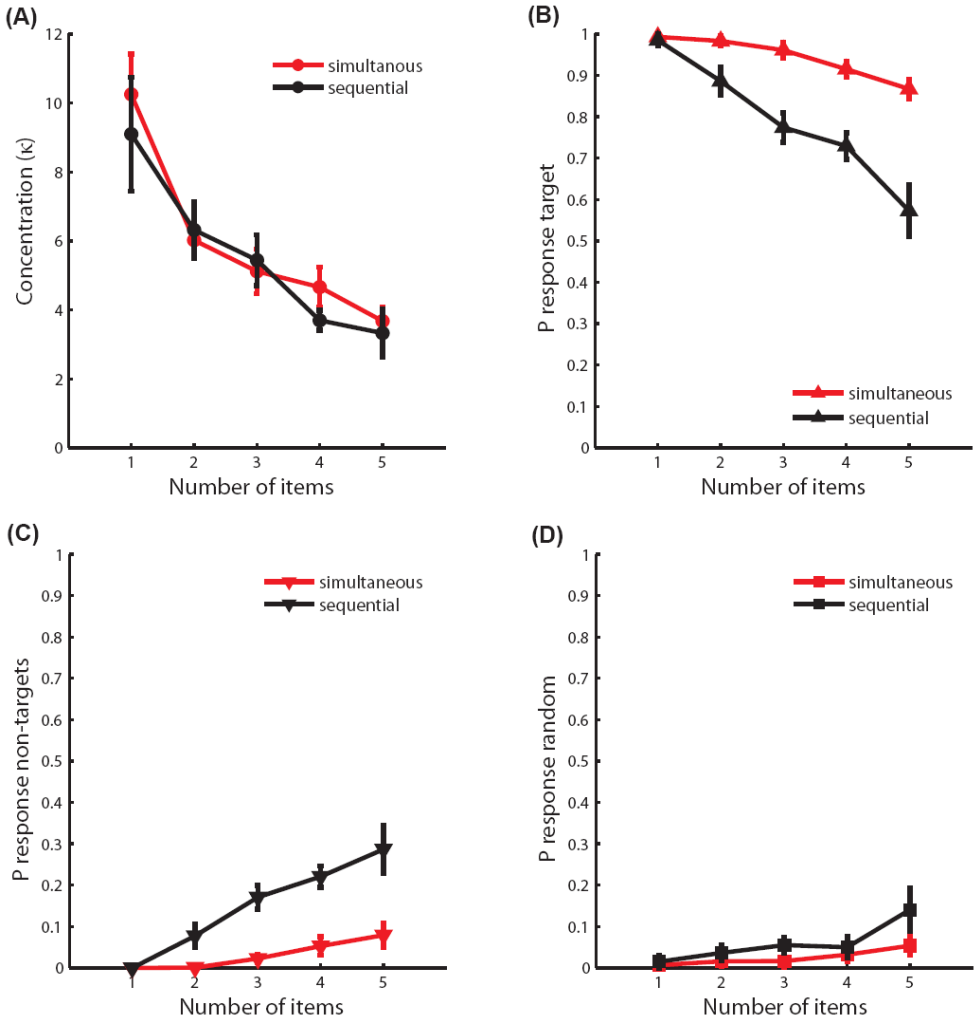


Figure 2.6: Model components for each set size; sequential vs. simultaneous.

Model parameters are shown for sequences (black) and for simultaneous presentation (red). (**A**) Variability of responses, as expressed by the concentration parameter of their distribution, increased as more items were stored in memory; this effect was not different between sequential and simultaneous presentation. (**B**) Probability of responding according to the target's orientation decreased with increasing set size and it was lower in sequences. (**C**) There was a corresponding significant increase in the probability of responding according to a non-target orientation; this component was greater in sequential than in simultaneous presentation. (**D**) Random responses (guessing) also increased with increasing number of items and were more likely in sequences. Note that, in sequences, the non-target component (**C**) was significantly higher than the random one (**D**); this was not the case in simultaneous presentation, where there was no significant difference between these two components.

Random responses were also significantly more probable in sequences ($F_{(1,75)}$=5.0, P=0.028) but to a much smaller extent than non-target responses (mean γ= 7% for sequential vs. mean γ= 3% for simultaneous presentation, for set size ≥ 2). It is important to note that in sequences of two or more items, misreporting accounts for a significantly greater proportion of the overall loss of precision when compared to random responses ($F_{(1,64)}$=23.0, P<0.001).

To investigate whether the contribution of the different sources of error to the overall loss of precision depends on the item's order in the sequence, I applied the model separately at each serial position and each sequence length. As shown in **Figure 2.7A-B**, both the probability of reporting the target item's orientation and the variability of those responses vary according to serial order of an item in the sequence (α: χ^2>13.5, P<0.003, for all sequence lengths; κ: χ^2>13.9, P<0.001, for all sequence lengths except in 2 items, where χ^2=2.8, P=0.096). Responses based on the correct target orientation were significantly more likely and less variable when the *last* item was probed (α: χ^2>13.5, P<0.003, for all sequence lengths; κ: χ^2>12.9, P<0.001, for all sequence lengths except in 2 items, as above).

Correspondingly, the probability of responding according to the orientation of a *non*-target depended significantly on the serial order of the tested item (**Figure 2.7C**; χ^2>11.4, P<0.004, for all sequence lengths), and was less likely for the last item than for any of the previous ones (Fig. 7C; χ^2>10.2, P<0.002, for all sequence lengths). Within the longest sequences (4 and 5 items), from earlier to later items, the probability of misbinding increases, and subsequently it decreases again for more recent items, producing an inverted U-shaped curve. This suggests both recency and a primacy effect in the probability of responding with the orientation of a *non-target* (**Figure 2.7C**).

The probability of responding randomly did not differ significantly with serial order: in sequences of any length, random responses were relatively rare (5.9%, on average) and unaffected by serial order (**Figure 2.7D**; χ^2<1.3, P>0.37). Overall, these results suggest that an increased probability of erroneously associating the colour of targets earlier in the sequence with the orientation of

non-targets could be an important mechanism giving rise to the overall precision cost of sequential presentation, particularly for items in the middle of a sequence.

Our findings also demonstrate that information about different objects held in WM are not independent once stored, but can interact – hence misbinding of object features across visual items. In addition, the comparison between sequential and simultaneous displays reveals an important factor about how WM resources are dynamically reallocated. Recall that, for sequences, subjects did not know how many items they would have to remember before a trial commenced, so they could not pre-allocate resources. Instead, each new object to-be-remembered (the current last item) was allocated its fair share of resources (as if it had appeared in a simultaneous array of the same total number of items). However, the resolution in memory for previous items became inferior. This reallocation of resources from earlier items was associated specifically with increased misbinding of features belonging to different objects. These findings place tight constraints on neural models of WM.

Note that, as the variability of responses and the number of non-targets increase, reliability of the fitted parameter estimates decreases, as indicated by the larger standard error e.g. set size 4 and 5 (**Figure 2.7**). In the case of two items, for example, a distribution of responses tightly centred on the only non-target orientation is easily distinguishable from a set of random responses. Conversely, in the case of five items, where each misbinding response can correspond to any of four different non-target orientations, distinguishing this from a uniform (random) distribution becomes increasingly difficult. However, while this unavoidable limitation reduces power, there were nonetheless statistically significant effects (e.g. of serial order) even in the longest sequences.

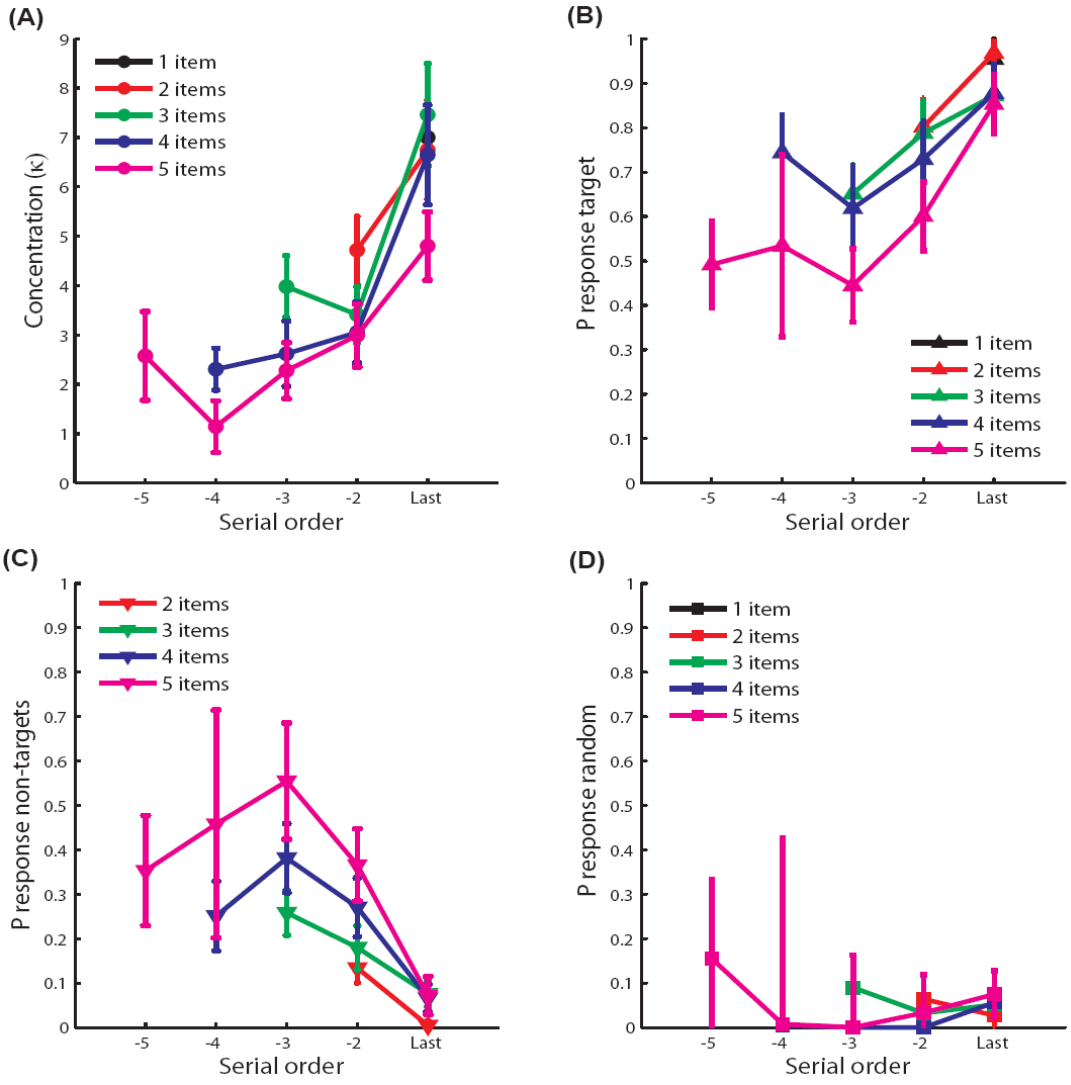


Figure 2.7: Model components for each serial position.

Variability (**A**) and probability (**B**) of responding according to the target's orientation depend on serial order, with responses on target being more probable when the last item was probed. (**C**) There was a corresponding increase in the probability of responding according to a non-target for items earlier than the last. (**D**) Conversely the probability of responding randomly was not significantly different for items with different order in the sequence. Error bars represent SEM.

2.3.5 Simultaneous versus sequential presentation at different locations

The comparison between simultaneous and sequential presentation in the previous experiments may have been confounded by the fact that sequentially presented items were shown at the same location, while this was not the case for simultaneous presentation. In Experiment 3, every object was presented at a different location, in either simultaneous or sequential display.

As shown in **Figure 2.8**, average memory precision for items presented sequentially *at different locations* (black line) was significantly lower than precision for the same number of items presented simultaneously (red line; repeated-measures ANOVA, $F_{(1,7)}=29.94$, $P=0.001$), in keeping with our results from Experiments 1 and 2. Also consistent with our previous results, precision for the most recent object in a sequence of items shown at different locations (**Figure 2.8**, blue dotted line) was no different than the average precision when the same number of objects were presented simultaneously (repeated-measures ANOVA, $F_{(1,7)}=0.33$, $P=0.58$). Therefore, the finding that memory precision is lower for sequential when compared to simultaneous presentation, cannot be simply attributed to *spatial* overwriting of earlier items, as precision is lower in sequential presentation also when each item in the sequence is presented at a different location.

Next, to quantify the parameters explaining the loss of memory resolution when objects are presented sequentially at different locations, I applied the probabilistic model analysis to the data from Experiment 3. Consistently with the previous results, while the variability of responses was similar to simultaneous presentation (κ: $F_{(1,7)}=0.62$, $P=0.457$; **Figure 2.9A**) responses to the target orientation were significantly less likely in sequential presentation (α: $F_{(1,7)}=47.4$, $P<0.001$; **Figure 2.9B**). Importantly, a significant proportion of the loss in memory resolution for sequentially presented items can be attributed to non-target responses (due to misbinding between visual features of different objects in the sequence) also when each object is projected at a different spatial location (β: $F_{(1,7)}=13.42$, $P=0.008$; **Figure 2.9C**). Therefore increased misbinding in sequences does not occur only when the spatial

locations of the misbound objects overlap. As previously, a significant increase in random responses in sequences when compared to simultaneous presentation is also noted (*γ*: $F_{(1,7)}$=6.48, P=0.038; **Figure 2.9A**).

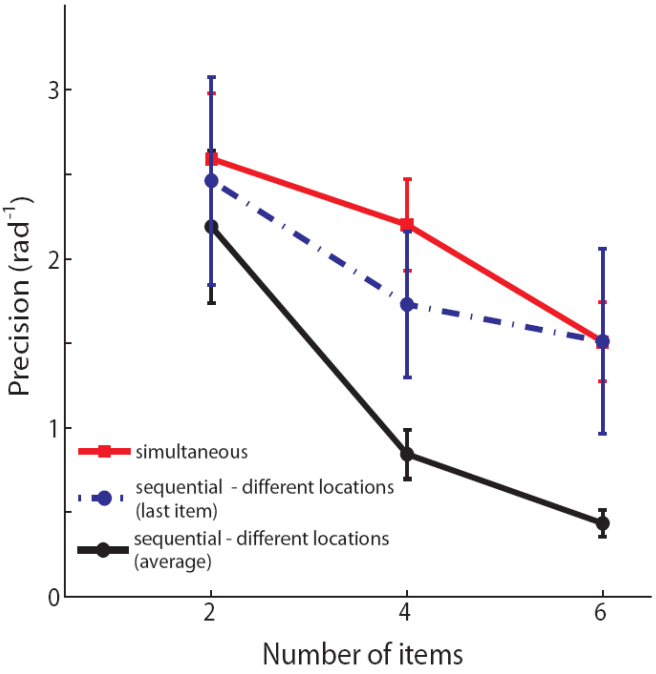


Figure 2.8: Comparing simultaneous and sequential presentation when all items are displayed at different locations.

When each object in a sequence was presented at a different spatial location, memory across all items in the sequence (black line) was, on average, less precise than when the same number of objects were presented simultaneously (red line). Precision for the last item in a sequence (blue dash-dotted line) is no different than for an item in an array of the same set size. Note that, for both simultaneous and sequential presentation, precision values are similar to those in Fig. 3. Error bars indicate SEM.

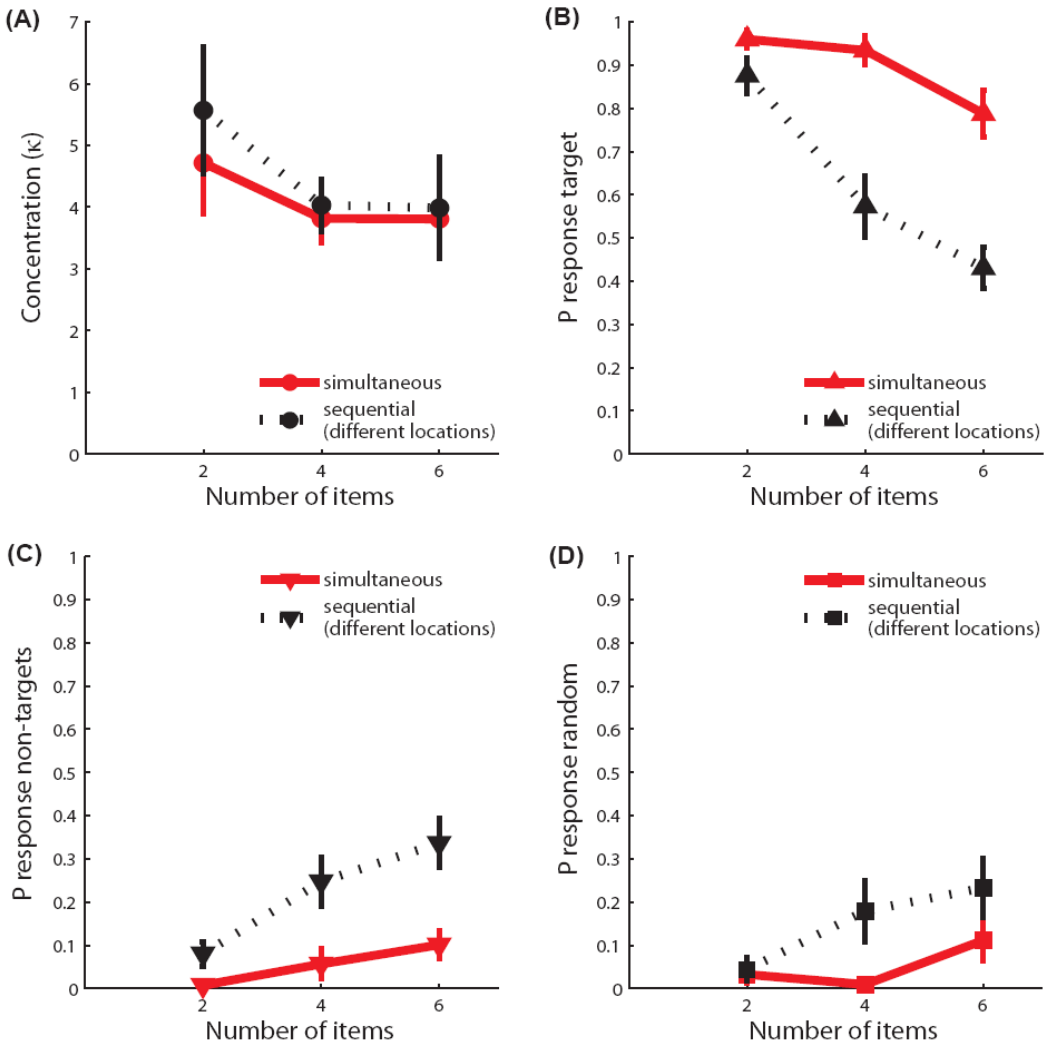


Figure 2.9: Model components for simultaneous and sequential presentation, when all items are displayed at different locations.

Model parameters are shown for items displayed sequentially at different locations (dotted black) and for simultaneous presentation (red). (**A**) The variability of responses was not different between the presentation modes. The probability of responding to the target orientation (**B**) was significantly lower for sequential presentation. This can be explained by an increase in non-target responses (due to misbinding of the target colour and a non-target orientation) in the case of sequential presentation (**C**) and, to a lesser extent, by an increase in random responses (**D**).

2.4 Discussion

In the experiments presented in this Chapter, I examined the fidelity of visual WM for orientation of objects displayed in sequence by analysing *precision* of observers' reports, rather than asking them about the presence or absence of a change (Luck and Vogel, 1997; Vogel et al., 2001).

There was a marked decrease in precision as the number of items to-be-remembered increased (**Figures 2.2** and **2.3**). Thus, memory capacity is indeed highly limited. Importantly, however, WM resolution decreased smoothly as total number of items increased (**Figure 2.3**), and this loss of fidelity affected every item in the sequence (**Figure 2.2**). Even adding a single item to a previous object held in memory was sufficient to produce a significant drop in mean precision of report (**Figure 2.3**).

These data cannot be adequately explained by a simple 'slot' model in which WM is limited to 3-4 items because this would predict optimal performance until the object capacity limit is reached, and a sharp drop in precision when that limit is exceeded (Pashler, 1988; Luck and Vogel, 1997; Cowan, 2001). Instead, our results are compatible with the concept of a limited memory *resource*, a proportion of which is allocated to each item as the total number of items increases. Such a proposal also provides a parsimonious account of WM limits in the case of simultaneously-presented objects (Bays and Husain, 2008; Bays et al., 2009).

Measuring WM precision revealed in addition that, although there is a recency effect for all sequence lengths, the fidelity of memory for the last item was strongly modulated by the number of items that preceded it (**Figure 2.2**). Precision for the last item was worse in longer sequences, a finding which would have implications for neural models of serial WM. Previous studies using similar display intervals have also reported recency effects (Phillips and Christie, 1977; Broadbent and Broadbent, 1981; Wright et al., 1985; Neath, 1993; Hay et al., 2007; Blalock and Clegg, 2010) but none have shown that last-

item recency is affected by sequence length in this way. Again, those studies used binary measures of report (correct or incorrect); precision, I argue, provides a more sensitive index that better constrains models of WM and their neurophysiological substrates.

Comparison of sequential versus simultaneous arrays (**Figure 2.3**) demonstrated that while precision in both cases fell smoothly with increasing number of objects, mean precision across all items was significantly worse for sequences than for simultaneous arrays (Lecerf and De Ribaupierre, 2005; Allen et al., 2006b; Blalock and Clegg, 2010). Crucially, however, this cost of sequential presentation was restricted to items preceding the last object. Thus, for example, the last item in a sequence of four objects was recalled with the same precision as if it had been tested in an array of four items presented simultaneously, while all other items in the sequence were recalled less precisely. This cannot be accounted for by temporal decay (**Figure 2.4**), consistent with studies of serial verbal WM (Lewandowsky et al., 2009). Furthermore, we show that lower precision in sequential versus simultaneous presentation is not due to spatial overwriting, as it is replicated when all items are presented sequentially at different locations (**Figure 2.8**). So how can this effect be explained?

To address this question, I applied a probabilistic model (**Figure 2.5**) to the distribution of recall errors that was previously developed for simultaneous presentation (Bays et al., 2009, 2011b). Here, the analysis revealed that the Gaussian variability in recalling an item's orientation was on average equivalent whether the set of items was presented sequentially or simultaneously (**Figure 2.6A**). Hence, the loss of overall fidelity observed with sequential presentation is not due to increased variability in storing each item's orientation.

However, in addition to accurate recall of orientation, successful performance also required accurate *binding* of orientation information with colour. A seminal study suggested that different visual features are stored independently but it is their integration that is vulnerable to interference (Wheeler and Treisman,

2002). Memory for bound objects in a sequence is also more susceptible to interference from subsequent items than WM for individual features (Allen et al., 2006b).

Our findings show that the probability of errors due to *misbinding* target colour with the orientation of a non-target was significantly higher for sequences than in simultaneous presentation (**Figure 2.6C**). Furthermore, these errors were more common for objects earlier in the sequence than for the last item (**Figure 2.7C**). It has been shown previously that spatial location has a central role in feature binding (Treisman and Zhang, 2006). Our results show that increased misbinding in sequential presentation occurs also when the locations of misbound objects do not overlap (**Figure 2.9C**).

The performance cost observed when comparing sequential to simultaneous presentation is primarily due to an increased probability of misbinding when items are presented in a sequence. Thus there is 'interference' across stored representations, a phenomenon that is also not predicted by independent object 'slots'. A smaller, but significant proportion of responses were attributed to a random component, which could correspond to simple guessing. However, this did not change significantly between the last and preceding items (**Figure 2.7D**), and so cannot account for the performance cost specific to earlier items.

While variability in the Gaussian component of error for items presented sequentially was, *on average*, equivalent to that observed in simultaneous presentation, when comparing this parameter between items at different serial orders, there was less variability in recalling orientation of the last item than previous ones (**Figure 2.7A**). Thus, whereas each object in a simultaneously presented array theoretically is allocated the same amount of WM resource, this is clearly not the case in sequences where each new object to-be-remembered (the current last item) was allocated its fair share of resources (as if it had appeared in a simultaneous array of the same total number of items). However, the resolution in memory for previous items became inferior.

Thus there is a dynamic redistribution of memory resource in sequences, and this reallocation from earlier items was associated specifically with increased

misbinding of features belonging to different objects. While this process can be conceptualized as a shift of 'internal resources' (Chun et al., 2011) from items already held in memory to a newly added item, there are alternative possibilities.

First, it might be argued that it is possible for a memory slot to abandon the object it currently holds and switch to maintaining a new object. Critically, the revised slot model (Zhang and Luck, 2009) predicts *fixed-resolution* memory representations which would be difficult to reconcile with some of the findings of the current study. For example, if the most recent item displaces a previous item from a fixed-resolution slot, responses for one or more items in the previous serial positions should be either equally accurate to those for the last item (when a previous item keeps its slot), or consistently below chance (when a previous item is left without a slot). But our findings suggest neither is the case, even if we assume that two or more slots "double-up" (Zhang and Luck, 2008) to accommodate the last item with higher precision than the previous objects.

Second, it might be argued that allocation of greater attention (i.e. 'external resources') (Chun et al., 2011) to the most recent item, plus increasing passive interference between items held in memory as new items are added might also explain our findings. But note that such a model would need to posit some separation between (internal) resources for working memory and extra (external) resources available for attention, an area of research that remains to be resolved (see Chun et al., 2011 for discussion). Moreover, this still remains updating of resources, as attention is redeployed to the new item.

Finally, although in the current study I investigated WM for one visual dimension (orientation), a recent study of sequential WM for visual motion has shown similar results (Zokaei et al., 2011). Thus the principles discussed here are not confined to only one feature. In summary, using precision as an index of WM provides important new insights into the nature of memory representations of objects viewed at different times, revealing how WM resources can be dynamically and flexibly reallocated.

Chapter 3

Voluntary Control over Working Memory Precision across Time

> "Now that I do know it I shall do my best to forget it."
> "To forget it!"
> "You see," he explained, "I consider that a man's brain originally is like a little empty attic […]. It is a mistake to think that that little room has elastic walls and can distend to any extent. Depend upon it there comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones."
> "But the Solar System!" I protested.
>
> *A Study in Scarlet*, Arthur Conan Doyle

3.1 Introduction

In our experience of the visual world, objects perceived across a period of time are rarely equally important, or equally relevant to the task at hand. As we depend on a limited memory resource (Cowan, 2005; Baddeley, 2007; Bays and Husain, 2008; Gorgoraptis et al., 2011), the ability to discard distracting items and retain the most useful objects which are relevant to current and future behaviour, is of obvious ecological importance.

Voluntary, 'top-down' control – sometimes also referred to as attention – has been described as a 'gatekeeper' of visual working memory (Awh et al., 2006; McNab and Klingberg, 2007). Selection of important information occurs both

at an early stage and later during processing: voluntary control can affect the sensory encoding phase (Corbetta et al., 1990; Luck et al., 1997; Chawla et al., 1999), but it also controls whether perceived sensory information gains access to further working memory processing and maintenance (Shapiro et al., 1997a; Awh and Jonides, 2001). Selection can also occur internally, within working memory, as demonstrated by experimental paradigms where objects were cued only *after* the stimuli were no longer visible – a technique also known as 'retro-cueing' (Lepsien and Nobre, 2007).

Neurally, the primary determinant of this voluntary selection process might be filtering irrelevant items out of working memory or preventing them entering, rather than enhancing relevant information (Zanto and Gazzaley, 2009). Filtering ability varies between individuals, and it has been shown to determine working memory capacity, and to relate to general intelligence (Gevins and Smith, 2000; Vogel et al., 2005; Astle and Scerif, 2011). Furthermore, the ability to suppress irrelevant information decreases with normal aging, while the ability to enhance task-relevant memories remains unaffected (Gazzaley et al., 2005b).

Voluntary control over working memory precision has not been studied before in the context of sequentially presented visual objects. This is a particularly interesting framework, because constraints posed by working memory *updating* every time a new item is added (see Chapter 2) may potentially limit voluntary control over memory resources.

In the two experiments presented in this Chapter, I examined how memory precision is affected by the relative behavioural relevance of each of the objects in a sequence. Task-relevance of items presented in sequence was manipulated by modulating how frequently each of them was probed. Memory precision was compared between more and less task-relevant items in each serial order, and a generative model was applied in each case, to examine the sources of error, including failure in visual feature binding. Finally, individuals' ability to filter out irrelevant items was studied in relation to their performance on standard measures of memory and intelligence.

3.2 Methods

To investigate how WM resources are allocated to a prioritized (cued) item in a sequence compared to lower priority (non-cued) objects, I examined the performance of healthy subjects on two variants of the sequential WM task introduced in Chapter 2. The critical new element in the experiments presented here is that one of the items in the sequence was made more *task-relevant* than the others, by being tested more frequently.

In Experiment 1, this difference in task-relevance was *relative*, meaning that non-cued items were still tested, albeit in a smaller proportion of the trials.

In Experiment 2, an item of a given colour was tested on all trials, with *absolute* (100%) validity. Therefore, all other items in the sequence in this case were task-irrelevant, and were never probed.

3.2.1 Experiment 1: cueing with relative validity

Subjects

Nine (three female, age: 25 ± 2.7) healthy volunteers participated in Experiment 1 after providing written informed consent to procedures approved by the local Ethics Committee. All participants had normal or corrected-to-normal visual acuity and reported normal colour vision.

Experimental procedure

In Experiment 1, a sequence of four coloured bars, each with different colour and orientation, was presented on each trial, using the same display settings, stimulus dimensions and display times as in the original sequential WM task presented in Chapter 2. However, here, participants were instructed prior to the experiment that items of one specified colour were more likely to be tested. This cue colour was fixed throughout each experimental session, but different for different participants. There were two experimental conditions, performed in separate blocks:

1) In the *cue present* condition, one of the four items on each trial was of the cue colour. This cued item was probed on a higher proportion of trials, 62.5%, as opposed to 12.5% for each of the other three, 'uncued', items.

2) In the *baseline* condition, the cue colour was not present in the sequence and all items were equally likely to be probed (25%), and therefore equally task-relevant.

The participant had to indicate the remembered orientation of the target item using a dial (Logitech Intl. SA) to rotate the probe bar, as in the previous experiments (Chapter 2). Each subject completed a total of 300 trials, consisting of four blocks of 50 trials for the *cue present* condition and two blocks of 50 trials for the *baseline* condition. The order of the blocks was randomized.

Analysis: WM precision

Memory precision was calculated as described in Chapter 2, based on previous studies using the fidelity of recall of a visual stimulus as a sensitive index of resolution in visual memory (Alvarez and Cavanagh, 2004; Bays and Husain, 2008; Bays et al., 2009, 2011b; Zokaei et al., 2011; Gorgoraptis et al., 2011). Briefly, for each trial, the angular deviation between the orientation reported by the subject and the correct orientation of the target bar in the preceding sequence was obtained, and precision was calculated as the reciprocal of the circular (Fisher, 1993) SD of error across trials ($1/\sigma$). As previously (Chapter 2), the value expected for chance was subtracted, therefore a precision value of zero corresponds to responding at random.

Additionally, to assess the effects of prioritizing items ('cued' objects) at different serial positions in Experiment 1, I calculated, for each serial position in the sequence, the fractional difference in precision between the *cue present* and *baseline* conditions as:

$$(P_C - P_B) / (P_C + P_B), \quad (3.1)$$

where P_C is the precision in a *cue present* sequence and P_B the precision in a *baseline* sequence. For this analysis, data were pooled across subjects, increasing the number of trials on which each precision calculation was based.

Model analysis

To quantify the contribution of different sources of error to overall precision estimates in each experiment, I applied a probabilistic model introduced previously by Bays et al. (2009), and described in detail in Chapters 1 and 2. This model attributes errors on the reproduction task to (1) Gaussian variability in memory for the target orientation; (2) a certain probability on each trial of misreporting one of the other, non-target, orientations in the sequence; and (3) a certain probability of responding with a random orientation not related to any of the items in the sequence.

Here, maximum likelihood estimates of these parameters were obtained separately for cued and for uncued items, from the trials where a cued was present, as well as for the baseline condition.

3.2.2 Experiment 2: cueing with absolute validity

Subjects

Twenty (ten female, age: 21.5 ± 2.9) healthy volunteers participated in Experiment 2 after providing written informed consent to procedures approved by the local Ethics Committee. All participants had normal or corrected-to-normal visual acuity and reported normal colour vision.

Experimental procedure: WM task

Experiment 2 was designed to investigate how WM precision for a visual object is affected by the presence of irrelevant distractors, which were never probed. In other words, I asked whether items that are entirely task-irrelevant are still involuntarily encoded in WM, reducing the memory resources available for a task-relevant object. I also examined individual differences in the ability to filter irrelevant objects out of memory and how such filtering ability relates to WM precision.

The task is presented on **Figure 3.3A**. There were three experimental conditions, given in separate blocks of 50 trials, and the order of the blocks was randomized. Subjects participated in two experimental sessions, completing a total of 600 trials, corresponding to 4 blocks for each of the following three conditions:

- In the *cueing* condition (**Figure 3.3A**, left panel), four items, each of a different colour and orientation, were presented in sequence. Each stimulus was displayed for 500ms, followed by a 500ms blank screen. Subjects were informed at the beginning of the block that an item of a given colour would be tested in every sequence. This cued item was present in every trial in this condition, could be presented at any serial order in the sequence, and was tested with 100% validity. The colour of the cued item was fixed for the entire experimental session and it was different between the two sessions.
- In the *one item* condition (**Figure 3.3A**, middle panel), at each trial, only one item was presented for 500ms, followed by a variable delay (of 500, 1500, 2500 or 3500ms) to match the time interval from each of the four possible serial positions of the tested item to the probe in cueing condition. The aim of this design was to compare WM precision for one item in the absence of distractors (one item condition) to WM for one item in the presence of distractors (cueing condition), taking into account any effect of the time elapsed from the stimulus to the probe.
- In the *baseline* condition (**Figure 3.3A**, right panel), four items of different colours were presented in every sequence, and any of them could be tested, with equal probability, exactly as in the baseline condition of Experiment 1. Each stimulus was displayed for 500ms, followed by a 500ms blank screen. The colour that was cued in Condition 1 was not included among the stimuli of the baseline condition.

Display settings, stimulus dimensions, and recording of responses were identical to those in Experiment 1.

WM precision compared between conditions

WM precision was calculated as in Experiment 1. WM precision for the tested item was compared in the presence or in the absence of three additional distracting items (cued versus one item condition), as well as in the case where the three other objects present in the sequence were as task-relevant as the tested item (baseline condition). For these comparisons, two-way ANOVA, taking into account the serial order of the tested item, was used.

Model analysis

Maximum likelihood estimates of the parameters of the three-component probabilistic model used previously (see Paragraph 3.2.1) were obtained for each subject, and compared between the three conditions of Experiment 2.

An index of the recency effect in the baseline condition

A simple measure was computed for the recency effect on the baseline condition of Experiment 2, where all four items presented have to be memorised:

$$(P_{last} - P_{previous}) / (P_{total}), \quad (3.2)$$

where P_{last} is WM precision for the last (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.

An index of filtering ability

As a measure of the ability to filter out the task-irrelevant items, I calculated the ratio of WM precision in the cued condition over WM precision in the one item condition. The smaller the value of this index, the more different WM precision is in the presence and in the absence of distractors, therefore the lesser the ability to filter task-irrelevant items out of memory. Correlations of the filtering index with WM precision, as measured in the baseline condition, were tested using Pearson coefficient.

Questionnaire-based measures of WM and intelligence

Each subject participated in a battery of standardised tests measuring WM and intelligence, including forward and backward digit span (Orsini et al., 1987), forward and backward spatial span (Corsi blocks task) (Corsi, 1972), Raven's Progressive Matrices Test (Raven, 1941), and Cognitive Failures Questionnaire (Broadbent et al., 1982). Correlations of the above measures with WM precision (as measured in the baseline condition of Experiment 2) and filtering ability were tested using Pearson coefficient.

3.3 Results

3.3.1 Effect of cueing with relative validity on WM precision

In Experiment 1, four items were displayed sequentially, and one of them was made more task-relevant by increasing its relative probability to be tested. This prioritized or *cued* item was always of the same colour, and subjects were informed that this colour was more likely to be tested than the others. We investigated memory precision for the cued item, and also for the remaining, *uncued* items in the sequence. Performance on this task was compared with a neutral *baseline* condition, where all four items were equally probable to be tested. As shown in **Figure 3.1A**, memory for the cued item was significantly more precise than baseline ($t_{(8)}$=5.8, P<0.001), with a significant corresponding cost for the uncued objects ($t_{(8)}$=3.5, P=0.008).

I also investigated whether the benefits of cueing on memory precision – and the cost to the uncued items – were evenly distributed across the sequence, with respect to the serial order of the prioritized item. More specifically, I asked whether the relative benefit of cueing depends on serial order, and also whether the cost is distributed to all of the uncued items or, alternatively, whether it is limited to those preceding, or those following the cued one. Therefore, for every item in the sequence, the fractional difference in precision between the baseline condition and the 'cue present' condition was calculated for each possible serial order of the cued item (Equation 3.1). Positive values of this measure signify a gain and negative values a cost in memory precision, when compared to the baseline condition. As shown in **Figure 3.1B**, the relative gain in precision was similar for the cued items, irrespective of their order in the sequence, and the relative cost was distributed between all of the uncued items, both to those preceded by the cued item and to those followed by it.

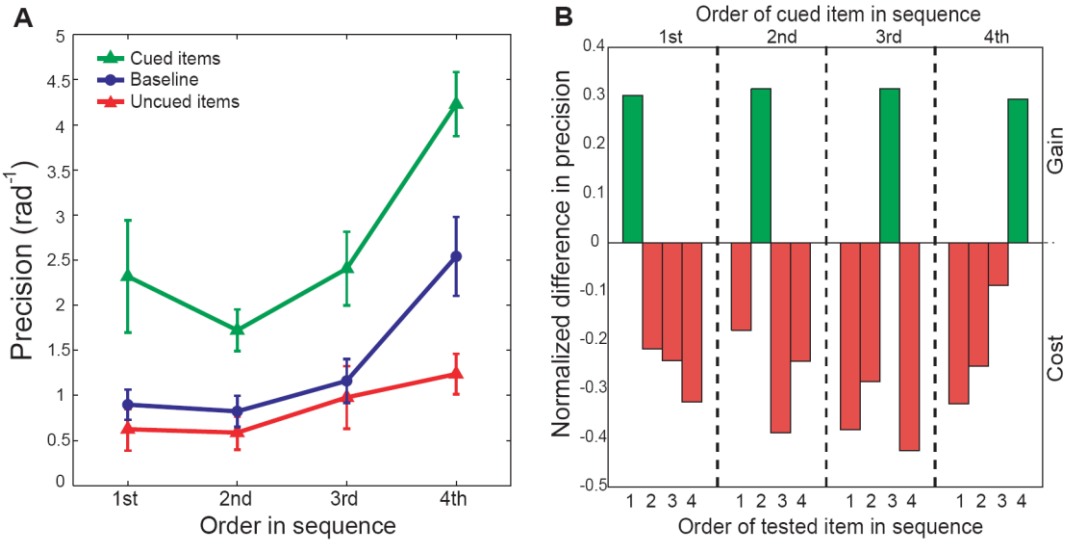


Figure 3.1: Predictive cueing by increasing relative validity.

A) The cued item was remembered significantly better than items in a baseline condition where no cue was present, with a corresponding cost in memory precision for the less task-relevant items, in the trials where a cue was present. Errorbars are SEM.

B) Fractional difference in precision between the trials where a cue was present and the baseline condition. Gain in memory precision for cued items (light shade), and a cost for the uncued ones (dark shade) was observed at all possible serial positions of the cued and the tested item.

3.3.2 Effect of cueing with relative validity on model parameters

Next, I sought to identify the sources of error resulting in decreases in memory precision for the less task-relevant items and the corresponding benefit for the cued objects in Experiment 1. To this end, using the probabilistic model which was described above, I estimated the Gaussian variability of the responses to the target, the probability of responding according to a non-target, and the probability of responding with a random orientation, separately for the cued and non-cued items (in the condition where a cue was present), and also for the baseline condition where all items were equally task relevant.

The results are presented in **Figure 3.2**. Gaussian variability for the cued item was significantly less than for an uncued item in the same sequence (χ^2=13.5, P=0.001), or an item in the condition where cueing was not present (χ^2=5.7, P=0.017; **Figure 3.2A**). The probability of responding with the target orientation was also significantly higher for the cued items when compared to baseline (χ^2=33.1, P<0.001; **Figure 3.2B**), with a corresponding decrease in target responses for the uncued items (χ^2=8.1, P=0.004; **Figure 3.2B**).

As shown in **Figure 3.2C**, a significant part of the gain in overall precision for the cued items can be attributed to a reduction in the probability of misreporting another item's orientation compared to uncued items (χ^2=23.8, P=0.017) or baseline (χ^2=20, P=0.018). In other words, increasing the task relevance of an item seemed to facilitate successful binding between its visual features (colour and orientation). The corresponding decrease in memory resolution for less task-relevant items was, to a significant extent, due to an increase in random responses (χ^2=5.3, P=0.022; **Figure 3.2D**), rather than an increase in misbinding, the probability of which is similar to the baseline condition (χ^2=0.1, P=0.66, **Figure 3.2D**).

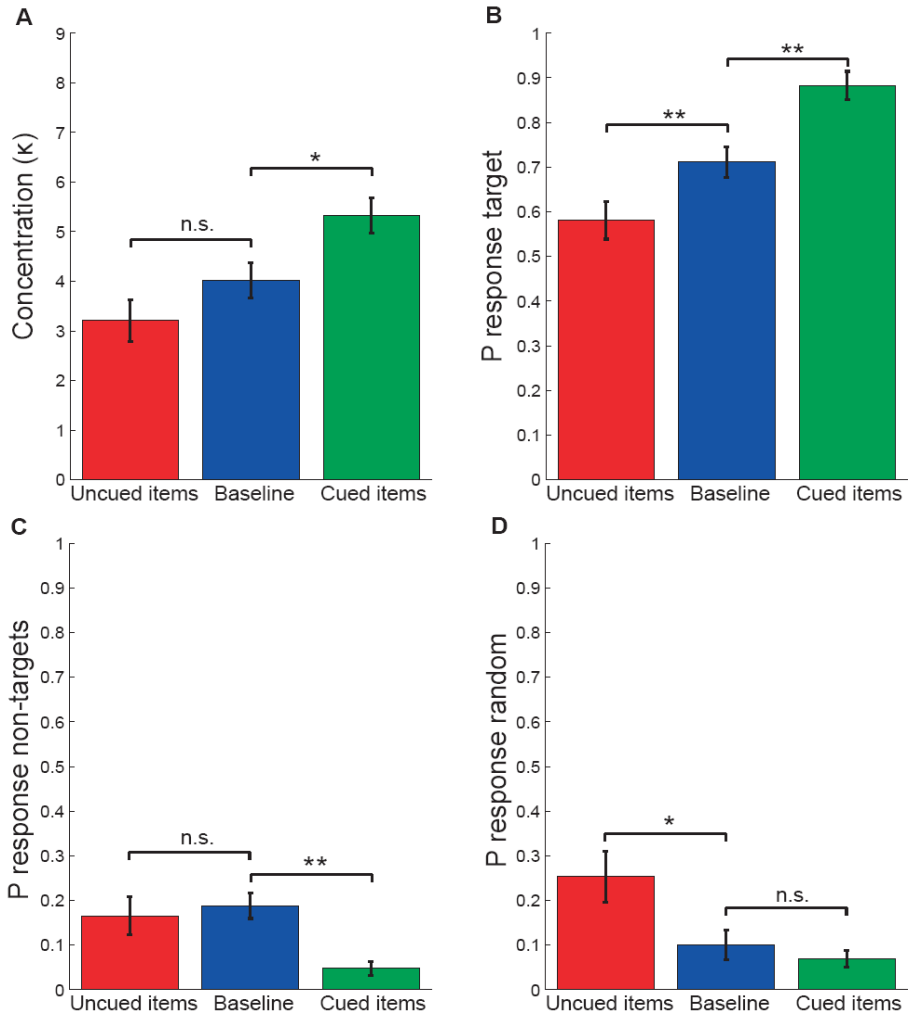


Figure 3.2: Model components in relation to task relevance (Experiment 1).

A) Responses centred at the target orientation were less variable for cued item when compared to baseline. There was a corresponding non-significant increase in variability for the remaining, less-task relevant items.

B) The probability of responding according to the target's orientation was enhanced for cued items, with a corresponding cost for uncued ones.

C) Probability of responding according to a non-target orientation was lower for the more task-relevant item, while this parameter was no different from baseline for the uncued items.

D) Conversely, random responses were increased for uncued items, and they were similar to baseline for the cued item. Error bars represent SEM. **P<0.001, *P<0.05, n.s: non-significant.

3.3.3 Effects of absolute validity cue on WM precision

The previous experiment demonstrated that WM resources can be voluntarily allocated to visual objects according to their relative task-relevance. In Experiment 2 (**Figure 3.3.A**), I sought to identify the limits of this voluntary control over WM resources. If healthy individuals have total control over the allocation of memory resources and can focus only on behaviourally relevant stimuli, then WM for a visual object among irrelevant distractors should be similar to WM for that visual object alone. Conversely, if WM is unavoidably intruded by task-irrelevant items, the accuracy of recall for the task relevant item should decrease in the presence of distractors.

As shown in **Figure 3.3B**, overall WM precision was similar between the cued condition, when distractors were present, and the one item condition, when they were replaced by a blank screen of the same time interval (Repeated measures ANOVA for condition and serial order, main effect of condition: $F_{(1,19)}$=1.35, P=0.26). However, there was a significant interaction of condition with serial order ($F_{(3,17)}$=6.11, P=0.005), with the first item in the sequence being remembered less precisely when followed by three subsequent distractors, when compared to an item followed by a matched blank delay ($t_{(19)}$=2.95, P=0.008; **Figure 3.3.B**). This difference was not significant for later items (second: $t_{(19)}$=1.6, P=0.12; third: $t_{(19)}$=0.8, P=0.42; fourth: $t_{(19)}$=-1.5, P=0.15). Therefore, subjects were capable of filtering out previous items, or one and two subsequent distractors, but this filtering ability was limited: three subsequent task-irrelevant items were sufficient to decrease WM resolution.

As expected, WM both in the one item and in the cued condition was more precise when compared to the baseline condition where all four items had to be memorised (one item vs baseline: $F_{(1,19)}$=130, P<0.001; cued vs baseline: $F_{(1,19)}$=165, P<0.001; **Figure 3.3B**).

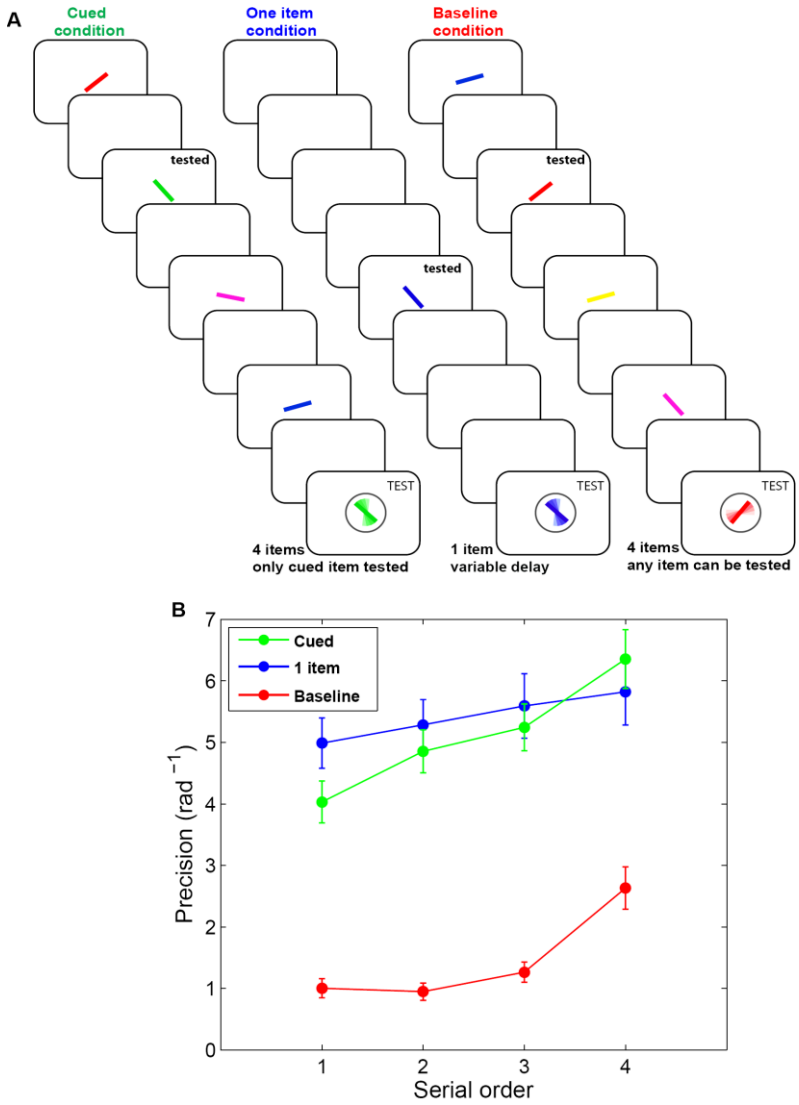


Figure 3.3: Experiment 2: experimental conditions and WM precision.

A) There were three experimental conditions: in the *cueing* condition (left), four items were displayed in sequence, but always the same one was tested (here, the green item); in the *one item* condition, a single item was presented, and tested after a delay period which matched in duration each of the 4 possible serial positions of the previous conditions; and a *baseline* condition, where four items were shown and any of them could be tested with equal probability.

B) WM in both cued and one item conditions is more precise than in the baseline condition. WM precision is lower for the first item in the cued condition, where there are four subsequent distractors, when compared to a single item without distractors (one item condition). This difference is not significant for the second, third, and fourth item in the sequence.

3.3.4 Absolute validity cue: model parameters

The data from the three conditions in Experiment 2 were further analysed using the three-component probabilistic model presented in detail in the previous chapters. Briefly, this model assumes that loss of precision in WM can be attributed to Gaussian variability when responding according to the correct target orientation (measured by the model's concentration parameter, κ), a certain probability of confusing the target colour with the orientation of a non-target – effectively misbinding visual features of different objects, with Gaussian error attached to these non-target responses, and lastly, a certain probability of responding randomly.

The concentration parameter was significantly lower in the baseline condition, where all four items had to be retained in memory, than in the cued ($F_{(1,19)}$=82.1, P<0.001; **Figure 3.4A**) or one item condition ($F_{(1,19)}$=71.9, P<0.001; **Figure 3.4A**). This parameter did not differ significantly between the cued and the one item condition ($F_{(1,19)}$=0.98, P=0.33; **Figure 3.4A**).

Responses to the correct target orientation were more likely in the cued and one item conditions than in the baseline condition (one item: $F_{(1,19)}$=108, P<0.001; cued: $F_{(1,19)}$=98.6, P<0.001; **Figure 3.4B**). There was a small but significant reduction in the probability of responding to the target for first item in the cued condition when compared to a single item ($t_{(19)}$=2.95, P=0.008; **Figure 3.4B**), although overall this parameter was not different between these two conditions ($F_{(1,19)}$=0.029, P=0.87; **Figure 3.4B**).

Interestingly, this decrease in target responses when the cued item was followed by three subsequent distractors (see green line in **Figure 3.4B**) was matched by a small increase in non-target responses for that first object (one-way ANOVA for cued condition, main effect of serial order: $F_{(3,76)}$=3.5, P=0.019; **Figure 3.4C**). Therefore, lower precision for the first item in this condition was associated with misbinding visual features of the first item with those of subsequent items. These 'illusory conjunctions' in working memory occurred even in the case where subsequent items were entirely task-irrelevant, but the effect was small.

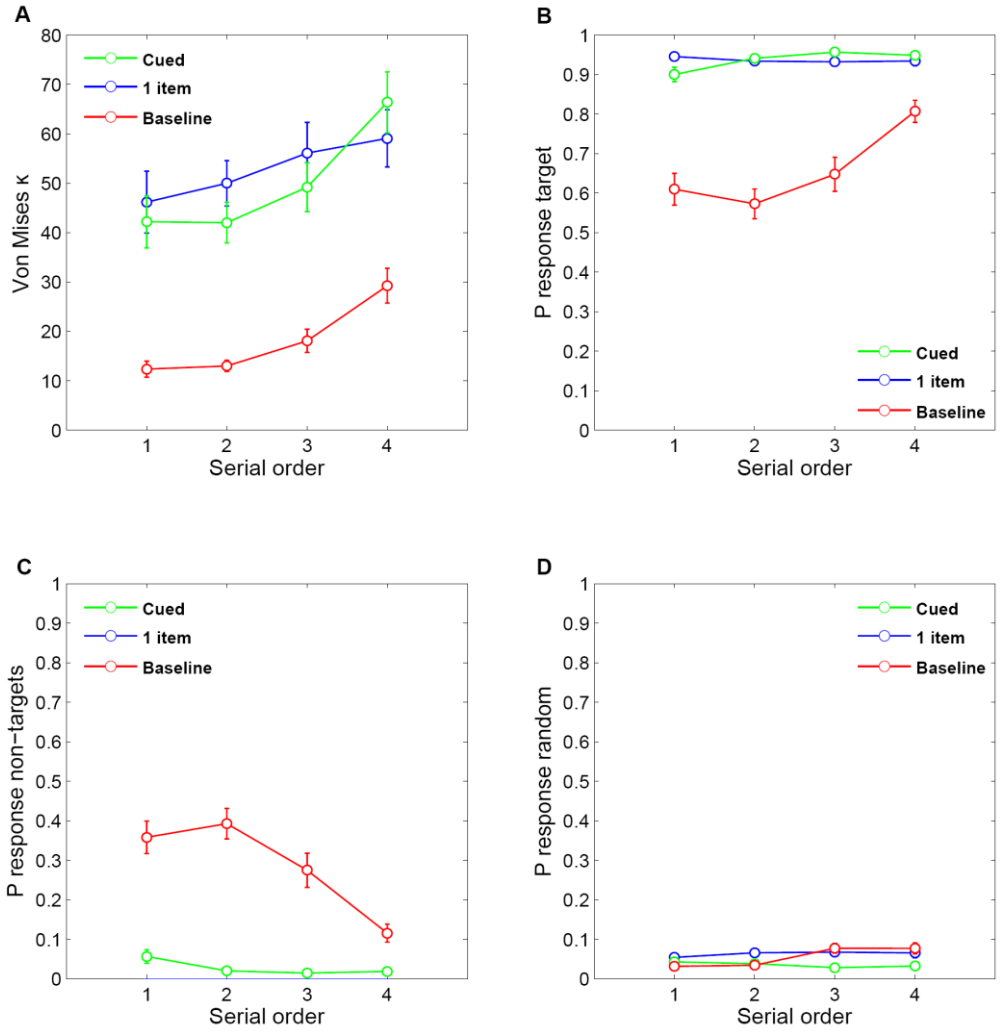


Figure 3.4: Experiment 2: model parameters in each condition.

A) The concentration parameter measuring variability of target responses is similar between the cued and one item conditions, and significantly lower (more variable responses) in the baseline condition.

B) Responses to the correct target orientation are more likely in the cued and one item conditions than in the baseline condition. There is a small but significant reduction in the probability of responding to the target for first item in the cued condition when compared to a single item.

C) Responses to the non-targets (misbinding) are more likely in the baseline condition. Interestingly, there is a small but significant increase in the probability of misbinding for first item in the cued condition when compared to a single item.

D) Random responses were of low probability but higher in the one item and baseline conditions than in the cueing condition.

Non-target responses when all four items had to be memorised (baseline condition) were in keeping with the results presented in Chapter 1, showing lower probability of misbinding for the last item in the sequence, compared to previous items. Non-target responses were also much higher than those in the cued condition, where only one item had to be memorised ($F_{(1,19)}$=74.1, P<0.001; **Figure 3.4C**).

Finally, random responses were very low, albeit significantly higher in the one item and baseline when compared to the cueing condition (one item *vs.* cueing: $F_{(1,19)}$=7.53, P=0.013; baseline *vs.* cueing: $F_{(1,19)}$=8.29, P=0.01; **Figure 3.4D**). This parameter did not differ between one item and baseline conditions ($F_{(1,19)}$=0.64, P=0.43; **Figure 3.4D**).

3.3.5 Filtering index and WM precision

To quantify the ability of each subject to filter the task-irrelevant objects out of WM, I calculated the ratio of WM precision for the cueing condition, over precision for a single item from Experiment 2. Thus a filtering ability value of 1 would mean that individuals were able to filter out all distractors, just as if they had not been presented, as in the single item case.

First, I examined correlations of this filtering index and WM precision, as well as with the magnitude of the recency effect (Equation 3.2). Filtering ability did not correlate significantly with average WM precision in the baseline condition (r=-0.4, P=0.78), or with WM precision for any specific serial order in this condition (1st item: r=-0.39, P=0.09; 2nd item: r=-0.44, P=0.052; 3rd item: r=-0.27, P=0.25; 4th item: r=-0.36, P=0.12).

There was a significant positive correlation between filtering ability and the magnitude of the recency effect (r=0.45, P=0.048; **Figure 3.5**), however this result was driven by one participant with very high filtering ability (**Figure 3.5**, red point), and the correlation was lost when that subject was excluded from the analysis (r=-0.25, P=0.92). This subject was not an outlier in any of the

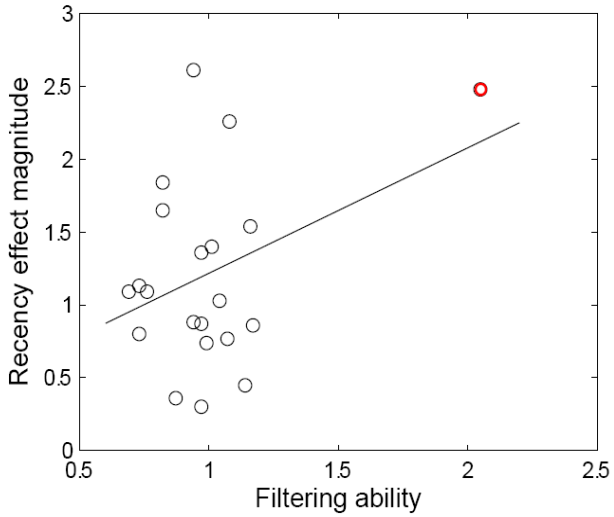


Figure 3.5: Correlation of filtering ability with recency.

A significant correlation between WM precision and magnitude of the recency effect was driven by a single subject with high filtering ability (red point). The correlation was no longer significant when this subject was excluded from the analysis.

other analyses, and therefore other results (**Figures 3.3, 3.4** and **3.6**) have not been unduly influenced by this subject.

Next, I investigated the relationship of WM precision, as quantified in Experiment 2, with performance in three standard tests of WM and intelligence: digit span, Raven's progressive matrices, and Cognitive Failures Questionnaire (CFQ). Individuals with higher WM precision in the baseline condition of Experiment 2 (where all four items displayed had to be memorised), scored higher in both forward (r=0.54, P=0.014; **Figure 3.6A**) and backward (r=0.58, P=0.007; **Figure 3.6B**) digit span.

There was also a positive correlation between WM precision from the same experimental condition and score in Raven's progressive matrices test (r=0.55, P=0.012; **Figure 3.6C**). However, WM precision did not correlate with CFQ (r=-0.058, P=0.81; **Figure 3.6D**).

Correlations of filtering ability and recency effect with standard WM and intelligence scores were also examined. Filtering ability did not correlate with any of the standard measures (forward digit span: r=-0.16, P=0.49; backward digit span: r=-0.13, P=0.59; Raven's matrices: r=-0.12, P=0.62; CFQ: r=-0.1, P=0.68). No correlation was observed between recency effect magnitude and any of the WM and intelligence scores (forward digit span: r=-0.18, P=0.46; backward digit span: r=-0.42, P=0.066; Raven's matrices: r=-0.11, P=0.64; CFQ: r=-0.06, P=0.8).

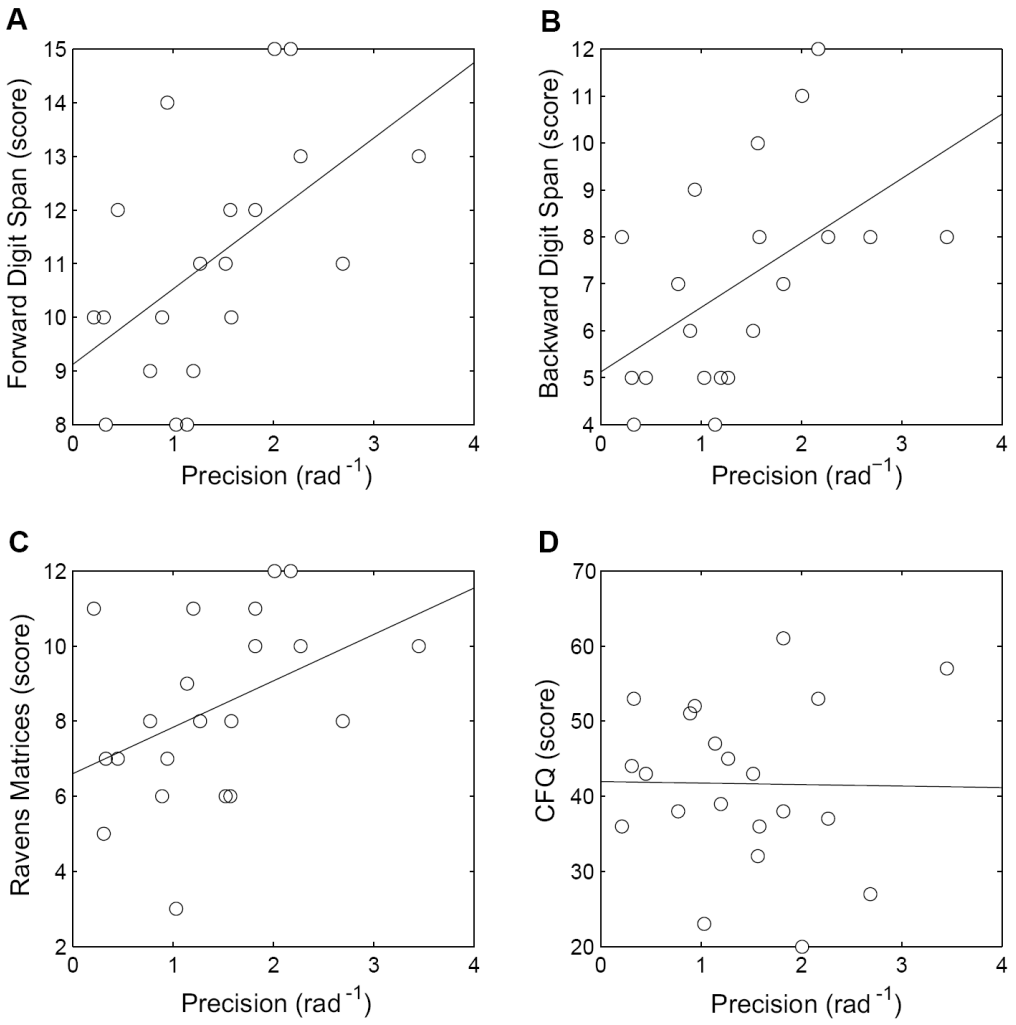


Figure 3.6: Correlations of WM precision with WM and intelligence.

Visual WM precision correlates significantly with forward **(A)** and backward **(B)** digit span, and Raven's Progressive Matrices score **(C)**. No significant correlation was observed between WM precision and CFQ score **(D)**.

3.4 Discussion

In the two experiments discussed in this Chapter, I examined the effects of predictive cueing on memory precision for the orientation of sequentially presented objects. The results of Experiment 1 indicate an uneven distribution of memory resources to the advantage of more frequently tested – and therefore more task-relevant – objects, over less frequently probed items in the sequence.

Note that the relative gain in precision for cued items here did *not* depend on their order in the sequence, and the relative cost was distributed between all of the 'uncued' items, both to those preceded by the cued item and to those followed by it. This novel finding is in keeping with a flexible memory resource, which can be dynamically allocated according to an item's behavioural priority, not only in space (Bays and Husain, 2008), but also across time.

An alternative explanation to distributing memory resources according to task relevance could implicate *involuntary* attentional effects. Numerous studies have shown that following an attended visual target, processing of subsequent visual information becomes impaired for several milliseconds, a phenomenon widely known as attentional blink (AB; Reeves and Sperling, 1986; Shapiro et al., 1997b; Marois et al., 2000). However, the loss of precision for the non-cued items in the results presented here cannot be explained by AB, as, firstly, stimuli were presented outside the time frame in which AB has been previously observed, typically 180-270ms (Raymond et al., 1995; Shapiro et al., 1997b), and, secondly, loss of precision was not limited to the item that followed the cued one; instead, all the less task-relevant items, both prior and after the cued one, suffered loss of memory resolution (**Figure 3.1B**).

What are the cognitive mechanisms behind the preferential distribution of memory resources to more important items across time? An insight can be offered by modelling responses according to whether they cluster around the target orientation, around the orientation of non-target items, or follow a random distribution (Bays et al., 2009; also see Paragraph 2.2.3 for

methodological details). This analysis revealed that cueing reduced non-target responses, suggesting more effective binding between orientation and colour (**Figure 3.2C**). The opposite did not seem to be the case, however, for the less task-relevant, 'uncued', items; reduced WM precision for these objects was better explained by an increase in random responses (**Figure 3.2D**), which could be attributed to incomplete encoding of these objects' individual visual features.

Therefore, the enhancement of memory precision for cued items and the corresponding reduction in precision for the 'uncued' ones may depend on two separable underlying processes: firstly, feature binding becomes more effective for better attended objects, which are protected from illusory conjunctions; secondly, individual features of 'uncued' items, receiving less attention, seem to be incompletely encoded. These findings extend previous results from behavioural research on working memory of simultaneously presented objects. Firstly, landmark studies have suggested that feature binding demands resources and requires active attentional focus (Wheeler and Treisman, 2002; Allen et al., 2006b). According to the influential Feature Integration Theory (FIT), individual features of visual objects are perceived independently during a pre-attentive stage, but focused attention is necessary in order to form an effective conjunction between an object's features (Treisman and Gelade, 1980; Treisman and Schmidt, 1982; Treisman, 1996). Secondly, recent results specified that, filtering of task-irrelevant items, which determines individual differences in WM performance, takes place during encoding rather than during maintenance in memory (Linke et al., 2011). Extending these findings in sequentially presented objects, I argue that effective voluntary allocation of WM resources across time depends on two parallel processes: improved visual feature binding, which is maintained across time for more important, better attended objects, and halting of encoding of visual features of less task-relevant items at the pre-attentive stage.

The results discussed so far illustrate a remarkable capability of working memory systems for voluntary attentional selection across time, depending on task-relevance. However, as suggested previously for simultaneously presented

items (Cowan and Morey, 2006), this filtering capacity is not unlimited. The results from Experiment 2 show that some irrelevant information is accumulated during a sequence of visual objects, causing a small but significant decline in memory precision for a target followed by four task-irrelevant distractors, when compared to a single item tested after the same time interval (**Figure 3.3B**).

The three-component model discussed above was applied once more to explore these limitations in voluntary selection. This analysis suggests that the small decline in WM precision for one target with three subsequent distractors can be attributed to a significant extent to failure in feature binding (**Figure 3.4C**). However, note that random variability, although accounting for a very small proportion of responses, was also significantly higher in the presence of task-irrelevant distractors, when compared to the single item condition, suggesting that not all loss of WM precision in the presence of distractors can be attributed to non-target responses (**Figure 3.4C**).

Using a neural measure of filtering ability, based on event-related potentials (ERP), previous authors have shown that the ability to keep task-irrelevant items out of WM when presented simultaneously with task-relevant targets differs between individuals and determines WM capacity (Vogel and Machizawa, 2004; Vogel et al., 2005). Here, I used a behavioural index of filtering ability (Paragraph 3.3.2). This filtering index is intended as a measure of how WM precision for each individual was affected by the presence of distracting, task-irrelevant items as opposed to a condition where distractors were absent. Surprisingly, there was no significant correlation between this filtering measure and WM precision. This result, however, may have been confounded by technical limitations, as discussed in the following paragraph.

WM capacity has been thought to account to a great extent for individual differences in general intelligence (Kyllonen and Christal, 1990; Conway et al., 2003). More recent data have casted doubt over this relationship, suggesting instead that it is individual differences in filtering and voluntary selection, rather than WM capacity itself, that determine differences in measures of

intelligence (Cusack et al., 2009). The results from Experiment 2 suggest that WM precision correlated with standard measures of WM and intelligence (Paragraph 3.3.5, **Figure 3.6**), but WM filtering index did not. While this comes in apparent contrast with the recent data discussed above, it may simply reflect the fact that filtering ability as defined here is a less robust measure than WM precision. Indeed, values >1 for the filtering index, suggesting worse performance on the single item versus the four item (out of which only one was task-relevant) condition, are difficult to interpret within the context of voluntary WM selection, and may instead represent higher general alertness in the multiple item condition. Therefore, WM precision shows a robust correlation with three of the four standard intelligence measures studied, confirming previous data that used different WM measures in simultaneous tasks (Baddeley, 1992; Fry and Hale, 1996; Conway et al., 2003; Jaeggi et al., 2008), but the lack of correlation of the filtering index with WM precision and standard measures of intelligence may have been driven by confounding factors, such as a difference in general alertness between experimental conditions.

In conclusion, the results presented in this Chapter suggest a remarkable, but not unlimited, capability of WM systems for voluntary distribution of resources according to task-relevance, across time. Further analysis using a generative model revealed that enhanced WM precision for more important, better attended items and reduced memory resolution for less important ones depend on two parallel processes, relating to more effective binding and less accurate encoding, respectively.

Chapter 4

Working Memory Precision in Visual Neglect

4.1 Introduction

Hemispatial neglect is a common and disabling disorder, most pronounced and long-lasting after right-hemisphere stroke. Up to two thirds of such patients manifest neglect in the acute phase (Stone et al., 1991; Bowen et al., 1999), and a significant proportion of these patients develop enduring, chronic neglect, a well-recognised negative prognostic indicator for functional independence following stroke (Denes et al., 1982; Fullerton et al., 1988; Kalra et al., 1997; Jehkonen et al., 2000; Cherney et al., 2001). Neglect patients demonstrate a striking difficulty to acknowledge or respond to people or objects to the left, and are often oblivious of their existence, even in the absence of a primary sensory deficit (Stone and Greenwood, 1991; Parton et al., 2004). In contrast to primary sensory deficits, such as left homonymous hemianopia, in neglect there is no clear-cut demarcation of the spatial deficit on a vertical meridian, but rather a gradient of unawareness, which becomes gradually more profound for stimuli located further towards the contralesional (usually left) side. Importantly, this gradient is not fixed, but it depends on the number and relative salience of stimuli competing for attention, with leftward neglect worsening as the number of stimuli on the right increases (Kaplan et al., 1991; Smania et al., 1998; Bays et al., 2010; Gorgoraptis and Husain, 2011; Schnider et al., 2011).

Rather than being a unitary disorder, neglect consists of several component deficits, which are not necessarily specific to the syndrome, but in combination

contribute to exacerbate its severity (Stone et al., 1998; Parton et al., 2004; Bartolomeo, 2007). Neglect can cause spatial biases at the personal, peri-personal, and extra-personal frame of reference, and even in representational space during mental imagery (Bisiach and Luzzatti, 1978; Pouget and Driver, 2000). Extending beyond the visual domain, it can affect awareness of auditory (Heilman and Valenstein, 1972; De Renzi et al., 1989) and somatosensory information (Vallar et al., 1991; Valenza et al., 2003). Independently of sensory awareness, it can result in a directional motor bias away from the contralesional side, causing difficulty in initiating leftward eye or hand movements (Laplane and Degos, 1983; Mattingley et al., 1998; Husain et al., 2000).

Crucially, these lateralised deficits may not be sufficient to explain some behavioural deficits that are characteristic in neglect, and several *non-lateralised* components of the syndrome have been proposed (Husain and Rorden, 2003; Buxbaum et al., 2004; Husain and Nachev, 2007). For instance, the ability to sustain attention to non-lateralised stimuli over an extended period of time is specifically impaired in neglect patients, and this deficit predicts performance on standard tests of neglect (Robertson et al., 1997) and follows the clinical course of lateralised aspects of the syndrome (Hjaltason et al., 1996). Impairment in non-lateralised selective attention has also been demonstrated: when displaying a sequential stream of targets and non-targets, the ability to detect a second stimulus following an attended target is impaired typically for 180-270ms in healthy individuals, a phenomenon known as Attentional Blink (AB) (Raymond et al., 1992; Shapiro et al., 1997b). The AB has been shown to be severely protracted, up to 1200ms, in neglect patients (Husain et al., 1997).

Impaired spatial working memory (WM) is another important component of neglect that need not be lateralised. Spatial WM deficits have been demonstrated in modified visual search tasks in which, when feedback regarding which items had been found was removed, neglect patients tended to revisit targets they had already identified (Wojciulik et al., 2001; Mannan et al., 2005; Parton et al., 2006) and regarded previously fixated targets as new

(Husain et al., 2001), indicating a deficit in remembering target locations across saccades. A study using a vertical equivalent of the Corsi blocks task demonstrated more directly a non-lateralised deficit in spatial WM: neglect patients were impaired in remembering locations of stimuli on a vertical array, and this deficit correlated inversely with performance on visual search tasks (Malhotra et al., 2005).

Is this non-lateralised working memory deficit purely spatial, i.e. specific to remembering object locations, or does it extend to other object properties, such as colour or shape? A study using a change detection task to probe working memory for location, colour, or shape in a small number of neglect patients compared detection of a change in any of these attributes with and without a 1s inter-stimulus interval (ISI) between the encoding and test arrays (Pisella et al., 2004). This study identified a deficit in memory for location, but not colour or shape. However, it is possible that the choice of task may have concealed deficits in WM for colour and shape due to incomplete encoding, especially of more leftward stimuli: indeed, even in the 0s ISI condition, which did not require WM, colour and shape changes were identified with only 70-80% accuracy, while the more salient location changes were identified with >90% accuracy, raising the possibility that the lack of significant difference with the 1s ISI condition for colour or shape represented a floor effect.

The question whether the non-lateralised working memory deficit in neglect is purely spatial or it extends to object attributes other than location, therefore remains. Furthermore, two important questions on WM in neglect have not been evaluated in previous studies: firstly, whether there is a specific impairment in the ability to *update* WM in time to accommodate further items, and, secondly, whether there is an impairment in *voluntary control* over WM resources based on task relevance.

In the present Chapter, I address these issues using modified versions of the sequential tasks described in Chapters 2 and 3. To investigate non-spatial WM precision and its updating across time, 1-3 stimuli were presented centrally, in sequence, subjects had to memorise the orientation and colour of each object,

and adjust the orientation of one of them, identified by its colour, from memory. I compared WM precision between neglect patients following right-hemisphere stroke, right-hemisphere stroke patients who did not manifest neglect on standard bedside tests, and healthy control subjects. To investigate the role of voluntary control over WM resources in neglect, I examined the effect of predictive cueing in each of the above groups, using a task which was introduced in Chapter 3.

Considerable effort has been made to understand the neural correlates of the neglect syndrome and, based on this understanding, to make inferences on the neural substrate of the syndrome's component cognitive processes in the human brain (Corbetta and Shulman, 2011). Lesion analysis indicates that neglect is typically caused by large right middle cerebral artery (MCA) territory strokes affecting the right posterior and inferior parietal lobe, including the angular gyrus (Heilman et al., 1983; Vallar and Perani, 1986; Vallar, 2001; Mort et al., 2003; Vandenberghe et al., 2012). However, the syndrome can also result from focal lesions in the right inferior frontal lobe (Husain and Kennard, 1996) or subcortical structures such as the basal ganglia and thalamus (Damasio et al., 1980; Cambier et al., 1982; Karnath et al., 2002), for example in MCA strokes which do not involve the posterior parietal cortex. Neglect can also arise from posterior cerebral artery (PCA) distribution strokes, especially those affecting the medial temporal lobe (Mort et al., 2003). Other studies, using diffusion tensor imaging (DTI) tractography or intra-operative electrical stimulation, indicated that neglect can result from damage to, or inactivation of white matter pathways, such as the superior longitudinal fasciculus (SLF) connecting posterior parietal and frontal cortical areas (Thiebaut de Schotten et al., 2005; Urbanski et al., 2008, 2011; Shinoura et al., 2009).

It is therefore becoming apparent that there is no simple association between neglect and a single brain region. Rather, neglect arises from disruption to a complex network when one, or several, of its cortical or subcortical nodes, or the white matter connections between them, are lesioned (Singh-Curry et al., 2008). In keeping with this idea, fMRI studies in neglect have shown disrupted functional connectivity (He et al., 2007), and abnormal patterns of activation in

structurally intact nodes (Corbetta et al., 2005) of dorsal and ventral frontoparietal networks which have a proposed role in goal-directed and stimulus-driven control of attention (Corbetta and Shulman, 2002).

However, as outlined above, neglect is not a unitary disorder and it does not present with the same combination of component cognitive deficits in every patient. Therefore, it can be hypothesised that damage to different parts of a complex network produces different combinations of cognitive deficits. Indeed, lesion studies on some of these component deficits in neglect support this hypothesis (Husain et al., 2000; Committeri et al., 2007; Bays et al., 2010; Verdon et al., 2010). The lesional correlates of non-spatial WM and its voluntary control have not been examined previously in this context. To identify damaged brain areas, associated with loss of WM precision or insensitivity to predictive cueing, in the present Chapter, I carried out a Voxel-based Lesion-Symptom Mapping (VLSM) study in a group of right hemisphere stroke patients, taking into account their performance in standard visual search tasks.

4.2 Methods

4.2.1 Subjects

Visual neglect patients and non-neglect stroke controls

18 patients with a clinically defined stroke affecting the right cerebral hemisphere were recruited from the Acute Brain Injury Unit, the Neuro-Rehabilitation Unit and general neurology clinics at The National Hospital for Neurology and Neurosurgery. Patients with previous neurological or psychiatric conditions or other acute concomitant illnesses that could confound cognitive assessment were not included. All patients underwent clinical assessment for hemispatial neglect, which included line bisection from the Behavioural Inattention Test battery (Wilson et al., 1987), and two standard visual search tasks: the Mesulam shape cancellation (Mesulam, 2000), and the bells cancellation task (Gauthier et al., 1989). Based on this assessment, I defined a group of 9 patients who manifested clinically significant neglect on standard bedside tests ('neglect group'), and a group of 9 stroke patients in whom neglect was not discernible using these tests ('stroke controls group'). Patients were included in the neglect group if they manifested a rightward bias of 10% or more in at least one neglect test.

Healthy controls

11 age-matched healthy control subjects with no history of neurological or psychiatric illness were also recruited.

The study was approved by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Local Research Ethics Committee. All study participants provided written informed consent.

4.2.2 Behavioural tests

Sequential WM task

All stroke patients and healthy controls were tested in a modified version of the sequential WM precision task (Gorgoraptis et al., 2011), described in Chapter 2. In this task, presented in **Figure 4.2A**, each trial consisted of a sequence of one to three coloured bars presented consecutively at the centre of a computer screen; the orientation and colour of each bar had to be memorised and one of the bars was presented at a random orientation at the end of each sequence. Subjects had to adjust the orientation of the probe as accurately as possible from memory using a response dial (Griffin Technology).

The experimental parameters were as described in Chapter 2, with the following differences: here, there was a maximum of three stimuli per sequence (i.e. sequences could contain one, two or three bars) and presentation was on a 15 inch laptop monitor at an approximate viewing distance of 50 cm. Patients controlled the response device with their ipsilesional (right) hand. Neglect patients completed an average (±SD) of 136 (±55) trials, stroke controls an average (±SD) of 128 (±43) trials, and each healthy control performed 240 trials from this task.

Sequential WM task with predictive cueing

Stroke patients and healthy controls also participated in a modified version of the sequential WM task where one of the items was cued (Gorgoraptis et al., 2011). The task is described in detail in Chapter 3. In the version used here (**Figure 4.5**), stroke patients and healthy controls were presented with sequences of three items, different in colour and orientation. As in the previous task, one of the colours was probed at the end of each sequence, at a random orientation, and subjects were asked to adjust the item's orientation from memory. However in this task, one of the colours, which was present in all trials and fixed for each subject, was predictively cued by being probed with increased frequency, in 66.7% of the trials versus 16.7% for each of the other colours in the sequence.

Here, I measured the effect of predicitive cueing on memory, by comparing memory precision for the cued item versus precision for the uncued ones. The rest of the experimental parameters were as described in the previous paragraph for the sequential WM precision task. Neglect patients completed an average (±SD) of 96 (±54) trials, stroke controls an average (±SD) of 131 (±37) trials, and healthy controls completed 200 trials from this task.

Perceptual / motor control task

To ensure that all subjects were able to use the response device, and to control for the potentially confounding elements of visual perception of the stimuli and visuo-motor coordination when responding, a control task was performed in all participants before testing on the sequential WM task.

In this control task, presented in **Figure 4.1A**, a single target bar was presented, at a random orientation, at screen centre. One second later, a probe bar of the same colour was presented at random orientation just above the first item, 5° of visual angle above the screen centre, on the vertical meridian. While the target item was always present on the screen, subjects were asked to adjust the orientation of the probe bar to match the target, using the same response device as in the tasks described above.

4.2.3 Behavioural analysis

Neglect tests

The variables obtained from the neglect tests included the signed value of deviation from the midline for line bisection (positive for rightward and negative for leftward deviation), the total number of targets found in the bells and Mesulam shape cancellation tasks, and an index of lateralisation of targets found, R_L, for each cancellation task, defined as follows:

$$R_L = (N_R - N_L)/(N_R + N_L) \quad (4.1)$$

where N_R is the number of targets found on the right half of the testing sheet, and N_L the number of targets found on the left. As follows from Equation 4.1,

L=0 would correspond to an equal number of targets identified on either side, and the greater the signed value of L, the more severe the rightward bias in visual search.

WM precision

Memory precision was calculated as described in Chapter 2, based on previous studies using the fidelity of recall of a visual stimulus as a sensitive index of resolution in visual memory (Alvarez and Cavanagh, 2004; Bays and Husain, 2008; Bays et al., 2009, 2011b; Zokaei et al., 2011; Gorgoraptis et al., 2011). Briefly, for each trial, the angular deviation between the orientation reported by the subject and the correct orientation of the target bar in the preceding sequence was obtained, and precision was calculated as the reciprocal of the circular (Fisher, 1993) SD of error across trials ($1/\sigma$). As previously (Chapter 2), the value expected for chance was subtracted; therefore a precision value of zero corresponds to responding at random.

Hypotheses regarding the effects of experimental parameters (number of items, order in sequence, cueing) on precision, and differences in precision between groups (neglect, stroke controls, healthy controls), were tested by ANOVA and t-tests, as stated in the Results. Where parametric tests were used, assumptions on normality and equal variances were tested using Kolmogorov-Smirnov and Levene tests, respectively.

Model analysis

To quantify the contribution of different sources of error to overall precision estimates in each experiment, I applied a probabilistic model introduced previously by Bays et al. (2009), and described in detail in Chapters 1 and 2. Briefly, this model attributes errors on the reproduction task to (1) Gaussian variability in memory for the target orientation; (2) a certain probability on each trial of misreporting one of the other, non-target, orientations in the sequence; and (3) a certain probability of responding with a random orientation not related to any of the items in the sequence. One subject (CM) from the stroke controls group was excluded from the model analysis due to insufficient

number of trials to obtain a reliable estimate of model parameters. Maximum likelihood estimates of each of these parameters were obtained for each subject, and were compared between groups using *t*-tests and ANOVA, as specified in the Results.

Correlations between WM measures and neglect scores

Next, I examined the possible correlation between visual neglect severity and measures obtained from the WM task. To this end, correlations between the scores obtained from standard bedside neglect tests in the neglect group, and measures of WM precision, cueing effect and model parameters, were tested using Pearson correlation coefficient.

To test for a possible correlation between neglect severity and the effect of cueing on memory precision, I calculated a simple measure, R_C, of this effect, by taking the difference in precision between the trials where the cued item was probed, minus those where one of the other (uncued) items was tested, divided by the sum of precision values in these two conditions:

$$R_C = (P_C - P_U)/(P_C + P_U) \quad (4.2)$$

where P_C and P_U is memory precision for the cued and uncued items, respectively.

Calculation of precision values, estimation of model parameters, and data plotting was performed using custom Matlab scripts (Matlab R2010b, MathWorks). Statistical comparisons were carried out in SPSS 18 (IBM Corp.).

4.2.4 Lesion mapping and analysis

Lesion mapping

Each patient's stroke lesion was manually delineated on 12 axial slices (z=56, 61, 66, 69, 75, 85, 88, 92, 96, 102, 108, 120) of a standard MRI template as a 3D volume of interest (VOI) using MRIcron software (Rorden and Brett, 2000; Rorden et al., 2007), http://www.cabiatl.com/mricro/. Lesion location was

defined by examining each patient's clinical MRI scan (in 16 patients) or CT (in 2 patients, in whom MRI was contraindicated / unavailable).

Lesion volume was calculated from each patient's VOI. Differences in lesion volume between the neglect group and the group of stroke controls were examined using *t*-test, and correlations of lesion volume with WM precision and cueing index were tested in each group using Pearson correlation coefficient.

Voxel-based Lesion-Symptom Mapping

I investigated whether the behavioural results from the WM precision tasks and the neglect assessments were associated with lesions in specific brain areas in the group of all 18 patients, by applying a technique known as Voxel-based Lesion-Symptom Mapping (VLSM) (Bates et al., 2003). The aim of this method is to map the relationship between brain injury and behavioural performance using a voxel-by-voxel approach. Specifically, for each voxel, patients are divided in two groups depending on whether or not the brain area corresponding to that voxel was lesioned. Behavioural tests are then compared between these groups, yelding a statistic for each voxel (Bates et al., 2003). VLSM examines the whole brain in such way, in order to identify the association between a behavioural measure and the presence or absence of lesion in each voxel. Bonferroni correction for multiple comparisons is applied to account for the probability of obtaining false positive results in the context of a large number of statistical comparisons.

Using the Non-Parametric Mapping (NPM) software incorporated in the MRIcron package (Rorden et al., 2007), I carried out a VLSM analysis in order to determine lesion locations that were associated with a deficit in WM precision, and also those that were associated with a reduced positive effect of cueing. However, as I hypothesised that the presence and severity of neglect as well as lesion volume may affect this relationship, I took these variables into account in my analysis. Therefore, voxelwise logistic regression was performed for WM precision and separately for cueing index (see Equation 4.2), using total scores in the bells and Mesulam tests as well as lesion volume as

regressors. In other words, this analysis aims to identify voxels which, when lesioned, predict the values of the behavioural measures of interest (WM precision or cueing index), given the extent of neglect and lesion volume. Bonferroni correction was applied to account for multiple comparisons, as mentioned earlier.

4.3 Results

4.3.1 Subjects' demographics

18 stroke patients were recruited in total. 9 patients (3 female, mean age (±SD): 61 (±10.9) years) were included in the neglect group and 9 patients without neglect (4 female, mean age (±SD): 61 (±16.5) years) in the stroke control group. Patient demographics and neglect scores are given on Table 4.1.

11 healthy controls (8 female, mean age (±SD): 64 (±12.7) years) took part in the study.

There was no significant age difference between groups (neglect *vs* healthy controls: $t_{(18)}$=-0.59, P=0.56, neglect *vs* stroke controls: $t_{(18)}$=0.02, P=0.99, stroke controls *vs* healthy controls: $t_{(18)}$=-0.51, P=0.62).

4.3.2 Controlling for perceptual and motor factors

Before participating in the sequential WM task, each subject took part in a simple control task, where the angle of the probe item was adjusted while the target item was visible on the screen (**Figure 4.1A**). This task does not require WM, and controls for any potential impairment of neglect patients in visual perception of the stimuli or in visuo-motor performance and motor control while using the response device.

As shown in **Figure 4.1B**, neglect patients performed in this task as well as healthy controls ($t_{(18)}$=0.41, P=0.68) or stroke controls ($t_{(18)}$=-0.01, P=0.99). The performance of stroke controls in this task was also no different to that of healthy controls ($t_{(18)}$=0.36, P=0.72).

4.3.3 Comparisons of WM measures between groups

Differences in memory precision between groups

Next, WM precision, derived from the serial WM task with 1-3 items, was com-

Patient	Age	Sex	Hand-edness	Stroke type	Days post stroke	Lesion vol. (cc)	BIT line (mm)	Bells (total)	Bells (R_L)	Mesulam (total)	Mesulam (R_L)
JK	60	F	Right	Haem.	26	17.27	-7.6	15	1	39	0.7
CB	81	M	Right	Isch.	29	4.28	6	19	0.58	8	0.86
PT	57	M	Right	Isch.	52	25.56	-2.3	17	0.17	5	1
AA	54	F	Right	Isch.	12	36.09	1.3	16	0.5	19	0.89
JL	53	M	Right	Isch.	14	10.71	3.7	30	0.13	59	0.02
KP	66	F	Left	Isch.	422	47.49	11.3	19	0.68	4	1
AK	46	M	Right	Isch.	1403	65	8	12	1	14	1
FA	58	M	Right	Isch.	606	36.28	8	19	0.68	27	0.85
RF	74	M	Right	Haem.	190	3.55	10.3	23	0.04	49	0.1
BH	68	M	Right	Isch.	38	3.54	4.3	32	0.06	58	0.03
JC	76	M	Right	Haem.	73	2.16	2.6	28	0.07	60	0
PaT	77	F	Right	Isch.	812	6.38	-8.67	32	0.06	58	-0.03
AW	77	M	Right	Isch.	62	0.67	0.6	24	-0.08	58	0
JS	37	F	Right	Isch.	67	0.31	0	34	0	60	0
GV	53	M	Left	Isch.	206	16.77	-14	31	0.1	55	0.02
CM	57	F	Right	Isch.	803	11.94	0.6	30	0	55	0.02
HK	68	F	Right	Haem.	123	2.16	0	34	0	60	0
GP	35	M	Right	Isch.	844	1.16	-0.6	31	-0.03	60	0

Table 4.1: Patient demographic data and neglect scores.

Patients in the neglect group are presented at the top half of the table; patients in the stroke control group at the bottom half.

F: female, M: male; Haem.: Haemorrhagic stroke, Isch.: Ischaemic stroke.

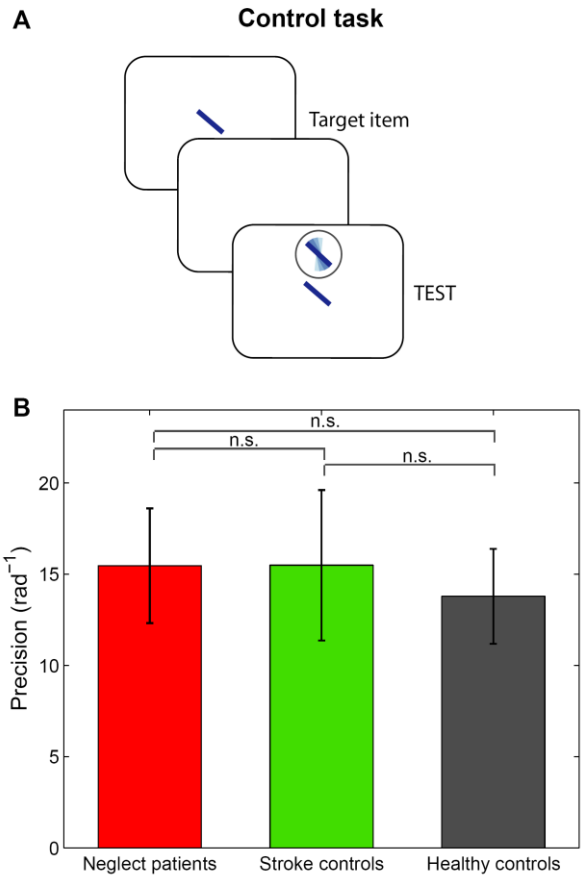


Figure 4.1: A control task for perceptual and visuomotor components of the WM precision task.

A) Subjects were asked to adjust the orientation of a single item to match that of a target item, which was visible on the screen.

B) Neglect patients and stroke controls performed as well as healthy controls in this task.

pared between the three groups (neglect, stroke controls, and healthy controls), taking into account the number of items in the sequence. As shown in **Figure 4.2B**, WM precision was significantly lower in neglect patients when compared to either healthy controls (two-way ANOVA (set size x group) between neglect and healthy controls, main effect of group: $F_{(1,54)}$=64.9, P<0.001), or stroke controls (two-way ANOVA between healthy and stroke controls, main effect of group: $F_{(1,48)}$=22.5, P<0.001). The difference in WM precision between stroke patients without neglect and healthy controls, albeit smaller, was also significant (two-way ANOVA between healthy and stroke controls, main effect of group: $F_{(1,54)}$=4.6, P=0.036). The interaction between group and set size (number of items in the sequence) was not significant in any of these comparisons.

Differences between groups in WM updating

A core feature of the WM task used here is that all stimuli are presented at the same location in space, but at different points in time. Therefore, information in WM has to be *updated* with every new item, to accommodate both this most recent object and all previous ones. As we saw previously, this updating process results in a cost in WM precision for all items prior to the most recent one (Chapter 2; see also Gorgoraptis et al., 2011), accounting for the recency effect in WM.

To examine differences between neglect patients, stroke controls and healthy controls in WM updating across sequentially presented objects, I compared WM precision between these groups taking into account the serial order of the tested item in each sequence length.

Crucially, as seen in **Figure 4.3A**, neglect patients were profoundly impaired in retaining even a single item in memory, when compared to healthy controls ($t_{(18)}$=-4.9, P<0.001) or stroke controls ($t_{(16)}$=-3.6, P=0.002).

Stroke patients without neglect, however, could remember a single item, or the most recent item in a sequence of two or three objects as precisely as healthy controls (one item: $t_{(18)}$=0.6, P=0.58; 2nd of two items: $t_{(18)}$=-0.6, P=0.58; 3rd of three items: $t_{(18)}$=-0.2, P=0.87; **Figure 4.3A-C**). Conversely, previous items (the

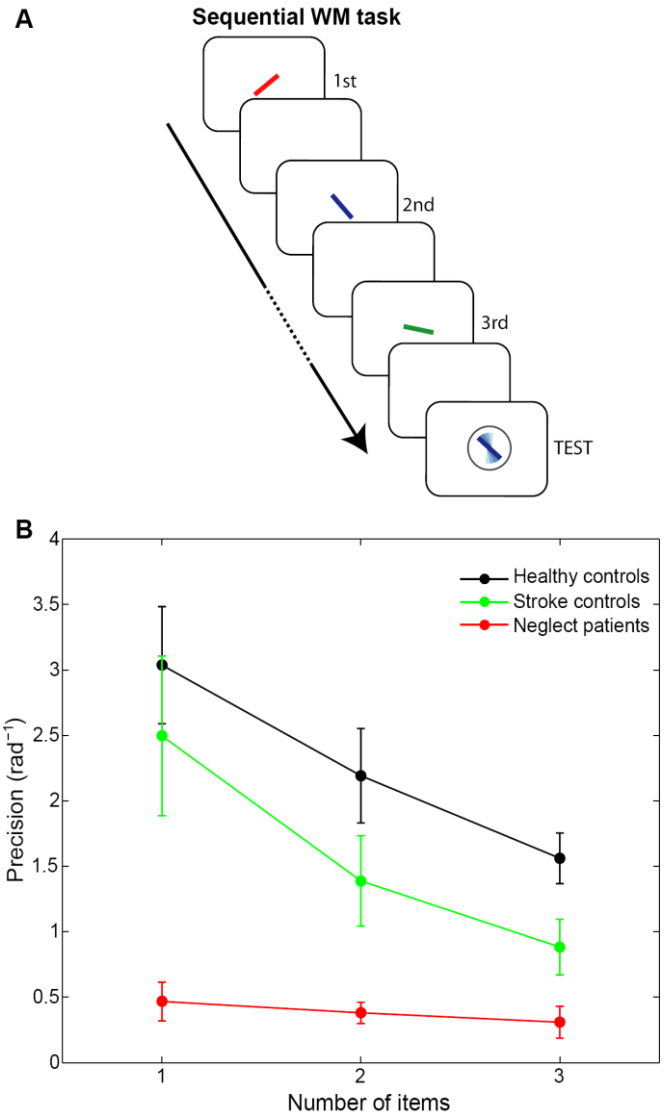


Figure 4.2: WM precision in neglect patients, stroke patients without neglect, and healthy individuals.

A) 1-3 coloured bars, each with different colour and orientation were presented at the screen centre. One of these objects (in this case, the 2nd item) was randomly probed at the end of the sequence, and subjects had to adjust its orientation from memory.

B) WM precision for any sequence length up to three items is significantly lower in neglect patients (in red) than in healthy controls (in black) or stroke controls without neglect (in green). WM in stroke controls is also significantly less accurate than in healthy controls, although to a much lesser extent when compared to the marked WM impairment observed in neglect.

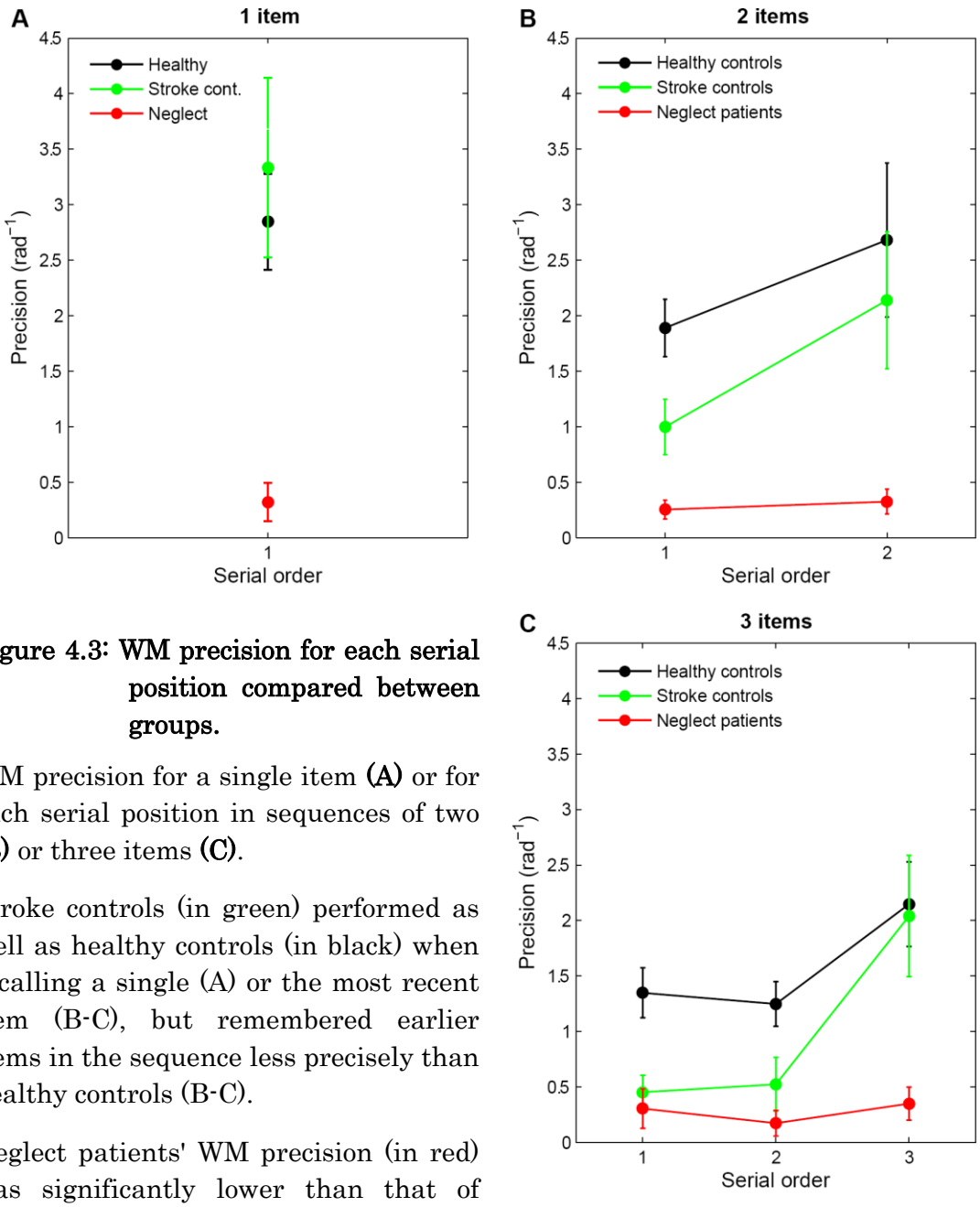


Figure 4.3: WM precision for each serial position compared between groups.

WM precision for a single item **(A)** or for each serial position in sequences of two **(B)** or three items **(C)**.

Stroke controls (in green) performed as well as healthy controls (in black) when recalling a single (A) or the most recent item (B-C), but remembered earlier items in the sequence less precisely than healthy controls (B-C).

Neglect patients' WM precision (in red) was significantly lower than that of healthy or stroke controls also for the most recent item in a sequence or even for a single object (A-C).

first out of two or the first and second out of three objects) were recalled by stroke controls with lower precision than by healthy controls (1st of two items: $t_{(18)}$=-2.4, P=0.025; 2nd and 3rd of three items: $F_{(1,36)}$=14.6, P=0.001; **Figure 4.3B-C**).

Neglect patients' WM for the most recent item in sequences of two or three objects was also markedly lower in comparison to healthy controls (2nd of two items: $t_{(18)}$=-3.03, P=0.007; 3rd of three items: $t_{(18)}$=-4.1, P=0.001) or stroke controls (2nd of two items: $t_{(16)}$=-2.9, P=0.011; 3rd of three items: $t_{(16)}$=-2.9, P=0.009).

As demonstrated in the control experiment, performance of neglect patients cannot be explained by perceptual or motor components of the WM task (Paragraph 4.3.2 and **Figure 4.1**), and therefore it can be better accounted for by a profound WM impairment, extending to the most recent object in a sequence, or even to a single item. Additionally, an unusual response behaviour was observed qualitatively in several of the neglect patients, who tended rotated the probe several times before deciding on a final response.

4.3.4 A probabilistic model of the sources of error

A probabilistic model was applied to responses in the sequential WM task, assuming three potential sources of error in the subjects' memory estimates: (1) Gaussian variability when responding to the target orientation, (2) a certain probability (with the same Gaussian variability attached to it) of responding to one of the non-target orientations, due to associating erroneously the target colour with the orientation of a non-target item, and (3) a probability of responding randomly. Each of these parameters was computed for each subject and each number of items in the sequence, and they were compared between neglect patients, stroke controls, and healthy controls.

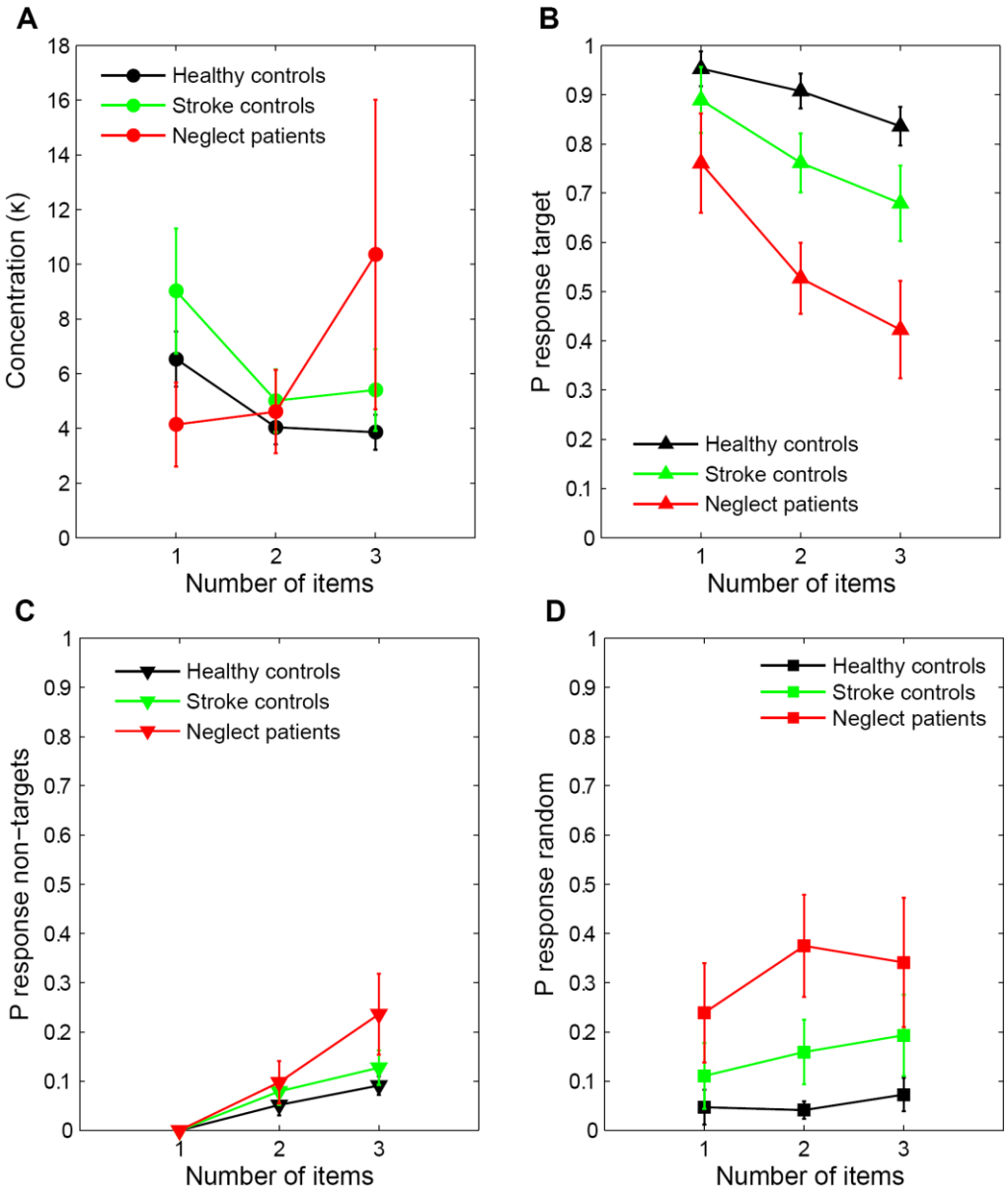


Figure 4.4: A probabilistic model of the sources of error in WM, in patients, stroke patients without neglect, and healthy individuals.

The concentration parameter describing the variability of non-random responses is similar between neglect patients (in red), stroke controls (in green) and healthy controls (in black) **(A)**. Neglect patients were less likely to produce responses centred around the target orientation than stroke controls or healthy controls **(B)**. When compared to the control groups, a larger proportion of neglect patients' responses were centred around the orientation of a non-target **(C)**, or were random **(D)**.

The probability of responses centred around the correct target orientation was significantly different between groups ($F_{(2,75)}$=19.9, P<0.001, **Figure 4.4B**), with neglect patients being less likely to respond using the correct target orientation than healthy controls ($F_{(1,54)}$=38.3, P<0.001, **Figure 4.4B**) or stroke patients without neglect ($F_{(1,45)}$=9.4, P=0.004, **Figure 4.4B**).

In parallel, the probability of responding to a non-target orientation, or, in other words, of misbinding the target colour with the orientation of a non-target, was significantly higher in neglect than in healthy controls ($F_{(1,54)}$=4.6, P=0.037, **Figure 4.4C**), but it was similar between neglect patients and stroke controls ($F_{(1,45)}$=4.6, P=0.24, **Figure 4.4C**), as well as between stroke controls and healthy participants ($F_{(1,51)}$=1.6, P=0.21, **Figure 4.4C**).

Variability of non-random responses (i.e. variability of responses to the target or to a non-target item) did not differ significantly between groups (two-way ANOVA group x number of items, main effect of group: $F_{(2,75)}$=0.59, P=0.56, **Figure 4.4A**), although the data for the neglect group were particularly noisy for 3 items.

Finally, the probability of responding at random differed significantly between groups ($F_{(2,75)}$=10, P<0.001, **Figure 4.4D**), with a significantly greater proportion of neglect patients' responses best explained by simple guessing when compared to healthy controls ($F_{(1,54)}$=18.4, P<0.001, **Figure 4.4D**) or stroke controls ($F_{(1,45)}$=4.2, P=0.045, **Figure 4.4D**). Of note, stroke controls also showed more frequent random responses in comparison to healthy controls ($F_{(1,51)}$=6.1, P=0.017, **Figure 4.4D**), albeit to a smaller extent than neglect patients.

4.3.5 Differences between groups in cueing effects

Group differences in effects of predictive cueing on WM precision

In a further experiment, I examined the subjects' ability to prioritise an object which had been predictively cued, and therefore had higher relevance to the task, and compared the effect of predictive cueing on WM precision between neglect patients, healthy controls and stroke patients without neglect.

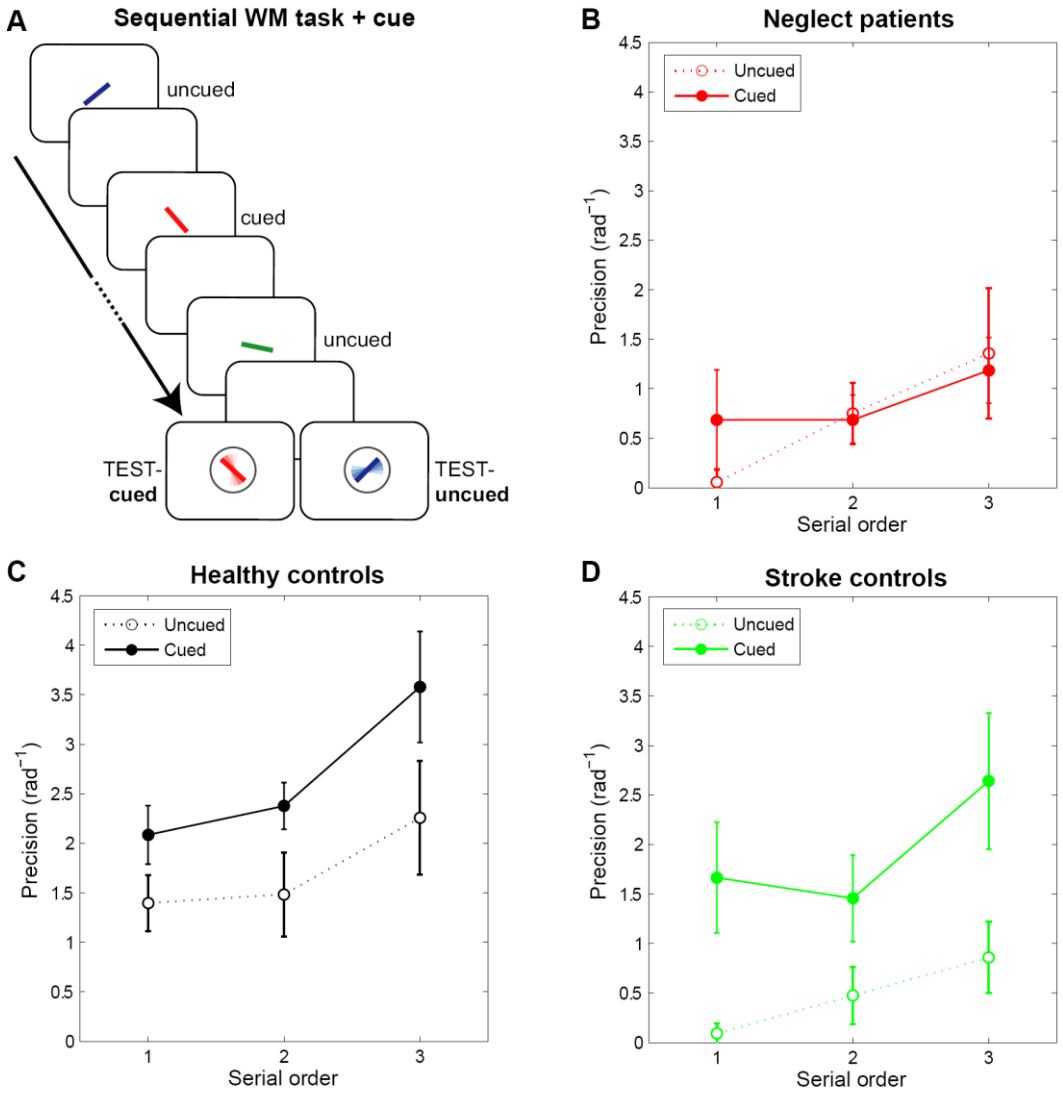


Figure 4.5: Ineffective predictive cueing in neglect.

A) 3 coloured bars were presented in sequence; one of these items (in this case, the red bar), was predictively cued, by being probed with higher frequency than any one of the other 'uncued' items.

Predictive cueing is ineffective in neglect patients **(B)** even though it enhances WM precision significantly in healthy controls **(C)** or stroke patients without neglect **(D)**.

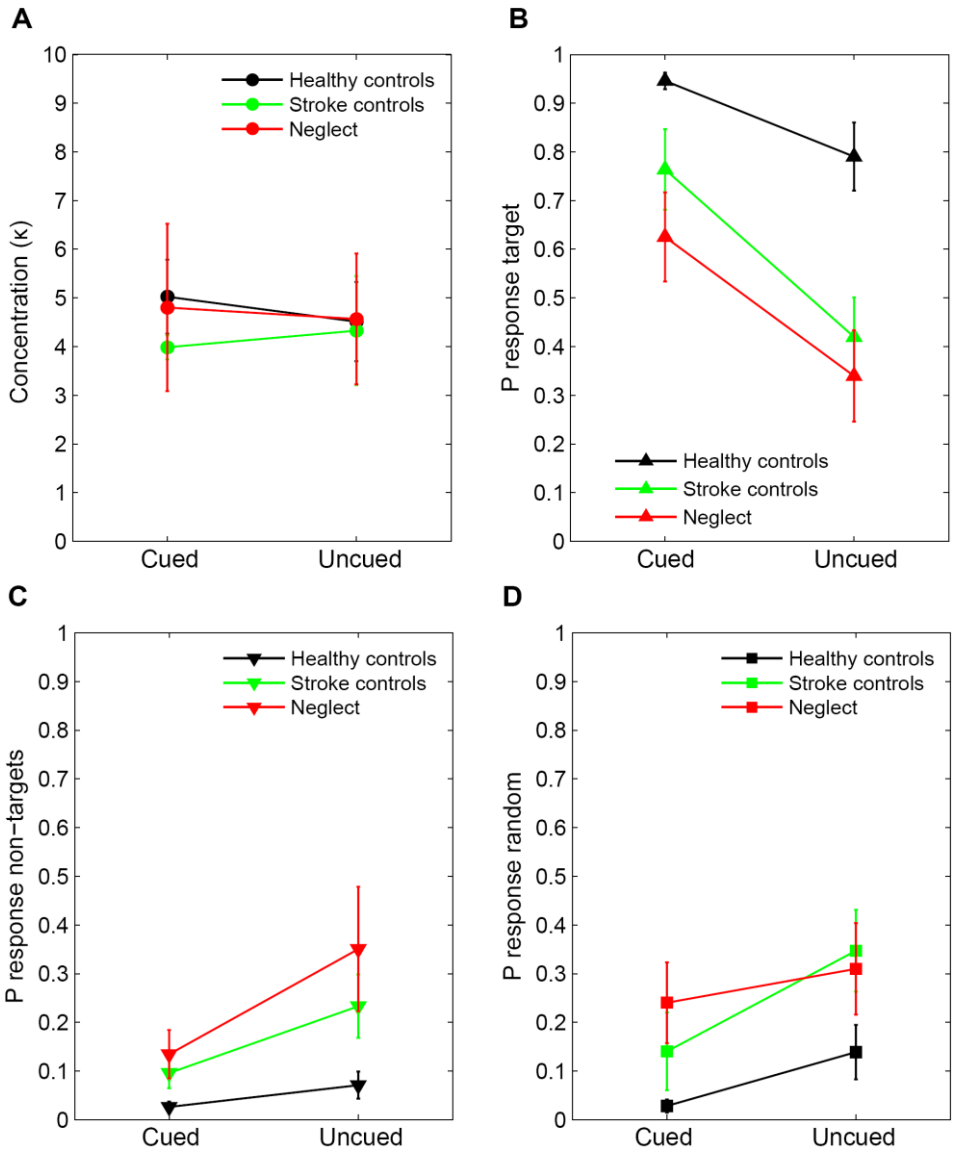


Figure 4.6: Effects of predictive cueing on model parameters in each group.

A) Variability of responses to targets or non-targets was not affected by predictive cueing in any of the groups.

B) Responses to the correct target orientation were more probable when the target was cued, significantly so in healthy controls and stroke patients without neglect.

C) Differences between conditions in the non-target responses were not significant in any of the groups.

D) Cueing was associated with a decrease in the probability of responding at random, but only in healthy controls and in patients without neglect; neglect patients were equally likely to guess in both conditions.

Predictive cueing increased WM precision significantly in both healthy controls (two-way ANOVA - cueing condition x serial order: $F_{(1,60)}$=8.1, P=0.006, **Figure 4.5C**) and stroke patients without neglect ($F_{(1,48)}$=15.7, P<0.001, **Figure 4.5D**). However, in neglect patients, WM precision was not affected by cueing ($F_{(1,48)}$=0.15, P=0.69, **Figure 4.5A**).

I also calculated a simple index to measure the magnitude of the effect of predictive cueing (Paragraph 4.2.3, Equation 4.2). This cueing index differed significantly between neglect patients and stroke controls ($t_{(16)}$=2.9, P=0.01) and it was similar between the two control groups ($t_{(18)}$=1.7, P=0.097), but it was not significantly different between neglect patients and controls ($t_{(18)}$=1.7, P=0.11).

Modulation of the model parameters by cueing in each group

In addition to examining differences between groups in WM precision, I also applied the same generative model used in the previous experiment (Paragraph 4.3.4), separately for responses to cued and to 'uncued' items.

As shown in **Figure 4.6A**, there were no significant differences in the variability of responses between cued and uncued items in any of the three groups (healthy controls: $t_{(10)}$ =-0.96, P=0.36; stroke controls: $t_{(6)}$ =0.33, P=0.75; neglect patients: $t_{(8)}$ =-0.09, P=0.92).

Responses to the target orientation were more probable when the target item was cued (healthy controls: $t_{(10)}$ =2.4, P=0.038; stroke controls: $t_{(6)}$ =4.03, P=0.007, **Figure 4.6B**), although in neglect that difference was of borderline significance ($t_{(8)}$ =2.23, P=0.056).

In both healthy and stroke control groups, this difference was predominantly accounted for by an increase in the random responses for the uncued items (healthy controls: $t_{(10)}$ =1.44, P=0.18; stroke controls: $t_{(6)}$ =3.65, P=0.011, **Figure 4.6D**), rather than by a change in non-target responses (healthy controls: $t_{(10)}$ =1.44, P=0.18; stroke controls: $t_{(6)}$ =3.65, P=0.064, **Figure 4.6C**), in keeping with previous results in a similar task in healthy individuals (Chapter 3; see also Gorgoraptis et al., 2011).

Conversely, in the neglect group, there was no difference in random responses between cued and uncued conditions ($t_{(6)}$ =0.55, P=0.599, **Figure 4.6D**), and an increase in non-target responses for uncued items (**Figure 4.6C**) was not significant ($t_{(6)}$ =1.52, P=0.17).

4.3.5 Correlations between WM measures and neglect scores in patients

Next, I examined whether, in the neglect group, WM precision and cueing index correlated with neglect scores.

There was no significant correlation of WM precision with deviation in the line bisection test (r=-0.22, P=0.56). WM precision did not correlate with either the total number of targets found or their lateralisation in either the bells cancellation task (r=-0.14, P=0.72; r=-0.17, P=0.66) or the Mesulam test (r=-0.03, P=0.94; r=-0.09, P=0.81).

No significant correlation was observed between the cueing index and any of the neglect scores (line bisection deviation: r=0.07, P=0.85; bells total targets: r=-0.10, P=0.79; bells lateralisation: r=0.35, P=0.36; Mesulam total targets: r=-0.29, P=0.45; Mesulam lateralisation: r=-0.22, P=0.57).

4.3.6 Lesion volume

Lesion plots of neglect patients and stroke patients without neglect are presented in **Figure 4.7A** and **B**, respectively. Lesion volume in the neglect group was significantly larger than in stroke controls ($t_{(16)}$=3.1, P=0.007).

To test the hypothesis that patients' performance on the WM tasks can be simply explained by the extent of their brain damage, I examined whether lesion volume correlated with WM precision and cueing index, in the two patient groups. In neglect patients, lesion volume did not correlate with WM precision (r=-0.39, P=0.30) or cueing index (r=0.35, P=0.35). In stroke controls, there was a negative correlation of borderline significance between lesion

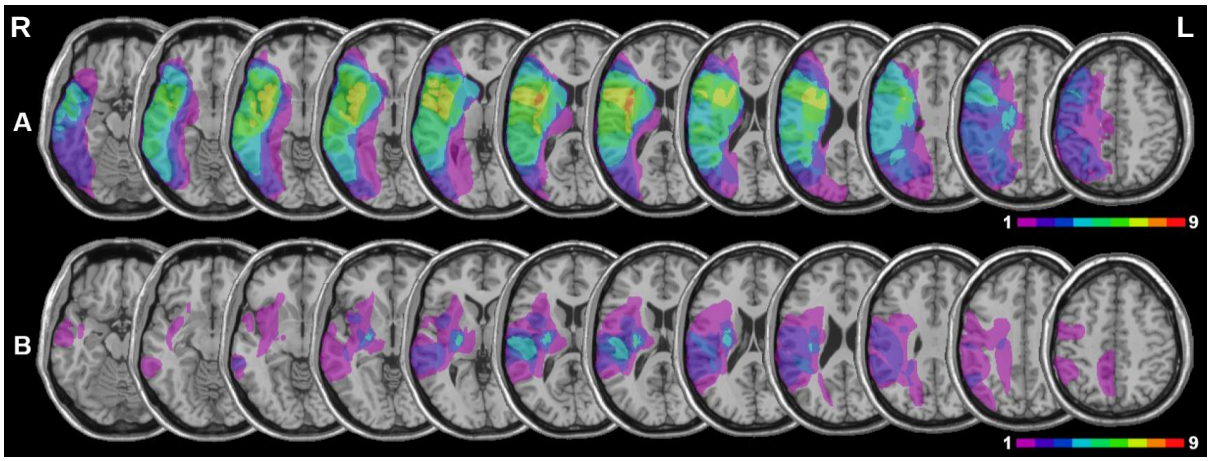


Figure 4.7: Lesion maps in neglect patients and stroke controls.

Colour values represent number of patients in whom a given voxel was lesioned. Radiological convention is used (right hemisphere displayed on the left of image); all lesions are right-sided (R: right; L: left).

A) Lesion overlap of the 9 patients with clinically significant neglect.

B) Lesion overlap of the 9 stroke patients without neglect.

volume and WM precision (r=-0.67, P=0.048), but no significant correlation between lesion volume and cueing index (r=0.55, P=0.13).

4.3.7 Voxel-based Lesion-Symptom Mapping

Next, using VLSM, I sought to identify the brain areas, lesions in which were specifically associated with a decrease in WM precision, and separately, those which, when lesioned, predicted the effect of cueing, in the entire group of 18 patients. For this analysis, I took into account each subject's performance in visual search (bells and Mesulam cancellation task scores), as well as lesion volume.

The results of this analysis are presented in **Figure 4.8**. Regions in the right inferior frontal gyrus and insula, as well as subcortical structures, including the globus pallidus, putamen and caudate, predicted WM precision (in red). Conversely, the effect of cueing (in blue) was associated with a region in the angular gyrus of the right inferior parietal lobule, an area in the right premotor cortex in proximity to the frontal eye field (FEF), and white matter areas, several of which may overlap with the SLF.

Note the relative paucity of parietal involvement in determining the effect on WM precision and the posterior parietal predominance with regard to cueing response. Remarkably, there was no overlap between regions of interest determining WM precision and those associated with response to predictive cueing (**Figure 4.8** – if present, overlap areas would appear in purple).

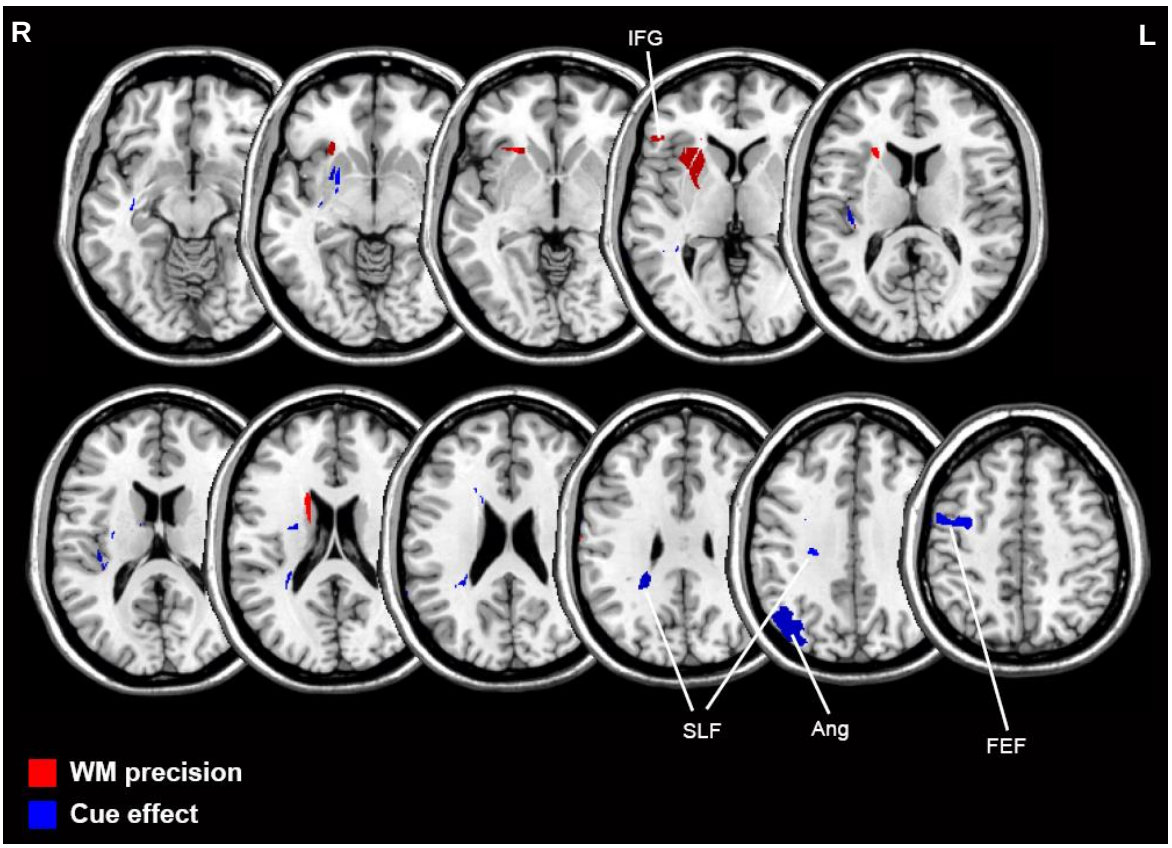


Figure 4.8: VLSM results for WM precision and effect of cueing.

Images are presented in radiological convention (right hemisphere on left of figure); all regions of interest (ROIs) are right-sided (R: right; L: left).

Brain regions predicting WM precision (in red) include the right inferior frontal gyrus (IFG), insula, basal ganglia (globus pallidus, putamen, caudate) and frontal white matter areas in proximity to these areas.

Brain regions that predict the effect of cueing (in blue) include the right angular gyrus (Ang), right frontal eye field (FEF), and subcortical areas several of which are in keeping with the location of the superior longitudinal fasciculus (SLF).

There is no overlap between the regions of interest relating to WM precision and those associated with cue effect (overlap areas would appear in purple in this figure).

4.4 Discussion

This is the first study demonstrating a non-lateralised WM deficit for a visual attribute other than location, in this case for orientation, in neglect. WM precision for orientation was profoundly impaired in neglect patients, even for a single item, when compared to healthy controls or stroke patients without clinically identifiable neglect. Stroke patients without neglect also performed significantly worse than healthy age-matched controls, but this was a mild impairment, in contrast to the striking, profound WM deficit affecting the neglect group (**Figure 4.2**). Therefore, although not exclusive to neglect, the deficit in WM precision for orientation was far more pronounced in patients with a significant lateralised deficit in standard neglect tests.

Neglect patients often manifest striking deficits in visual perception and visuomotor control (Driver and Mattingley, 1998). Therefore, it might be argued that the profoundly impaired performance of neglect patients in this task does not represent a WM deficit, but rather simply a perceptual impairment, or a visuomotor difficulty when manipulating the response dial. The results on the control experiment (**Figure 4.1**) show that when the target item remained visible while responding, both stroke controls and neglect patients were unimpaired on this task, suggesting that the results from the sequential task reflect a true impairment in WM precision.

WM precision in the neglect group was profoundly impaired, close to responding at random even for only one item (**Figure 4.2B**), therefore it is not possible to draw conclusions on WM updating with subsequent items. Conversely, stroke patients without neglect performed as well as healthy controls when recalling a single item, or the most recent of two or three items (**Figure 4.3**). In contrast, WM precision for previous items was significantly lower than in healthy controls, suggesting impairment in active maintenance in WM of items that were no longer attended in stroke patients without neglect.

Subjects' responses were also examined using a generative model which assumes responses are distributed with a certain concentration either around the target, or a non-target, or drawn from a random distribution (Bays et al., 2009; Gorgoraptis et al., 2011; also see Chapter 2 for more details on this model). A large proportion of neglect patients' responses were either centred on non-targets or distributed randomly. This suggests that misbinding between visual features (i.e. colour of a target being erroneously associated with orientation of a non-target) may explain some of the responses, but it is not the sole contributor to the poor WM performance in this group.

When voluntary attention was manipulated by predictive cueing (**Figure 4.5**), WM precision for cued items of any order in the sequence improved in stroke patients without neglect, in a similar way to healthy controls. Remarkably, however, neglect patients did not respond to predictive cueing. Although this result may in part be explained by the profound WM impairment even for a single item in this group, it could also indicate a non-spatial deficit in reallocating attentional resources voluntarily across time in neglect. This would also be keeping with previously recognised deficits in detection of behaviourally relevant stimuli, which need not be lateralised, in neglect (Husain et al., 1997; Samuelsson et al., 1998; Robertson, 2001; Husain and Rorden, 2003; Malhotra et al., 2009).

Does the profound impairment in neglect patients on the sequential task represent a WM deficit, or could it be explained as a pure impairment in temporal dynamics of attention? Indeed, previous studies have demonstrated a protracted attentional blink (AB) in neglect, whereby the physiological impairment in the ability to detect a second stimulus following an attended target, normally for 180-270ms (Raymond et al., 1992), is prolonged up to 1200ms in neglect patients (Husain et al., 1997). In our task, each target appeared for 1000ms, followed by a 1000ms ISI, without visual masking, allowing 2000ms for visual processing of each target. This timescale extends beyond even the remarkably protracted AB noted in neglect patients. It is therefore unlikely that the impairment on the sequential task in neglect patients is solely explained by a prolonged AB. Hence, the results from the

sequential task are in keeping with a non-spatial deficit in WM precision (**Figure 4.2**), while an impairment in selective attention is also apparent, as demonstrated by the ineffectiveness of predictive cueing (**Figure 4.5**).

Within the neglect group, there was no significant correlation between standard neglect test scores and either WM precision or cueing index. It is likely that this is owed to the small sample size, and further studies with more extensive patient samples might identify a relationship between these measures. Alternatively, the lack of correlation could suggest that even patients with relatively mild impairment in cancellation or line bisection tests exhibit a profound impairment in WM precision in the sequential task. If true, this possibility would suggest that the striking impairment in WM precision and the inability to benefit from predictive cueing are core components of the neglect syndrome.

Lesions in patients with neglect were significantly larger than in stroke controls, in keeping with the previous observation that neglect is commoner in patients with more extensive lesions (Vallar et al., 1988; Mort et al., 2003; Ringman et al., 2004). I found no evidence that effects were driven by higher lesion volume in the neglect group in comparison to the group of stroke patients without neglect, although the absence of correlation between lesion volume and WM precision or response to cueing does not rule out this possibility with certainty, especially given the relatively small sample size. In any case, lesion volume was taken into account in the VLSM analysis; therefore lesional correlations of these parameters should not be driven by lesion volume.

To identify regions of interest (ROIs) which, when lesioned, were associated with WM impairment, and separately, those associated with lack of response to cueing, I employed VLSM analysis taking into account patients' neglect test scores. This technique has some general limitations which should be discussed here. Firstly, statistical power to detect an involvement of a particular ROI in determining a behavioural deficit depends on having adequate numbers of patients with *and* patients without a lesion in that area. In other words, if a

certain voxel is not lesioned in any patient, or if it is lesioned in all, VLSM will be uninformative on the role of the corresponding area in determining the behavioural deficit of question (Kimberg et al., 2007). Secondly, Bonferroni correction for multiple comparisons, commonly used in VLSM, might be too stringent, posing a further limitation on the sensitivity of this technique. This problem comes into focus if we consider the inherent spatial coherence of lesion maps: in the case of stroke, the shape and distribution of lesions depends on vascular anatomy, therefore the presence or absence of lesion in a voxel can be well predicted by lesion status in contiguous voxels (Kimberg et al., 2007). In that context, as comparisons between voxels are not independent, Bonferroni correction might increase the risk of Type II error (Kimberg et al., 2007). Thirdly, VLSM, and lesion mapping more generally, consider lesions as an all-or-nothing event: areas within the lesion are regarded as entirely non-functional, and areas that were not (directly) lesioned are considered as functional as they would be in a healthy brain. However, both of these assumptions might be inaccurate: it is conceivable that there are functioning neurons and circuits within regions that appear abnormal on imaging, and more importantly, islands of normal-appearing tissue in a lesioned brain might not function normally, as their afferent and efferent connections might be severed by adjacent or remote lesions (Nachev et al., 2009; Mah et al., 2012). Finally, regarding the data presented here, the VLSM analysis has to be taken with some added caution because lesions were plotted from clinically acquired scans and not dedicated high-resolution imaging.

Notwithstanding its limitations, the current VLSM analysis produced interesting results. There is a rather striking lack of overlap between areas which, when lesioned, were associated with WM impairment and those related to lack of response to cueing. WM precision was associated with regions in the right inferior frontal gyrus (IFG), insula, extensive areas in the basal ganglia, including the putamen and caudate, and also frontal white matter areas, likely including tracts connecting these cortical and subcortical areas. These results are in keeping with extensive evidence for the involvement of these areas in WM. Several fMRI studies have suggested that IFG is active in non-spatial

WM tasks during the delay period (McCarthy et al., 1996; Cohen et al., 1997, 2004; Courtney et al., 1997; Owen et al., 1998). There is also evidence from fMRI and lesion studies suggesting a specific role of the right IFG in response inhibition – the suppression of responses that are inappropriate in a given context (Garavan et al., 1999; Aron et al., 2003, 2004; Hampshire et al., 2010). Furthermore, an influential study suggested that activity in the prefrontal cortex and the basal ganglia, particularly in the globus pallidus, precedes filtering of irrelevant information in WM (McNab and Klingberg, 2007). Given that reduced WM precision in the results presented here was associated with an increased number of non-target responses, taken together, this evidence raises the possibility that the lesional components in the right IFG and basal ganglia might have resulted in inability to suppress the non-target orientations (i.e. items other than the one that was probed) in WM. In conclusion, WM performance was determined by a frontal network involving the basal ganglia and IFG, known to play a role in response inhibition and filtering in WM.

Conversely, VLSM analysis indicated a separate set of areas determining response to predictive cueing. These included the right inferior parietal lobe (IPL), a region which is commonly lesioned in neglect (Vallar and Perani, 1986; Heilman and Watson, 2001; Mort et al., 2003). Considerable experimental and theoretical effort has been made to elucidate the involvement of this area in spatial perception, spatial attention and action (Vandenberghe et al., 2001, 2012; Corbetta and Shulman, 2002; Rizzolatti and Matelli, 2003; Husain and Nachev, 2007; Gillebert et al., 2011). However, a separate line of evidence has demonstrated that the right IPL is also active in a range of non-spatial tasks (Husain and Nachev, 2007), which, importantly, include non-spatial, sequential selective attention tasks (Coull and Frith, 1998; Wojciulik and Kanwisher, 1999; Marois et al., 2000). Both in its spatial and non-spatial functions, the IPL has been shown to be part of several fronto-parietal networks (Corbetta and Shulman, 2002; Husain and Nachev, 2007; Catani and Thiebaut de Schotten, 2008a). Frontal components of fronto-parietal networks implicated in neglect include the posterior dorsolateral frontal cortex, and, within that, the frontal eye field (Mort et al., 2003; Corbetta et al., 2005), another area indicated in

association with cueing effects by the VSLM analysis presented here. Additionally, lesional correlates of cueing effects included subcortical areas the location of which is in keeping with white matter tracts such as the superior longitudinal fasciculus, which form part of these frontoparietal networks (Catani and Thiebaut de Schotten, 2008a).

Therefore, the results from the lesion analysis presented here suggest that the posterior parietal cortex might not be simply implicated in passive storage of locations and objects within WM (Constantinidis and Steinmetz, 1996; Pesaran et al., 2002; Todd and Marois, 2004, 2005; Xu and Chun, 2006; McNab and Klingberg, 2007), but it is actively involved in goal-directed selection. Posterior parietal activation has been noted during *n*-back tasks, where a sequence of stimuli is presented at fixation and subjects are required to respond when an item matches one that was presented *n* items before (Cohen et al., 2004; Owen et al., 2005). It could be argued that these tasks involve goal-directed selection, which would be in keeping with the results presented here, again for sequentially presented items.

The relative paucity of regions in the frontal lobe and basal ganglia and the predominance of the posterior parietal lobe in determining the effect of cueing might be seen as somewhat surprising. The basal ganglia, and particularly the globus pallidus, have been implicated in attentional filtering within WM in healthy individuals (McNab and Klingberg, 2007). Prefrontal areas, particularly the ventrolateral prefrontal cortex, have been also associated with goal-directed attentional selection in WM (Jonides et al., 2002; Badre and Wagner, 2007; Champod and Petrides, 2007; Dove et al., 2008). However, in this group of patients with right posterior parietal lesions, recruitment of regions in the frontal cortex and basal ganglia might not be effective in the absence of intact function in posterior areas. Therefore, one possibility might be that activity related to selection within WM in frontal and subcortical areas might require intact attentional deployment in the posterior parietal cortex.

In conclusion, the results presented in this Chapter demonstrate a profound non-spatial impairment in WM and its voluntary attentional control in neglect.

Lesion analysis identified separable neural correlates of these deficits, and indicated a network of cortical and subcortical areas in the right IFG and basal ganglia relating to WM precision, and, conversely, regions in the right IPL and posterior dorsolateral frontal areas associated with the effect of predictive cueing.

Chapter 5

Dopaminergic Modulation of Visual Neglect

5.1 Introduction

As discussed in Chapter 4, neglect can be seen as a syndrome consisting of several component deficits (Heilman and Valenstein, 1979; Mesulam, 1999; Husain and Rorden, 2003; Hillis, 2006; Bartolomeo, 2007), with different patients suffering different combinations of cognitive impairment (Buxbaum et al., 2004). Difficulties in disengaging or directing spatial attention, initiating or executing movements, sustaining attention over time and representing space to the left have all been reported in individuals with the syndrome (Bisiach and Luzzatti, 1978; Posner et al., 1984; Gainotti et al., 1991; Robertson et al., 1997, 1998; Mattingley et al., 1998; Bartolomeo et al., 1998; Bartolomeo and Chokron, 2002; Coulthard et al., 2006). A deficit in spatial working memory is an important such component (Wojciulik et al., 2001; Pisella et al., 2004; Mannan et al., 2005; Ferber and Danckert, 2006; Parton et al., 2006), which can interact with deficits in sustained attention to exacerbate neglect (Malhotra et al., 2005).

Dopamine within the prefrontal cortex has been established to play a crucial role in both attention and working memory. Landmark studies in monkeys have shown that visuospatial working memory in monkeys is modulated by dopamine (Funahashi and Kubota, 1994; Goldman-Rakic, 1996; Goldman-Rakic et al., 2000), specifically via prefrontal dopamine D_1 receptors (Williams and Goldman-Rakic, 1995). Indeed, a selective D_1 agonist can enhance working

memory in aged monkeys (Castner and Goldman-Rakic, 2004), or reverse experimentally-induced spatial working memory deficits (Castner et al., 2000). In healthy humans too, D_1 – but not D_2 – dopamine receptor agonists can facilitate spatial working memory (Müller et al., 1998).

In addition to its pivotal role in working memory, new findings suggest that frontal D_1 receptor activity can have long-range, modulatory effects on visual areas subserving attention. Thus local infusion of a D_1 antagonist into monkey frontal cortex not only modulated the firing of neurones in visual cortex but also altered the animal's ability to select visual targets (Noudoost and Moore, 2011). Furthermore, dopaminergic neuronal networks have a well-recognised role in alerting or allocating attention to unexpected sensory cues based on the potential importance or behavioural relevance of the stimulus (Bromberg-Martin et al., 2010).

The study presented in this Chapter tested the hypothesis that pharmacological modulation of dopamine receptor activity to alter attention and/or working memory, two core components of the neglect syndrome, could ameliorate neglect in stroke patients.

There have been a few previous attempts to test modulation of dopaminergic activity as a therapeutic option in hemispatial neglect, but the largest trial tested only four patients. Despite some initial promising results from an open-label study using bromocriptine, a predominantly D_2 dopamine receptor agonist, in two patients (Fleet et al., 1987), a further small open-label trial and a case report revealed worsening of neglect with the drug (Grujic et al., 1998; Barrett et al., 1999). Apomorphine, which has both D_1 and D_2 receptor activity, induced a transient improvement in three out of four neglect patients tested (Geminiani et al., 1998). In keeping with this finding, an open-label study showed some improvement in standard neglect tests following treatment with levodopa in three of four cases studied (Mukand et al., 2001). Finally, a small-scale trial of amantadine in four neglect patients did not demonstrate any beneficial effect of the drug (Buxbaum et al., 2007).

A double-blind, randomised, placebo controlled trial of the dopamine agonist rotigotine was conducted in 16 patients with hemispatial neglect and unilateral weakness following right hemisphere stroke. In contrast to the substances tested in previous studies, the current one used rotigotine, which has high affinity for the D_1 receptor compared to many other licensed oral dopamine agonists (Jenner, 2005; Naidu and Chaudhuri, 2007). The primary objective was to evaluate whether the drug improves neglect and its cognitive components, including selective and sustained attention, as well as spatial working memory. A further aim was to assess the effects of rotigotine on motor performance, because some previous studies have suggested that levodopa may have a positive effect on motor deficits following stroke (Scheidtmann et al., 2001; Scheidtmann, 2004; Floel et al., 2005). As prefrontal cortex is an important potential candidate area for the cognitive effects of dopamine agonists, one of the study's aims was to determine whether any beneficial effects of rotigotine depend on the extent of preservation of the right prefrontal cortex.

Patients were assessed with a battery of standardised neglect tests, as well as with tests of working memory, selective and sustained attention, and motor function. A replicated ABA double-blind, placebo-controlled N-of-1 randomised design was used, which allowed us to evaluate the effectiveness of an intervention in small sample sizes. Each patient's performance was measured in three phases, each consisting of several assessment sessions: before treatment (**phase A1**), while receiving transdermal rotigotine (**phase B**) and after discontinuation of the drug (**phase A2**). Crucially, the exact duration of each phase was randomised across patients. Performance on rotigotine was compared with the pre-treatment baseline and post-treatment follow-up phases.

The principles of randomised N-of-1 designs (Edgington and Onghena, 2007) such as the one used here were originally described by Fisher for intervention studies (Fisher, 1935) but were difficult to conduct on a large scale because they require substantial computing power. As a result, few investigators used

them. However, modern day computers make the mathematical demands far less problematic, and replicated randomised N-of-1 designs provide a powerful way to assess effects in highly focused studies using a large number of assessments on small patient samples. Randomisation or permutation tests are used for analysis of these designs. Importantly, such tests are distribution-free. They are based simply on rearrangements of raw scores and compare a computed statistic (e.g., the difference in means or medians between two conditions) with the value of that statistic for all other possible arrangements of the data obtained *in that patient*. The P-value is simply the proportion of arrangements leading to a value of the statistic as large as, or larger than, the value obtained from the actual data. The key question is how likely is it by chance that a difference in means was as large as the observed difference between two conditions, e.g., treatment vs. no treatment.

In the design used here (**Figure 5.1**) it is possible to compare the difference in mean scores between two phases of the trial, e.g., off treatment (Phase A1 and Phase A2) compared to on drug (Phase B). Suppose the difference in mean scores on vs. off treatment for the patient who underwent the protocol shown in **Figure 5.1a** is *Z*. Randomisation tests consider all other possible rearrangements of the data *for this patient*, within the constraints of the trial design (shown in **Figure 5.1b**). For each of these different permutations of when the drug might start and duration of treatment, the difference in means for *each possible* A1, A2 and B period is computed using the dataset from the patient. Then the probability that other possible rearrangements of the data result in a value as large as, or larger than *Z*, is calculated. This simple permutation principle allows us to ask whether there was a significant change in performance on drug by comparing the actual difference in means on and off treatment, with all the other potential differences in means. If the drug has a significant effect during the period it is given, we would expect that the mean of performance on the drug compared to periods off it would be larger than all the other possible arrangements of the dataset from this patient.

Note that this particular patient only had the drug for the period shown in **Figure 5.1a**, but the data from the patient is simply reshuffled to produce potential means for on and off treatment *if* the drug period had been as shown for all the other permutations. If there is no significant effect of drug, we would expect the actual difference in mean performance on and off drug to be very similar to the means from all other possible permutations from this dataset. In effect, therefore, each patient acts as their own control. We calculate what the means would have been for phases A1, B and A2, as if the patient had started the drug a day earlier, or a day later or even two days later; or if the time on the drug had been longer or shorter than it actually was within the constraints of all the permutations possible (**Figure 5.1b**). Then we compare the differences in means for all these permutations with the actual, observed difference in means on and off treatment. The P-value gives us the likelihood of obtaining a value as large as *Z* by chance, computed *from the dataset of the patient,* not by comparing mean scores across patients randomised to receiving treatment or no treatment. Individual p-values are then combined to obtain a P-value for the entire patient group, and separately for two subgroups with different degrees of prefrontal lesion involvement by stroke.

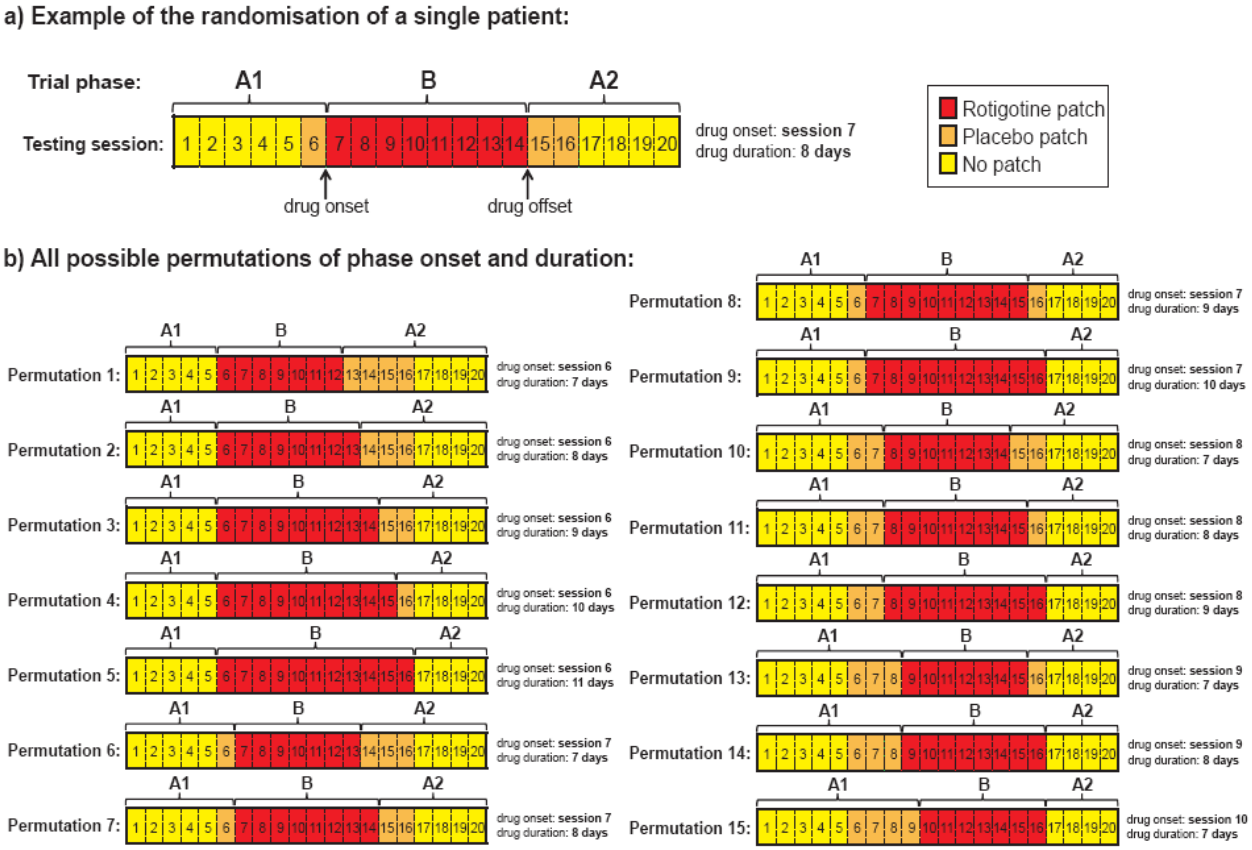


Figure 5.1: Randomisation of treatment allocation and permutation tests.

a) Randomisation profile for a single patient. In this case, the treatment phase with rotigotine (phase B, denoted in red) started on day 7, and its duration was randomised to 8 days. Therefore, the patient participated in 6 baseline assessments (phase A1, sessions 1-6) and 6 follow-up sessions after discontinuation of rotigotine (phase A2, sessions 15-20). Placebo patch sessions are denoted in orange while sessions without any patches are shown in yellow. The *actual* difference in performance between treatment (B) and the off-treatment phases (A1 and A2) was ranked against the differences between phases produced by *all other possible combinations* of treatment allocation, given the limits in phase onset and duration.

b) All the possible permutations of pre-treatment (phase A1), treatment (phase B) and post-treatment (phase A2).

5.2 Methods

5.2.1 Patients

16 individuals aged over 18 years with left hemispatial neglect and a motor deficit due to their first-ever clinically defined right-hemisphere stroke were prospectively recruited from referrals to the trial team at The National Hospital for Neurology and Neurosurgery, London. Left hemispatial neglect was defined as a significant deficit in finding leftward targets on standard cancellation or visual search tasks, using established criteria (Wilson et al., 1987, 1987; Mesulam, 2000). A deficit on the line bisection test *alone* was not sufficient for inclusion. Motor deficit was defined as weakness of at least wrist and finger extension and finger abduction to ≤ 4+ on the MRC scale. Patients were eligible only if stroke onset was at least 9 days before the first assessment session.

Exclusion criteria were:

- A pre-existing neurological condition (e.g. dementia, Parkinson's disease, multiple sclerosis) that would confound cognitive or motor assessments.
- Acute concomitant illness (e.g. infection, unstable angina, myocardial infarction or heart, respiratory, renal or liver failure)
- Systolic blood pressure less than 120 mmHg and / or diastolic less than 70 mmHg, (as dopamine agonists may lead to postural hypotension, especially during dose escalation)
- Exposure to any other investigational drug within 30 days of enrolment in the study
- Presence of clinically significant drug or alcohol abuse within the previous 6 months
- Pregnancy and breast feeding.

All patients provided written informed consent before participating in the trial. The study protocol and all relevant documents and procedures were approved by the National Research Ethics Service (NRES) and the Medicines and Healthcare products Regulatory Agency (MHRA).

5.2.2 Lesion analysis

According to the study hypothesis, the major target of rotigotine for cognitive effects is likely to be dopamine D_1 receptors in prefrontal cortex. Therefore, to assess whether response to rotigotine depends on the degree of preservation of the prefrontal cortex, the patients were stratified into two subgroups according to the extent of the prefrontal cortical involvement, as quantified by high-resolution MRI. To this end, I used the lesion mapping technique described in Mort et al. (Mort et al., 2003). Briefly, each patient's stroke lesion was manually delineated at every single axial slice of their native T1 MRI as a 3D volume of interest (VOI) using MRIcron software (Rorden and Brett, 2000; Rorden et al., 2007) http://www.cabiatl.com/mricro/. The VOI of each patient's lesion was then registered to a standard Montreal Neurological Institute (MNI) T1 template in SPM8b (http://www.fil.ion.ucl.ac.uk/spm/), applying cost function masking of the lesioned area to obtain optimal normalisation (Brett et al., 2001).

The percentage of prefrontal involvement was quantified for each patient, by comparing their normalised brain lesion to a prefrontal template, defined using the PickAtlas SPM toolbox (http://fmri.wfubmc.edu/software/PickAtlas).

In addition to this hypothesis driven comparison of response to treatment between patients with extensive and patients with minimal prefrontal involvement, a post-hoc data driven analysis was also performed. Two patient groups (of 8 patients each) were defined based on their response to rotigotine in the Mesulam visual search task, and a voxel-based lesion symptom mapping (VLSM) analysis was carried out to explore whether the absence or presence of lesion in certain areas determined response to treatment, using the non-

parametric mapping software (http://www.mccauslandcenter.sc.edu/mricro/npm/) included in MRIcron (Rorden et al., 2007). The technique is discussed in more detail in Chapter 4 (paragraph 4.2.4).

5.2.3 Study design

A double-blind, placebo-controlled 'ABA' randomised design consisting of three consecutive phases was employed:

- Baseline pre-treatment phase (A1)
- Treatment with rotigotine transdermal patches (phase B)
- Post-treatment phase (A2)

The duration of each phase was randomised within limits, such that, in each patient, A1+B+A2 consisted of a total of 20 assessment sessions. However, the precise durations of A1, B and A2 varied across individuals, with both patients and investigators blind to the precise duration of each of these phases in any given patient. Note that in this design *all patients* receive placebo and drug at different stages of the trial, with the exact time at which drug is started and the duration of treatment randomised across individuals.

Phase A1 started on session 1 and its duration was randomised (across individuals) to between 5 and 9 days. Observations during this phase established the baseline performance. **Phase B**, when rotigotine was administered, could commence on day 6 to day 10, and its duration was a minimum of 7 and a maximum of 11 sessions. Finally, **phase A2**, when patients were assessed after the discontinuation of rotigotine, was randomised to begin between sessions 13 and 17, and it lasted for the remaining 4 to 8 sessions.

For the purpose of placebo control, all patients received a placebo patch in the period between sessions 6-16, on the days they were not receiving rotigotine.

Placebo and rotigotine patches were visually identical. All investigators, clinical staff, patients and carers were masked to treatment assignment.

Each patient was randomly assigned a pattern of onset and duration of the treatment and baseline phases, within the duration limits described above. As an example, the randomisation profile of one of the participants is presented in **Figure 5.1a**. In this example, the patient had 6 baseline assessments, followed by 8 days on rotigotine (sessions 7-14) and 6 follow-up assessments after discontinuation of the drug. In the figure the yellow shading shows the minimum number of sessions in phases A1 and A2, while red shading denotes the treatment phase (phase B). Orange depicts any additional sessions in phases A1 and A2 when the patient received placebo patches. All possible permutations of pre-treatment, treatment and post-treatment phases within the constraints of the design are shown in **Figure 5.1b**. In total, there were 15 possible permutations.

5.2.4 Clinical and behavioural testing

Each patient participated in 20 consecutive assessment sessions. The first 17 sessions were performed daily. The final 3 follow-up assessments were conducted at weekly intervals. Each session consisted of tests of spatial neglect, spatial working memory, selective and sustained attention and motor performance.

Spatial neglect was evaluated with the line bisection test from the Behavioural Inattention Test Battery (Wilson et al., 1987), and with three visual search tasks: Mesulam shape cancellation (Mesulam, 2000) and bells cancellation task (Wilson et al., 1987), performed on A3 sheets, and a visual search task performed on a touchscreen (18" diagonal), in which no visible markings were left at the location of the cancelled targets (Parton et al., 2006). There was a 2 minute time limit for all visual search tasks.

Spatial working memory was measured with a vertical analogue of the Corsi spatial span test (Malhotra et al., 2005), and also using the rate of revisiting of

previously cancelled targets obtained from the touchscreen visual search task (Mannan et al., 2005; Parton et al., 2006). Selective attention and sustained attention were assessed using a visual salience and vigilance task, which has been previously used in patients with prefrontal lesions (Barcelo et al., 2000). As shown in **Figure 5.8a**, in this task, participants were asked to detect targets (inverted triangles) among sequences of distractors (upright triangles) randomly presented to the ipsilesional and contralesional visual fields, and to respond to targets with a speeded button press. Targets could be of the same colour as the distractors (low visual salience) or of a different colour (high visual salience targets). As a measure of selective attention, we used the ratio of the reaction time (RT) to high visual salience targets over the RT to low visual salience targets. Furthermore, using this task, we quantified sustained attention *over time*, by measuring the difference in RT and % correct responses between the first and the second half of each experimental session.

Motor performance was evaluated in all patients using the Motricity Index (Wade, 1992; Bohannon, 1999) and with grip and pinch dynamometry (Sunderland et al., 1989). Where the patient's level of weakness permitted, motor performance was also assessed using the 9-hole peg test (Mathiowetz et al., 1985), box and blocks test (Mathiowetz et al., 1985) and timed 10 metre walk (Wade, 1992).

5.2.5 Drug and placebo administration

During the treatment phase, a rotigotine 9.0 mg skin patch (equivalent to 4mg/24hr transdermal absorption) was applied daily by the investigator. Patients were instructed to wear it 24 hours a day. Because rotigotine takes up to 24 hours to reach steady-state levels, application of the drug patch started immediately after behavioural testing the day before the drug would be effective. Thus, a patch (drug / placebo) was applied on the last session of phase A1, and immediately after behavioural testing on sessions 5-15. Therefore, either placebo or rotigotine was in place during behavioural testing on sessions 6-16. In the example shown in **Figure 5.1a**, the patient had a placebo patch

applied immediately after behavioural testing on day 5, and an active rotigotine patch was applied after testing on day 6; the treatment phase B commenced on day 7.

To prevent nausea, a common adverse effect of dopamine agonists, patients received domperidone 10mg orally three times daily from sessions 1 to 16. As domperidone does not penetrate the blood-brain barrier, it should not interfere with the central response to rotigotine (Quinn et al., 1981). Blood pressure and pulse were recorded and patients were asked to report any adverse events at each assessment session.

5.2.6 Statistical analysis

We used a replicated randomised N-of-1 design (Edgington and Onghena, 2007), which makes it possible to investigate the effects of an intervention on small groups of patients, provided sufficient assessments are made. Hence, the intensive testing procedure consisting of 17 consecutive daily assessments, followed by 3 weekly ones. This design methodology, the principle of which was developed by Fisher (Fisher, 1935) is sometimes also referred to as permutation testing. Critically, it makes no assumptions about the underlying distribution of the data (Todman and Dugard, 2001), and has been shown to be particularly robust for studies with small sample sizes (Guyatt et al., 1990; Ferron and Onghena, 1996).

The aim of the analysis was to identify whether performance during the treatment phase (B) was significantly improved when compared to the pre-treatment baseline (phase A1) and to the post-treatment follow-up (phase A2). For each patient and each outcome measure, three statistics, expressing the difference between phases, were first computed:

1. Difference of the median observation of phase B from the median of phase A1 (B-A1),

2. Difference between the medians of phases B and A2 (B-A2), and

3. Difference between the median of phase B and the median of phases A1 and A2 averaged (B-Am). Therefore B-Am is the difference between the median of the treatment phase (B) and the average of the medians of both off-treatment phases.

Then, each of these measures was ranked against the values of the same measure computed for all possible rearrangements of the data. An example of this approach is presented in **Figure 5.1b**. The higher the ranking of the actual difference on- and off- rotigotine among all possible permutations, the higher the probability that the observed difference was due to the drug. Based on this ranking, for each outcome measure, a P-value was obtained for each individual patient. This P-value is derived from the proportion of arrangements leading to a difference between phases which is as large as, or larger than, the difference on- and off-treatment obtained from the actual data.

A group P-value was obtained for each outcome measure, by combining the individual patients' P-values, using Edgington's additive method (Edgington, 1972). The same method was used to obtain P-values for each of the prefrontal subgroups. The general formula describing this method of obtaining a general P-value from a group of individual P-values is as follows:

$$\frac{S^n}{n!} - \binom{n}{1}\frac{(S-1)^n}{n!} + \binom{n}{2}\frac{(S-2)^n}{n!} - \binom{n}{3}\frac{(S-3)^n}{n!} + \cdots \qquad (5.1)$$

where S is the sum of n combined P-values, and where the minus and plus signs preceding the terms alternate and additional terms are used as long as the number subtracted from S in the numerator is less than S (Edgington, 1972). This method has been shown to be more powerful than the previously proposed multiplicative method (Jones and Fiske, 1953), having a greater probability of yelding significant results when there actually are treatment effects (Edgington, 1972).

Analyses were performed using the R statistical software (http://www.r-project.org/).

5.3 Results

5.3.1 Patient demographics, adherence and adverse effects

16 patients fulfilling the inclusion criteria were prospectively enrolled in the trial. Patients' demographics are presented in **Table 5.1**, and lesion maps are shown in **Figure 5.2**. Compliance with the treatment protocol was 100%: none of the patients missed any dose of rotigotine or placebo. All patients attended 20 assessment sessions as per protocol, apart from patient 7 who missed one session (session 11, on rotigotine), for reasons unrelated to the trial. There were no serious adverse events during treatment with rotigotine. Mild adverse effects included fatigue, mild skin irritation at the site of the patch, and gastrointestinal disturbance, including nausea, vomiting and diarrhoea which are all known potential side effects of rotigotine (**Table 5.2**). Importantly, neither treatment nor assessments were interrupted due to adverse events.

5.3.2 Effects of treatment on the Mesulam task at the group level

Treatment with rotigotine was associated with significant improvement in visual search, as quantified by the Mesulam shape cancellation task. As shown in **Figure 5.3**, for the entire group of 16 neglect patients, the number of targets found on the left side was significantly higher while on rotigotine than in the pre- and post-treatment phases averaged (P=0.012) or in the post-treatment phase alone (P=0.039). The difference on- and off-treatment in the number of targets found on the left side relative to baseline was 12.8% higher in the actual treatment allocation than the mean difference between phases produced by all possible combinations of treatment onset and duration (for an overview of the methodology used in this permutation analysis, see **Figure 5.1**). Although the number of targets found on the right side was somewhat decreased on treatment (**Figure 5.3**), the relative difference on- and off-treatment was only 0.7% smaller in the actual treatment allocation when compared to all possible permutations, and this was not statistically significant (P=0.466).

	Age	Gender	Hand-edness	Stroke type	Days post stroke	% prefrontal involvement	Mesulam L targets OFF drug	Mesulam L targets ON drug	Mesulam R targets OFF drug	Mesulam R targets ON drug
P1	42	Male	Right	Ischaemic	728	39.4%	13.25	22	26.5	26
P2	62	Male	Right	Ischaemic	70	14.6%	24.75	22.5	25.5	27.5
P3	46	Male	Right	Ischaemic	1381	32.5%	1.5	5	24.5	27
P4	63	Female	Right	Ischaemic	42	11.8%	0.25	0	20.75	23
P5	58	Male	Right	Ischaemic	327	35%	0	0	13.5	13
P6	66	Male	Right	Ischaemic	202	54.7%	1	0	18	19
P7	62	Male	Right	Haemorrh-agic	232	0.2%	1.75	2.5	16.75	16
P8	74	Male	Right	Ischaemic	341	35.3%	9.75	10.5	22	19.5
P9	53	Male	Left	Ischaemic	385	5.6%	22	28	27	29
P10	24	Male	Right	Haemorrh-agic	221	7.2%	0	0	16.25	8
P11	60	Male	Right	Haemorrh-agic	1990	2.4%	10.75	20.5	23.25	25.5
P12	62	Male	Right	Ischaemic	941	33.5%	2	0.5	26	28
P13	72	Female	Right	Haemorrh-agic	1712	32.6%	2	8	25.5	22
P14	80	Male	Right	Ischaemic	30	0%	22.75	23	24.25	26
P15	51	Male	Right	Haemorrh-agic	104	52.9%	6.5	7	23.25	23
P16	49	Male	Right	Ischaemic	85	9.1%	11.75	13	20.25	18

Table 5.1: Patient demographics and Mesulam search task results.

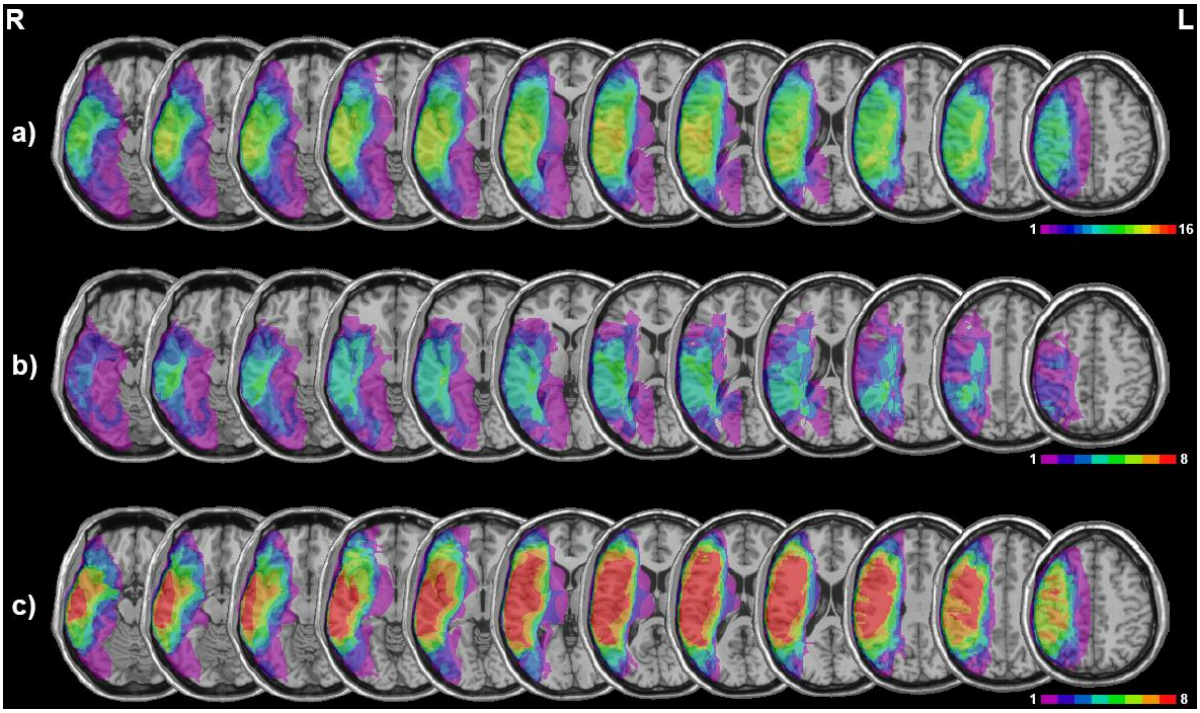


Figure 5.2: Lesion overlap maps.

Images are presented in radiological convention (right hemisphere on left of image); all lesions are right-sided (R: right; L: left).

Axial MRI slices of stroke lesions in **a)** the entire group of all 16 patients, **b)** the minimal prefrontal involvement subgroup (8 patients) and **c)** the extensive prefrontal involvement subgroup (8 patients). Colour values represent the number of patients in whom a given voxel was lesioned; note the scale is different for the entire group (a) compared to the subgroups (b and c).

	Rotigotine		**Placebo**	
	Number of patients	**Patient** (occurences)	**Number of patients**	**Patient** (occurences)
Fatigue	4 (25%)	P8(1), P9(3), P10(2), P14(1)	1 (6%)	P9(1)
Topical skin reaction	1 (6%)	P6(3)	0	-
Nausea	5 (31%)	P1(1), P3(1), P4(2), P8(3), P9(2)	0	-
Vomiting	1 (6%)	P3(1)	0	-
Diarrhoea	2 (13%)	P4(2), P8(1)	0	-

Table 5.2: Adverse events.

Number of patients who had at least one adverse event, patient codes (corresponding to those in Table 1) and number of occurrences per patient on rotigotine and on placebo.

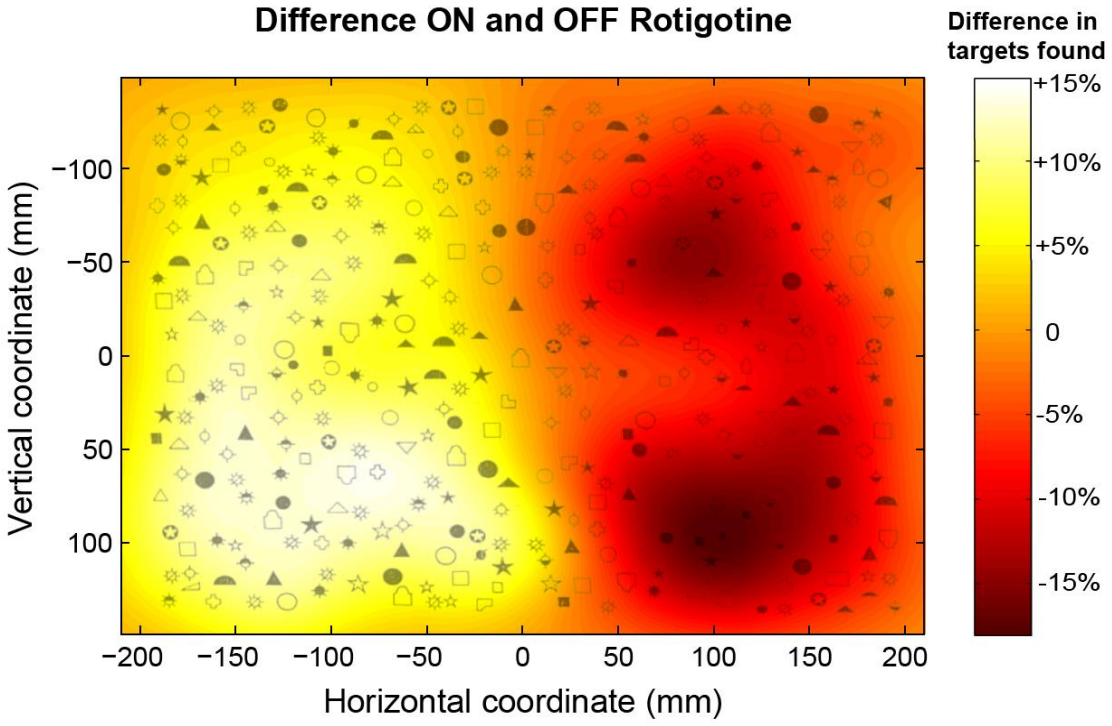


Figure 5.3: Difference in performance on the Mesulam cancellation task on and off Rotigotine for all patients.

A heatmap of the difference in targets found on- and off-treatment for the entire patient group is overlaid on a Mesulam test sheet. Colour represents difference on- and off-treatment in the number of targets found per session per patient at each target location. Treatment with rotigotine was associated with a significant increase in the number of targets identified on the left side. A decrease in the number of targets found during treatment in a smaller area on the right hand side was not statistically significant.

Spatial bias in visual search (ratio of difference in the number of targets found on either side to total number of targets found on the Mesulam test) also improved significantly on rotigotine when compared to the post-treatment phase (P=0.018) or to both off-treatment phases (P=0.016, **Figure 5.3).** There was 8.1% less rightward bias relative to baseline in the actual treatment allocation, in comparison to all possible permutations (**Figure 5.4b**).

5.3.3 Treatment effects in each prefrontal subgroup

Next, the effect of rotigotine on performance in the Mesulam test was evaluated in two patient subgroups, defined according to the extent of involvement of the prefrontal cortex in the stroke lesion: a minimal prefrontal involvement subgroup (0%-15% of the prefrontal cortex affected, **Figure 5.2b**) and an extensive prefrontal subgroup (33%-55% of the prefrontal cortex affected, **Figure 5.2c**). A significant benefit of treatment with rotigotine was noted in *both* subgroups (**Figure 5.5**), but for different study parameters.

The number of targets found on the left was significantly higher on rotigotine than off treatment in the minimal prefrontal subgroup (P=0.036), while this effect did not reach significance in the extensive prefrontal subgroup (P=0.084). Conversely, spatial bias improved significantly on rotigotine in the extensive prefrontal group (P=0.018), but not in the minimal prefrontal group (P=0.177). Therefore, rotigotine was associated with significant improvement in the Mesulam shape cancellation task in the entire patient group and in both prefrontal subgroups, but the significant measures varied between the two sub-groups.

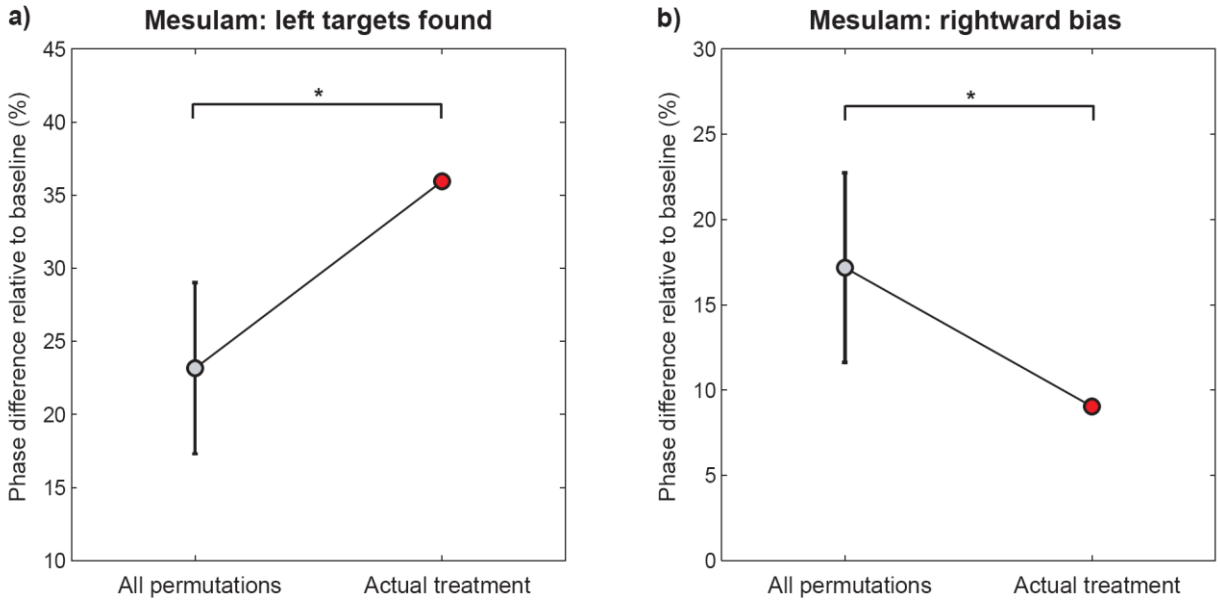


Figure 5.4: Overall effect of rotigotine treatment on Mesulam cancellation task.

Y axes represent % difference between performance on treatment (phase B) and off-treatment (average of phases A1 and A2), relative to off-treatment baseline. The actual differences on- and off-treatment (in red) are compared to the average (±average SEM) of differences between phases B and the average of A1 and A2 produced by all possible combinations of the data (in grey). *P<0.05.

a) The difference on- and off-treatment in the number of targets found on the left side relative to baseline was higher in the actual treatment allocation, compared to all other possible permutations.

b) There was significantly less rightward bias in the location of the targets found during treatment with rotigotine, in comparison to differences produced by all possible permutations of the data.

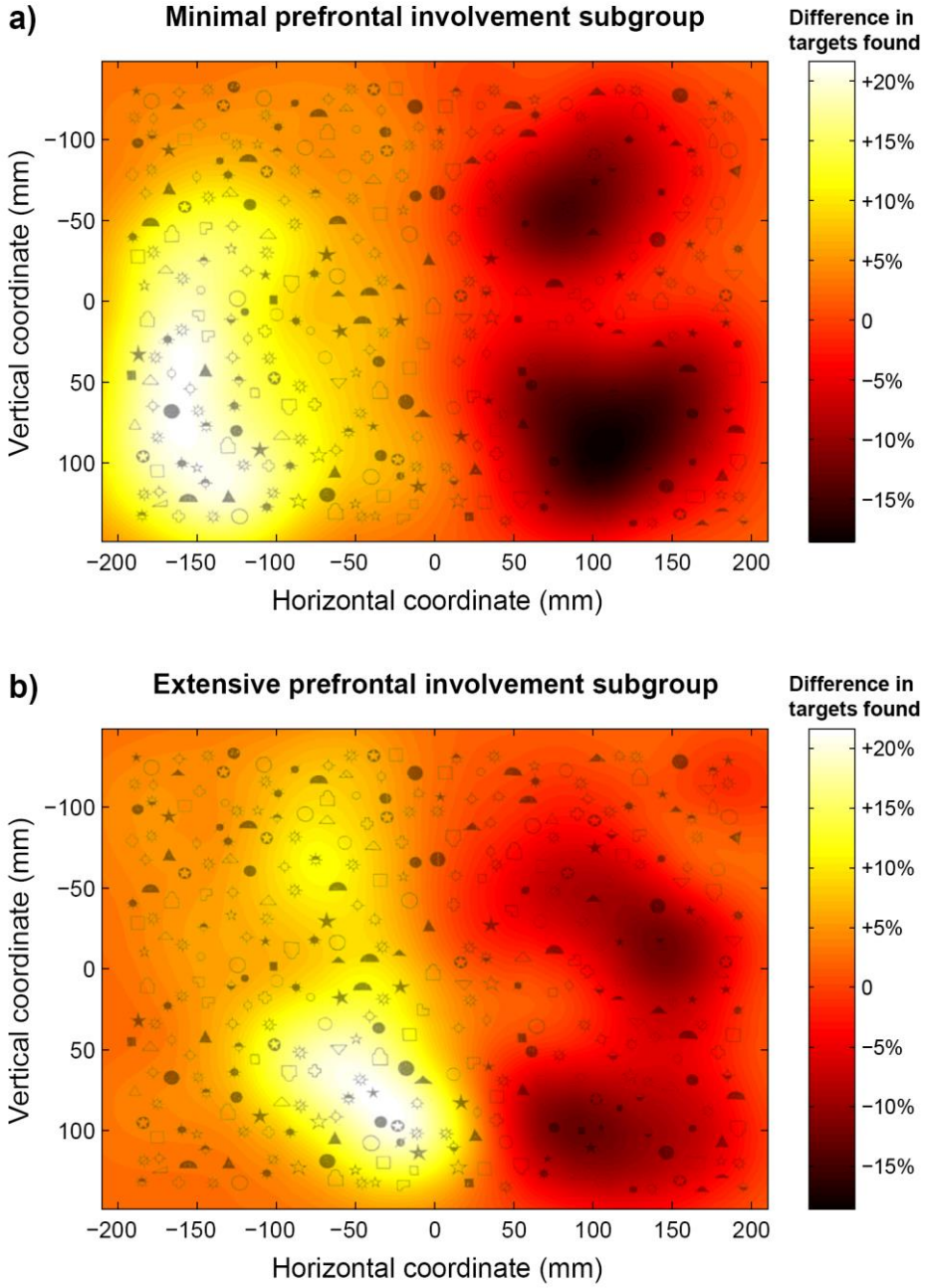


Figure 5.5: Difference in Mesulam task performance on and off Rotigotine in the two subgroups defined according to involvement of prefrontal cortex in the stroke lesion.

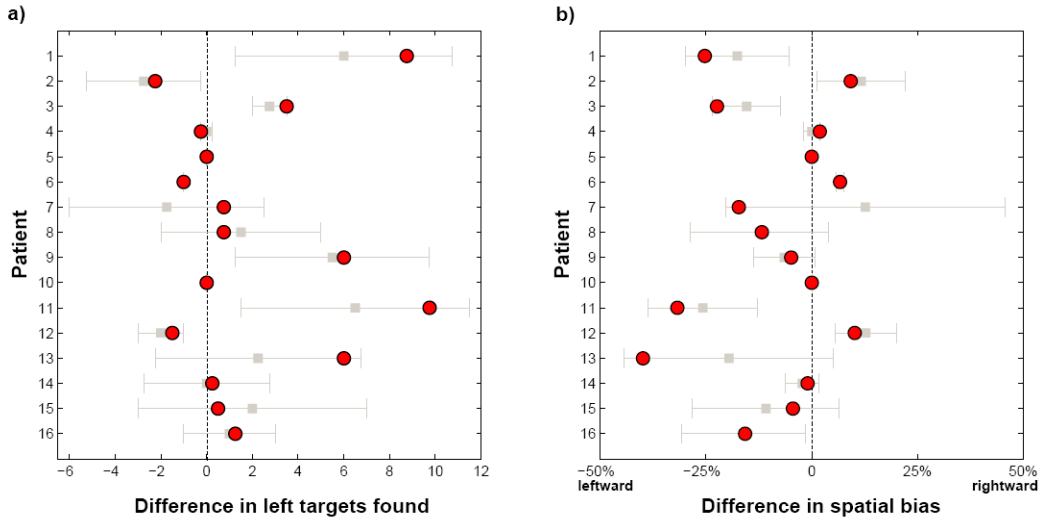
a) In the subgroup with minimal prefrontal involvement, the number of targets found on the left side increased significantly on treatment.

b) Patients with extensive prefrontal involvement showed a significant reduction in rightward spatial bias during treatment.

5.3.4 Treatment effects in individual patients

The effect of rotigotine on performance on the Mesulam cancellation task was also assessed on a subject-by-subject basis (**Figure 5.6** and **Table 5.1**). Response to the drug was characterised by considerable variability, with some subjects showing remarkable improvement on the drug when compared with average performance in the phases off rotigotine, and others showing smaller positive effects or even a small decline in the number of targets found on the left side while on the drug (see also **Table 5.1**). The results of permutation analysis for each patient on the Mesulam task are illustrated in **Figures 5.6a** and **b** for difference in the targets found on the left side (positive values in **Figure 5.6a** indicate improvement) and alteration in spatial bias (leftward shifts in **Figure 5.6b** denote improvement). Red circles demonstrate on vs. off treatment values (i.e. the actual treatment allocation data); grey lines show the range of such values for all possible permutations of the data in that patient and grey squares indicate the mean difference derived from all possible permutations of the data. Note that the ranges for each patient vary depending upon the variability of performance measures across all permutations of the dataset in each patient.

Some patients showed a strong effect on drug when compared to all possible permutations of the data (red circles well to the right of the range). Conversely, in other patients the differences in the actual treatment allocation were comparable to differences in other arrangements of the data, suggesting little effect of rotigotine on performance. Moreover, as shown in **Figure 5.6c**, the effect of rotigotine did not appear to depend on baseline performance (degree of neglect), as a beneficial effect – or otherwise – was observed across a range of baseline performance. Additionally, the effect of rotigotine was not determined be age, as there was no significant difference between the age of patients who responded best to treatment (1, 3, 9, 11 and 13) and that of patients who showed poor response ($t_{(14)} = -0.61$; $P=0.55$).



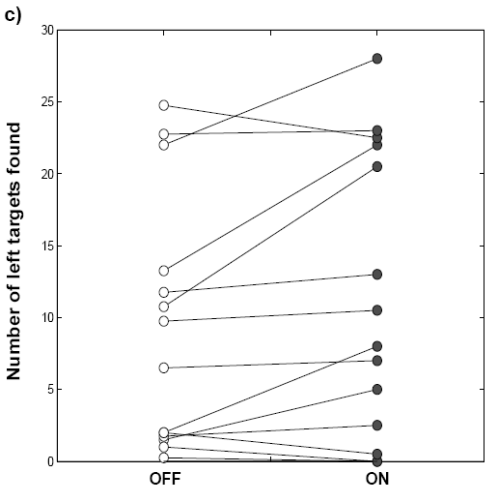


Figure 5.6: Mesulam task performance on and off Rotigotine in individual patients.

Response to rotigotine across patients (in the same order as in Table 1).

a) Difference in left targets found on- versus off-treatment. Red circles represent the actual difference in performance on and off rotigotine for each individual. Grey squares denote the mean difference derived from all possible permutations of the data while the error bars show the range of values of such means for all possible permutations. Red circles situated on the right of errorbars signify a greater number of targets found while on the drug when compared to all possible allocations of treatment and placebo.

b) Difference in spatial bias on- versus off-treatment. Here leftward shifts in search are displayed to the left. Red circles on the left of errorbars signify less rightward bias in the location of the targets found while on the drug when compared to all possible allocations of treatment and placebo.

c) Difference in number of targets found on left as a function of number of targets found off-tretament. Improvements occurred both in patients with poor performance at baseline (small number of targets found on the left side) and in those with good baseline performance.

5.3.5 Lesional correlates of response to treatment

In order to identify whether response to treatment was determined by damage in specific brain regions, a post-hoc analysis was also performed. Non-parametric mapping was used to compare the lesions of patients 1, 3, 9, 11 and 13, who showed maximal response to treatment in the Mesulam visual search task, and all other patients. As shown in **Figure 5.7**, damage to superior frontal cortical areas (including the Frontal Eye Field - FEF), temporal pole and smaller posterior temporal and frontal white matter areas in the right hemisphere may determine response to rotigotine in visual search. It should however be emphasised that this analysis is based on a very small sample of patients, therefore these results should be treated with caution.

5.3.6 Effects of rotigotine on other neglect tests

Unlike the results for the Mesulam cancellation task, there were no significant positive or negative effects of treatment with rotigotine on bells cancellation or touchscreen visual search tasks at the group or subgroups level. Similarly, no significant alteration in line bisection performance was observed, although I note that mean pre-treatment baseline performance in line bisection in the sample tested was relatively close to normal (mean rightward deviation: 4.5mm).

5.3.7 Effect of treatment on spatial working memory

One possible mechanism by which rotigotine might have exerted its positive effect on visual search in the Mesulam cancellation task could be by enhancing spatial working memory. Working memory perforance was quantified using a vertical analogue of the Corsi blocks task, and also by measuring the number of revisits of previously identified targets in the touchscreen visual search task. There was no evidence from either measure that treatment was associated with improvement of spatial working memory. Thus, performance on the vertical

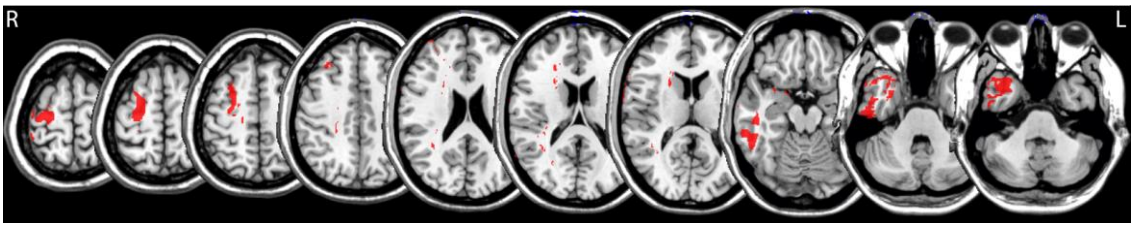


Figure 5.7: Lesional correlates of treatment response.

Non-parametric comparison of the lesions of patients 1, 3, 9, 11 and 13 who responded well to treatment in the Mesulam task, versus other patients, suggested that damage to right superior frontal cortical areas (including the right FEF), right temporal pole and smaller posterior temporal and frontal white matter areas may determine response to rotigotine in visual search.

Radiological convention is used; all ROIs are right-sided (R: right; L: left).

Corsi task did not improve on rotigotine (spatial memory span for the entire group: P=0.377; minimal prefrontal subgroup: P=0.548; extensive prefrontal subgroup: P=0.287), and treatment was not associated with a significant decrease in the number of revisits in the touchscreen task (entire group: P=0.821; minimal prefrontal subgroup: P=0.489; extensive prefrontal subgroup: P=0.909).

5.3.8 Effect of treatment on selective attention

An alternative hypothesis is that the effect of rotigotine on visual search might be due to an improvement of selective attention through D_1 receptor modulation (Noudoost and Moore, 2011). A specific task was used to quantify attention directly (visual salience and vigilance task; see Methods). This task measured the ratio of reaction times to respond to high salience targets versus low salience targets presented on the left or right of fixation. At the group level, there was a significant increase in this ratio for left sided targets during treatment, in comparison to the pre-treatment baseline (P=0.03, **Figure 5.8).** This effect was of only marginal significance when comparing treatment to the post-treatment baseline alone (P=0.068), or to the average of both off-treatment phases (P=0.063).

In the subgroup with extensive prefrontal involvement, treatment with rotigotine was associated with an increase in reaction time ratio to respond to salient / non-salient targets. This was when compared to the pre-treatment baseline or to the average of both treatment phases, both for left sided targets (P=0.016 and P=0.039, respectively), and overall for both left and right-sided targets (comparison with pre-treatment phase: P=0.008, and with off-treatment average: P=0.008). Conversely, in the minimal prefrontal subgroup, the effect of rotigotine on the same measure of selective attention was not significant (left sided targets, comparison with off-treatment average: P=0.113), even though at baseline reaction times ratios were not significantly different between the two patient subgroups (P=0.537). Therefore, treatment with rotigotine might be

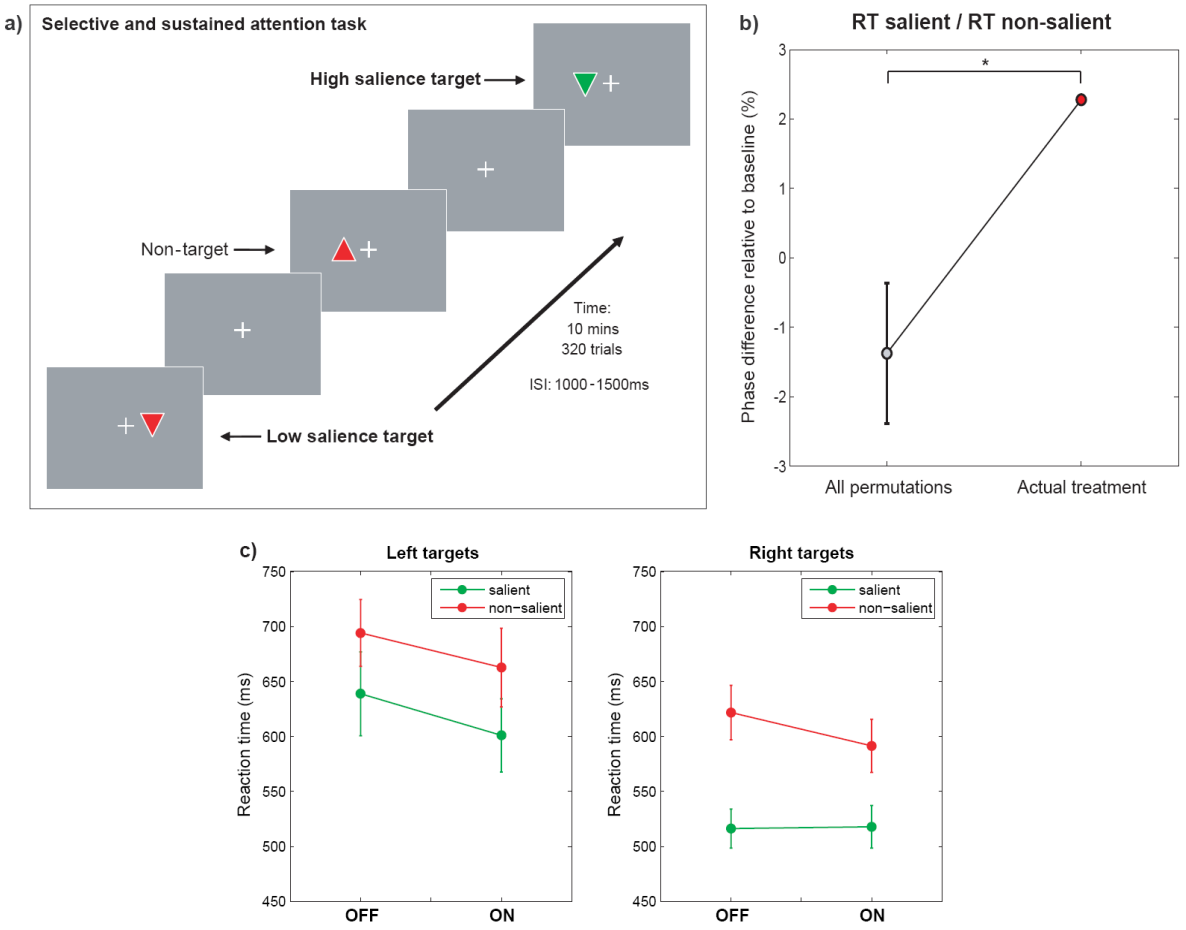


Figure 5.8: Selective and sustained attention.

a) Selective and sustained attention task. Participants detected targets (inverted triangles) among sequences of distractors (upright triangles) randomly presented to the ipsilesional and contralesional visual fields. Targets could be of the same colour as the distractors (red - low visual salience) or of a different colour (green - high visual salience). Participants were asked to respond with a button press as soon as they saw a target of any type.

b) Effect of rotigotine treatment on selective attention for left sided targets. Y axes represent % difference between performance on- (phase B) and pre-treatment (phase A1), relative to pre-treatment baseline. The actual differences on- and pre-treatment (in red) are compared to the average (±average SEM) of difference between phases B and A1 produced by all possible combinations of the data (in grey). The difference on- and pre-treatment in the ratio of the reaction time (RT) to salient targets over non-salient targets on the left side relative to baseline was higher in the actual treatment allocation, when compared to all possible permutations. *P=0.03.

c) Absolute reaction times (±SEM) OFF (phase A1) and ON treatment (phase B) for left- and right- sided stimuli of high or low salience.

associated with a modulation of selective attention in neglect, especially in patients with extensive damage in the prefrontal cortex.

5.3.9 Effect of treatment on sustained attention

A further possibility could be that rotigotine improved visual search by enhancing non-selective sustained attention, a cognitive ability that can be impaired in neglect (Hjaltason et al., 1996; Robertson et al., 1997). To control for this possibility, the difference in performance between the first and the second half of each session of the visual salience and vigilance task was used as a measure of sustained attention and alertness across time. However, rotigotine was not associated with a change in this measure in either the entire group (P=0.697) or the two patient subgroups (minimal prefrontal: P=0.555; extensive prefrontal: P=0.727).

5.3.10 Effect of rotigotine on motor tasks

Finally, treatment with rotigotine was not associated with any significant improvement or worsening in any of the motor tasks in the patient group as a whole, or in either of the prefrontal subgroups. Thus, in this sample, there was no evidence of a positive effect of rotigotine on motor control following stroke.

5.4 Discussion

In this Chapter, I presented the results of a randomised, double-blind, placebo controlled study of the dopamine agonist rotigotine in patients with hemispatial neglect and left-sided motor weakness following right-hemisphere stroke. A randomised ABA design was employed, with each patient assessed in three phases: before, during, and after treatment with rotigotine, for a total of 20 consecutive sessions. The exact number of sessions within each phase was randomised, and the difference on- and off- rotigotine in the actual treatment allocation was compared with the differences derived from all possible permutations of phase durations computed from each patient's data. This rigorous methodology enabled us to assess the effectiveness of rotigotine without the need for an extensive sample size (Ferron and Onghena, 1996; Edgington and Onghena, 2007). Nevertheless, the relatively small sample of 16 patients in this study is still the largest that has been reported to date in any study on drug treatment in neglect following stroke (Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998; Hurford et al., 1998; Barrett et al., 1999; Mukand et al., 2001; Malhotra et al., 2006; Buxbaum et al., 2007; Vossel et al., 2010).

Treatment with rotigotine was associated with a significant increase in the number of targets identified on the left side and a decrease in the pathological rightward spatial bias in the Mesulam shape cancellation task, a visual search test widely used to assess neglect in clinical practice. Of note, rotigotine was associated with a 12.8% increase in the number of targets found on the left in the actual treatment allocation in comparison to all possible permutations of the data. However, there was considerable variation across individuals and it is, as yet, unclear which patients are most likely to benefit. Importantly, response did not appear to depend upon baseline degree of neglect or extent of prefrontal involvement.

Although the positive effect of rotigotine was moderate, it is potentially important, bearing in mind that this study design investigated short-term treatment over only 7-11 days. The result compares favourably with the effects of most other neuromodulatory agents established in the clinical treatment of cognitive deficits, which overall are typically very modest (Husain and Mehta, 2011), e.g. of the order of 3% over several months for cholinesterase inhibitors used for the treatment of dementia (Erkinjuntti et al., 2002). Of course, the clinical use of such treatments has been challenged on the basis of their small overall effect sizes, but it is also apparent that there is considerable heterogeneity of response, with some patients demonstrating very strong effects while others show none.

Using non-parametric mapping lesion analysis, I suggested that damage in certain brain regions may determine response to rotigotine. Important limitations of this technique are discussed in Chapter 4 (paragraph 4.4). It cannot be emphasised enough that this approach requires a considerably larger sample size to produce reliable results (Medina et al., 2010), and therefore the conclusions from it may well not replicate or generalise. However, the results are potentially interesting. The superior prefrontal area indicated by this analysis (**Figure 5.7**) shows substantial overlap with the right Frontal Eye Field (FEF – Brodmann area 8), which has a well-known role in visual search and attentional shifting (Gitelman et al., 2002; Moore and Fallah, 2004). The more ventral and rostral temporal area identified is in close proximity to the parahippocampal gyrus, which has critical role in neglect (Mort et al., 2003). Finally, the white matter areas shown in **Figure 5.7** could be in keeping with parts of the superior longitudinal fasciculus (Catani and Thiebaut de Schotten, 2008b; Thiebaut de Schotten et al., 2008), which has been implicated in spatial awareness (Thiebaut de Schotten et al., 2005) and neglect (Bartolomeo et al., 2007; Urbanski et al., 2008).

Although the relatively small sample size of the current study does not allow for a reliable systematic data-driven investigation of the possible determinants of between-subject variability, larger studies in future might identify possible

predictors of treatment response, which could permit patient selection for targeted treatment. For example, in this study, patients with a wide range of time since stroke were included, and I did not differentiate between patients with an ischaemic or haemorrhagic aetiology. Future investigations, with larger samples, might attempt to control for such variables and also attempt to study the effects of the drug on functional measures of neglect (Azouvi et al., 2003) and / or activities of daily living.

It should be noted that there were no significant effects of rotigotine on two other visual search tasks (bells cancellation and touchscreen cancellation tests). Possible reasons for this discrepancy might relate to display parameters in these tasks. Specifically, in the bells cancellation task there is a smaller number of targets and distractors than in the Mesulam test (34 versus 60 targets; 278 versus 311 distractors) and in the touchscreen visual search task the targets and distractors were presented on a smaller area. These parameters may render the bells and touchscreen visual search tests less sensitive than the Mesulam shape cancellation task (Kaplan et al., 1991), making the effects of treatment less discernible. Rightward deviation in line bisection also did not improve significantly on treatment. Given that performance in the pre-treatment baseline phase was already close to normal, this may represent a ceiling effect. Response to treatment did not depend on task difficulty or complexity, as rotigotine had a significant improvement in the Mesulam task, while there was no significant effect of the drug in both simpler (line bisection, Bells cancellation), and more complex tasks (touchscreen cancellation).

The current study was designed not only to assess the effectiveness of rotigotine in ameliorating spatial bias in neglect, but also to identify possible cognitive mechanisms which may mediate this effect. Based on existing evidence on the role of D_1 dopamine receptor activity in spatial working memory (Funahashi and Kubota, 1994; Castner et al., 2000; Castner and Goldman-Rakic, 2004), it was hypothesized that rotigotine might improve performance on cancellation tasks by enhancing working memory for the

location of previously cancelled targets, and therefore diminishing 'revisiting' of previously explored locations (Mannan et al., 2005; Parton et al., 2006). However, rotigotine was not associated with improvement of spatial working memory, indexed either indirectly, by measuring the number of revisits in the touchscreen cancellation task (Parton et al., 2006), or directly, using a vertical variant of the Corsi spatial memory task (Malhotra et al., 2005).

An alternative mechanism which may explain the positive effects of rotigotine in the Mesulam cancellation task would consist of a direct enhancement of selective attention by increased dopaminergic activity. This hypothesis is compatible with recent evidence that local administration of a D_1 dopamine receptor modulator in the monkey frontal lobe alters selectivity and reliability of eye movements to visual targets, and modulates neuronal activity in visual area V4 in the same way that selective voluntary attention does (Noudoost and Moore, 2011). If this were the case also in humans with visual neglect, one might expect the drug to induce more effective allocation of *voluntary* attention to task-relevant target stimuli and, correspondingly, less *involuntary* attentional capture by the task-irrelevant (but visually salient) distractors, therefore making identification of correct items more effective.

Interestingly, the results from the combined visual salience and vigilance task suggest that responses to *less salient* (but equally *task-relevant)* targets relative to the more salient ones became faster on the left with rotigotine. This result may be in keeping with more effective voluntary allocation of selective attention to the task-relevant visual targets, and less involuntary attentional capture, driven by stimulus salience, on rotigotine. Therefore, it is possible that rotigotine improved performance on the Mesulam shape cancellation task by enhancing selective attention to the targets, while reducing involuntary attentional capture by the distractors. This result is in keeping with the known role of dopamine in attention switching, arousal to behaviourally relevant stimuli and goal-directed behaviour (Bromberg-Martin et al., 2010; Cools, 2011).

Non-selective sustained attention can be attenuated in neglect and has been shown to correlate with neglect severity (Hjaltason et al., 1996; Robertson et al., 1997). Therefore, an additional possibility tested was that rotigotine may have enhanced the patients' ability to sustain non-selective attention and alertness over time. However, there was no significant effect of treatment on performance in the visual salience and vigilance task across time. Therefore, rotigotine, rather than enhancing sustaining of non-selective attention across time, seems to improve selective, voluntary attention. Note that the effects of treatment were highly specific, suggesting that the enhancement of visual search occurred through dopaminergic modulation of selective attention, rather than through aspecific motivational effects, unrelated to neglect.

According to the study hypothesis, the effects of rotigotine in neglect are likely to have been mediated by increased dopaminergic activity in the right prefrontal cortex. In that case, one would expect to find benefit from treatment with rotigotine only in patients with relative preservation of the right prefrontal cortex. However, treatment was associated with significant improvement in the Mesulam shape cancellation task in both the minimal and the extensive prefrontal involvement subgroup. This suggests that integrity of the right prefrontal cortex is not critical in determining response to rotigotine, at least in the sample of patients assessed in this study. An alternative hypothesis could be that rotigotine modulates the activity in intact fronto-parietal or fronto-occipital networks (Bartolomeo et al., 2007; Urbanski et al., 2008; Doricchi et al., 2008; Vuilleumier et al., 2008), either in the lesioned, or in the contralesional hemisphere, effectively "re-balancing" pathological overactivity in structurally intact brain networks, which may contribute to lateralised attentional imbalance in neglect (Corbetta et al., 2005).

We hypothesised that modulation of D_1 receptor activity may provide a possible mechanism by which visual search in neglect can be ameliorated through enhancement of working memory or selective attention. In comparison to other dopamine agonists approved for clinical use, rotigotine has a relatively high D_1 receptor affinity, however it should be noted that it has an even higher affinity

to D_2 and D_3 receptors (Belluzzi et al., 1994; Jenner, 2005; Naidu and Chaudhuri, 2007). Therefore, the effect of rotigotine on visual search may also be mediated, at least in part, by D_2 and/or D_3 agonist activity. Future studies should address the effects of a highly selective D_1 receptor agonist in neglect, and compare those with the effects of D_2/D_3 agonists.

In a prospective study, L-dopa as an adjuvant of physiotherapy has been demonstrated to improve motor function in stroke patients with unilateral weakness (Scheidtmann et al., 2001). In the current study, there was no significant effect of rotigotine treatment on motor performance. However, the study was not designed to assess drug effects prospectively, and the amount of physiotherapy received by each patient was not controlled, therefore although an effect of rotigotine alone on motor performance was not demonstrated, it remains an open question whether this drug may benefit motor rehabilitation when used as adjuvant of physiotherapy. Indeed, given the well-recognised role of dopamine in complex reinforcement learning (Dayan and Balleine, 2002; Wise, 2004), a possible synergistic role of dopamine agonists in novel rehabilitative approaches that aim to improve spatial awareness in neglect (Parton et al., 2004) also presents itself as an important question for future research.

The current Chapter presented the first successful randomised double-blind placebo controlled study of the dopamine agonist rotigotine in a group of stroke patients with hemispatial neglect and unilateral weakness. Rotigotine was reasonably well tolerated in this setting and was associated with significant improvement in one visual search task. Placebo-controlled N-of-1 randomised designs such as the one used here provide a useful means to test proof-of-principle for potential new therapies. However, larger trials, including measures of functional efficacy, will be needed to confirm whether this treatment may be practical for widespread clinical use in hemispatial neglect following stroke.

Chapter 6

Working Memory Precision in Medial Temporal Lesion Patients

6.1 Introduction

In their seminal study more than half a century ago, Scoville and Milner (Scoville and Milner, 1957) showed that individuals, including famous HM, with bilateral damage to their medial temporal lobe (MTL) exhibit complete anterograde amnesia. New incidents in their daily life were practically forgotten "as fast as they occur". Most interestingly, these patients were still able to retain a three figure number or a pair of words as long as attention was not diverted to a new topic. Thus, it was considered that short term memory (STM), or working memory (WM), remains intact after MTL damage. By contrast long-term memory (LTM) is severely impaired.

This differential involvement of MTL in memory processes is one of the main pillars supporting the dogma that WM and LTM are functionally and anatomically distinct memory systems. However, the classic distinction between LTM and WM, despite its general acceptance (Baddeley, 2003, 2007), has always attracted some dissent (Crowder, 1982, 1993; Nairne, 2002). Recent criticism has specifically addressed the claim that MTL is not involved in WM (Hannula et al., 2006; Olson et al., 2006a, 2006b; Ezzyat and Olson, 2008; Finke et al., 2008). In these studies, patients with MTL lesions were found to be impaired on various tasks even when the retention interval was as short as

a few seconds. Such deficits were discovered mainly on paradigms requiring memory for associations, such as object-to-location links (Ranganath and Blumenfeld, 2005; Cashdollar et al., 2011). These findings support an alternative view of MTL, based on ideas originally expressed by Marr, which highlights the role of the MTL in associating or binding information represented in different parts of the neocortex (Marr, 1971) – critically, regardless of memory duration: short or long.

More recently, though, a series of studies by Squire and colleagues has re-examined this issue. They have presented evidence which they argue is best interpreted as being in favour of the traditional view of WM not depending upon MTL integrity (Jeneson et al., 2010, 2012; Jeneson and Squire, 2012). For example, Jeneson et al (2012) tested five patients with MTL damage using a standard change detection task in which a change in colour has to be detected between two successive displays of an array of coloured squares. Patients performed as well as controls at several delays when only a few squares were presented (up to ~3). However, their performance was worse than controls when more items had to be maintained for more than one second. The authors concluded that visual WM is intact in MTL patients; any deficits that emerge on such tasks, they argue, occur only when WM capacity is breached (i.e. when the number of items held in memory is greater than ~3 objects). In such circumstances, according to these authors, healthy participants are at an advantage over patients because they can rapidly recruit intact LTM processes to assist in retaining information beyond the capacity limit of WM.

Clearly the debate around the involvement of MTL in WM remains unresolved. The study presented in the current Chapter was designed to shed light on this controversy using a novel approach. Unlike previous studies on patients with MTL lesions, the task used here examines the precision of recall (Bays and Husain, 2008; Bays et al., 2009; Wilken and Ma, 2004) rather than the number of errors as studied in the conventional change detection paradigm which requires binary decisions (e.g., change or no change). If an individual fails to report a change when it occurs on a change detection task, it does not necessarily mean that they did not have any memory of the item. Conversely, if

they do report change or no change correctly, this does not mean they remembered the item perfectly. In contrast, in the task employed here, participants were required to choose the remembered feature of an item from a continuous space (Wilken and Ma, 2004; Zhang and Luck, 2008; Bays et al., 2009; Gorgoraptis et al., 2011). Such paradigms have two main advantages over the more conventional tasks with binary decisions. First, they provide much more information per trial (several bits versus one bit of information) and therefore are potentially more sensitive. Second, the continuous space of responses opens a window to investigate not just the frequency of errors, but also the type of errors made by participants, by examining the distribution of responses using a generative model (Bays et al., 2009).

Most previous studies on MTL involvement in WM have studied patients suffering from Korsakoff's syndrome (Cave and Squire, 1992; Nichols et al., 2006), anoxia (Cave and Squire, 1992; Hannula et al., 2006; Olson et al., 2006b; Jeneson et al., 2010), or Herpes Simplex Virus (HSV) encephalitis (Olson et al., 2006a; Ezzyat and Olson, 2008; Jeneson et al., 2010). These conditions typically affect the MTL (Kapur et al., 1994; Sullivan and Marsh, 2003; Di Paola et al., 2008), but they also commonly cause more widespread brain damage extending outside the temporal lobes (Kapur et al., 1994; Visser et al., 1999; Allen et al., 2006a).

Here, I studied WM precision in two patients with extensive lesions involving the MTL following HSV encephalitis, but also in two patients with a recently recognized condition associated with much more focal medial temporal lobe involvement (Vincent et al., 2011). Less than a decade ago, Vincent and her colleagues described a series of individuals with a potentially reversible limbic encephalitis associated with antibodies to voltage-gated potassium channels (VGKC) (Vincent et al., 2004). It has subsequently become clear that the specific antigens to which antibodies are produced in this condition are not usually the voltage-gated potassium channel itself, but associated components of the channels such as LGI1 (leucine-rich, glioma-inactivated 1) which appear to be important for synaptic communication (Lai et al., 2010; Vincent et al., 2011; Benarroch, 2012). Although previous studies have investigated some

cognitive aspects of patients with VGCK-associated encephalitis (Maguire et al., 2006; Chan et al., 2007; Hartley et al., 2007), the full spectrum of cognitive impairment – and specifically WM performance – in this population is still unknown.

Several lines of evidence suggest that VGCK-associated encephalitis specifically targets the MTL, mainly the hippocampus. A recent study found LGI1 gene expression appears to be very restricted to intrahippocampal circuitry (Herranz-Pérez et al., 2010). Post-mortem study of a VGCK-associated encephalitis patient has revealed neural loss restricted to the hippocampus, and amygdala to a lesser extent, but no damage has thus far been evident in other MTL regions or neocortex (Khan et al., 2009). Additional imaging studies have provided further support that the damage as a result of VGCK-associated encephalitis predominantly affects the MTL, specifically the hippocampus (Ances et al., 2005; Harrower et al., 2006). This anatomical selectivity puts forward this recently recognised condition as a good potential model of the role of the MTL in WM processes.

6.2 Methods

6.2.1 Subjects

Two patients with focal MTL lesions following Voltage Gated K^+ Channel (VGKC) - associated encephalitis, and two patients with more extensive temporal lobe lesions due to Herpes Simplex Virus (HSV) encephalitis, also involving the MTL, were recruited from the general neurology clinic and through direct referrals by the neuropsychology team at The National Hospital for Neurology and Neurosurgery. Patients underwent formal assessment on the WAIS-III battery (Wechsler, 2001) by a qualified neuropsychologist.

Patients with focal MTL lesions due to VGKC-associated encephalitis

HG is a 70 year-old man who presented in March 2010 with progressive behavioural change over a period of 3 months, including altered mood, agitation, fatigue and confusion. Subsequently, he developed paroxysmal sensory symptoms associated with ictal EEG changes. MRI brain revealed a focal area of increased signal in the MTL bilaterally, but predominantly on the left side (Figure 6.1A). A specific immunological assay confirmed a diagnosis of VGKC-associated encephalitis. The patient received treatment with plasma exchange and intravenous immunoglobulin (IVIg), following which a modest improvement in the patient's symptoms and cognitive performance was noted. HG's assessment on the WAIS-III battery before treatment revealed intact visual perceptual, visual spatial and speed of information processing skills (VOSP Incomplete Letters and Cube Analysis: both 100% correct). However, verbal memory was impaired (Recognition Memory Test for Words: <5th%ile, above chance) and visual memory was at the lower end of the low average range (RMT Faces: 10th%ile). Immediate and delayed recall was reduced (AMIPB Story recall: <10th%ile). There was also some evidence of executive dysfunction (½ categories on the Weigl Sorting Test). Post-treatment, HG showed a modest improvement in verbal (RMT for Words: 10-25th%ile), and visual memory (RMT Faces: 50-75th%ile), however both immediate and

delayed recall remained impaired (AMIPB Story recall <10th%ile; AMIPB Figure recall <10th%ile).

RW is a 63 year-old man who developed behavioural change of insidious onset in 2006, including confusion, confabulation and mania. Three months after his initial presentation, his confusion deteriorated acutely, and he had two generalised tonic-clonic seizures. He was diagnosed with VGKC-associated encephalitis, and treated with plasma exchange and corticosteroids. His cognitive state improved significantly, but he was left with profound retrograde amnesia for events that occurred from about 1980 until 2008. MRI brain in June 2007 revealed bilateral hippocampal lesions (Figure 6.1B). In his neurosychology assessment, RW presented with a selective verbal memory impairment in the WAIS-III, with RMT Words <1st%ile and similar performance in the immediate and delayed story recall test. In contrast, visual memory appeared to be satisfactory (RMT Faces: 50-75th%ile). Performance in all other cognitive domains, including visual perception, ranged from average to superior.

Patients with HSV encephalitis and more extensive temporal lesions

DC is a 47 year-old man who presented acutely in 2003 with severe encephalopathy and generalised tonic-clonic seizures. He was diagnosed with HSV encephalitis, which caused extensive bilateral damage in the temporal lobes, more severe on the right side (Figure 6.1C), also with some inferior frontal and parietal involvement on that side. Following treatment, he showed remarkable improvement, and was eventually able to live independently, however there remain significant problems with navigation in space and long-term memory. DC showed evidence of impairment in verbal memory (10th%ile) but he was less impaired on a visual memory task (25th%ile). His performance on tests of visuo-spatial processing and naming was intact.

JB is a 59 year-old woman who presented in 2006 with a week's history of behavioural change, including emotional lability and confusion. Her cognitive state then deteriorated acutely and she had a generalised tonic-clonic seizure. She was diagnosed with HSV encephalitis, causing extensive damage

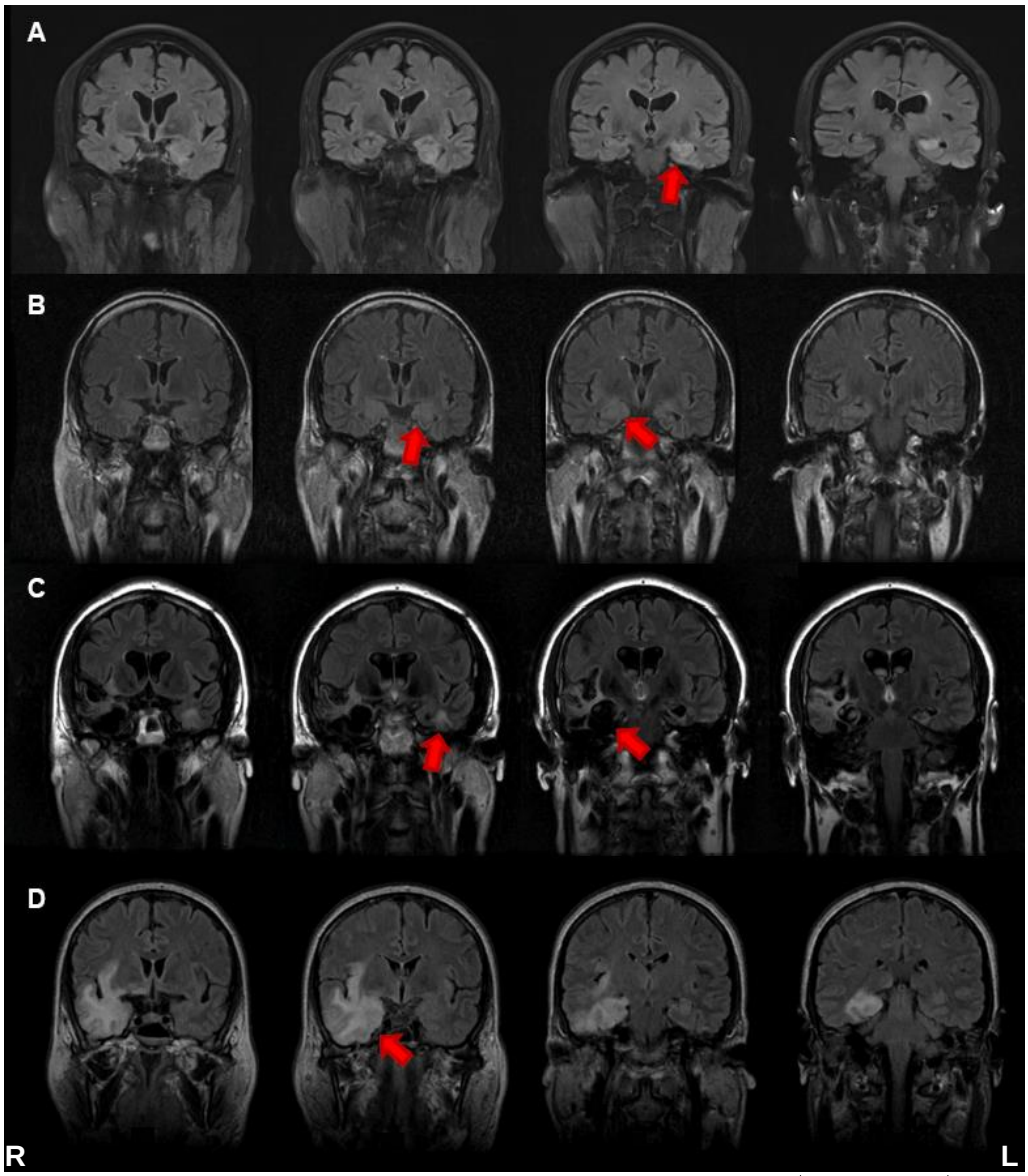


Figure 6.1: Coronal FLAIR MRI showing patients' lesions (red arrows).

Images are presented in radiological convention (left hemisphere on right side); R: right, L: left.

A) MRI of patient HG on diagnosis. A highly focal lesion is evident, affecting predominantly the left hippocampus.

B) MRI of patient RW one year after symptom onset demonstrates focal bilateral lesions, restricted to the hippocampi.

C) MRI of patient DC reveals extensive bilateral lesions. There is widespread damage in the right temporal lobe with accompanying ex vacuo changes, while the left medial temporal lobe is also lesioned.

D) MRI of patient JB demonstrates an extensive right temporal lesion.

predominantly in the right temporal lobe (**Figure 6.1D**). She had significant improvement following treatment, and at present she is able to function independently on a day-to-day basis. However, JB's WAIS-III assessment revealed a selective visual memory impairment (RMT Faces: <5th%ile, delayed complex figure recall <10th%ile). Conversely, verbal memory was intact ranging from average to superior (AMIPB Story recall: 25-50th%ile; RMT Words: 75-90th%ile). No impairment was identified in other cognitive domains, including visual and spatial perception.

Healthy controls

Nine healthy control subjects, (7 female, mean age (±SD): 69 (±6.1) years) took part in the sequential WM tasks.

The study was approved by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Local Research Ethics Committee. All study participants provided written informed consent.

6.2.2 Behavioural tests

Digit and spatial spans

The following standard measures of WM were obtained for all patients: forward and backward auditory digit span (Blankenship, 1938); forward and backward Corsi spatial span (Corsi, 1972). To assess digit span, sequences of gradually increasing numbers of digits were read out loud by the examiner, at a rate of one digit per second. Participants were asked to repeat each sequence as given (forward digit span), or backwards (backward digit span). To assess Corsi spatial WM span, the examiner tapped a sequence of spatial locations on a Corsi blocks board, and the participant was asked to replicate the sequence as given (forward spatial span), or backwards (backward spatial span). Gradually increasing numbers of spatial locations were given on subsequent trials. In both tests, two attempts were allowed at each sequence length, and the test was terminated after two incorrect responses on the same sequence length. Each correct response scored one mark. Total score (sum of marks from all

correct trials) and span (length of the longest sequence the subject was able to replicate correctly) were recorded for each participant. Results were compared to standardised normative data (Orsini et al., 1987; Kessels et al., 2000).

Sequential WM task

Patients and healthy controls were tested in the sequential WM precision task (Gorgoraptis et al., 2011) described in Chapter 4. In this task, presented in Figure 4.2A, each trial consisted of a sequence of one to three coloured bars presented consecutively at the centre of a computer screen; the orientation and colour of each bar had to be memorised and one of the bars was presented at a random orientation at the end of each sequence. Subjects had to adjust the orientation of the probe as accurately as possible from memory using a response dial (Griffin Technology). The rest of the experimental parameters were as described in Chapter 4. Note that, in this experiment, that the longest time interval from offset of an item to testing was 2500ms (for the first of 3 items).

Patient HG was tested on this task on four occasions: on diagnosis (April 2010), following treatment with IVIg (September 2010), and in two follow-up sessions (November 2010 and February 2011). He completed 120 trials in each session.

Patients RW, DC and JB completed one session of 120 trials each post treatment, and healthy controls performed 240 trials from this task.

Sequential WM task with predictive cueing

Patients HG, RW and healthy controls also participated in a version of the sequential WM task where one of the items was cued (Gorgoraptis et al., 2011). The task is described in detail in Chapters 3 and 4 (Figure 4.5). Subjects were presented with sequences of three items, different in colour and orientation. As in the previous task, one of the colours was probed at the end of each sequence, at a random orientation, and subjects were asked to adjust the item's orientation from memory. However in this task, one of the colours, which was present in all trials and fixed for each subject, was predictively cued by being probed with increased frequency, in 66.7% of the trials versus 16.7% for each of the other colours in the sequence. The effect of predicitive cueing on memory

was examined by comparing memory precision for the cued item versus precision for the uncued ones.

HG performed 200 trials, RW did 100 trials and healthy controls completed 200 trials from this task. Both patients were tested on this task after treatment.

Perceptual / motor control task

As previously (Chapter 4), to ensure that all subjects were able to use the response device, and to control for potential impairments in visual perception of the stimuli and visuo-motor coordination when responding, a control task, which did not require WM, was performed in all participants before testing on the sequential WM task. In this control task, presented in Figure 4.1A, a single target bar was presented, at a random orientation, at the screen centre. One second later, a probe bar of the same colour was presented at random orientation just above the first item, 5° of visual angle above the screen centre, on the vertical meridian. While the target item was always present on the screen, subjects were asked to adjust the orientation of the probe bar to match the target, using the same response device as in the tasks described above.

6.2.3 Analysis

Memory precision was calculated as described in Chapter 2, based on previous studies using the fidelity of recall of a visual stimulus as a sensitive index of resolution in visual memory (Bays and Husain, 2008; Bays et al., 2009, 2009, 2009; Zokaei et al., 2011; Gorgoraptis et al., 2011). Briefly, for each trial, the angular deviation between the orientation reported by the subject and the correct orientation of the target bar in the preceding sequence was obtained, and precision was calculated as the reciprocal of the circular (Fisher, 1993) SD of error across trials ($1/\sigma$). As previously (Chapter 2), the value expected for chance was subtracted; therefore a precision value of zero corresponds to responding at random.

Z-scores were obtained for each patient and experimental condition. Effect sizes were therefore expressed as units of the controls' standard deviation, and P-values were obtained from the Z distribution.

Model analysis

In order to quantify the contribution of different sources of error to loss of WM precision, as previously, I applied a probabilistic model introduced by Bays et al. (2009), and described in detail in Chapters 1 and 2. Briefly, this model attributes errors on the reproduction task to (1) Gaussian variability in memory for the target orientation; (2) a certain probability on each trial of misreporting one of the other, non-target, orientations in the sequence; and (3) a certain probability of responding with a random orientation not related to any of the items in the sequence. Maximum likelihood estimates of each of these parameters were obtained for each subject, and were compared between each patient and controls using ANOVA, as specified in the Results.

Nearest neighbour control

Errors due to misreporting the orientation of a non-target item, instead of that of a target, were examined more directly by applying the 'nearest neighbour' procedure introduced by Pertzov et al., (2013). The minimum angle between the reported orientation and any one of the items in the sequence was calculated. When the reported orientation was distant from the target orientation and closer to that of a non-target item, that (non-target) item was treated as if it was the target. If non-target responses account for a significant proportion of errors, then this procedure should diminish the apparent error (Pertzov et al., 2013). The results of VGCK-antibody associated encephalitis patients (HG and RW) were examined using this technique.

Calculation of precision, model fitting and data plotting was performed using custom Matlab scripts (Matlab R2010b, MathWorks). Statistical comparisons were carried out in Matlab R2010b (MathWorks) and SPSS 18 (IBM Corp.).

6.3 Results

6.3.1 Standard WM tests: digit span and spatial span

Patients' digit span and Corsi spatial span results are presented on **Table 6.1**. Digit and spatial span results were within normal limits in all four patients when compared to normative data from age-matched healthy subjects (Orsini et al., 1987; Kessels et al., 2000).

6.3.2 Controlling for perceptual and motor confounds

Patients and controls took part in a simple control task, where the angle of the probe item was adjusted while the target item was visible on the screen. This task does not require WM, and controls for any potential impairment of visual perception or in visuo-motor performance and motor control while using the response device.

As shown in Figure 6.2, performance of all four patients in this control task was not significantly worse than that of healthy controls. HG was as precise as controls (Z-score: Z=0.64, *P*=0.26), and the precision of RW, DC and JB was significantly better than in healthy controls (correspondingly: Z=1.70, *P*=0.045; Z=1.93, *P*=0.027; Z=2.47, P=0.007). Note that precision of healthy controls on this task is already very high, corresponding to an average deviation from the correct orientation of only 5.3º.

Therefore, lower performance in patients in the subsequent WM tasks cannot be accounted for by perceptual or visuo-motor impairments, or difficulty in using the response device.

	Digit span		Corsi span	
Patient	**Forward span (score)**	**Backward span (score)**	**Forward span (score)**	**Backward span (score)**
HG	5 (7)	4 (4)	6 (8)	4 (5)
RW	5 (8)	3 (3)	5 (7)	5 (7)
DC	5 (8)	4 (6)	5 (8)	4 (6)
JB	7 (11)	6 (10)	6 (9)	5 (8)

Table 6.1: Digit span and Corsi spatial span results in patients.

Digit span and Corsi spatial span –the number of items in the longest sequence that was correctly replicated on each task– are presented for each patient. The total scores –number of correct trials– are given in parentheses. Performance was within normal limits when compared to age-matched normative data (Orsini et al., 1987; Kessels et al., 2000).

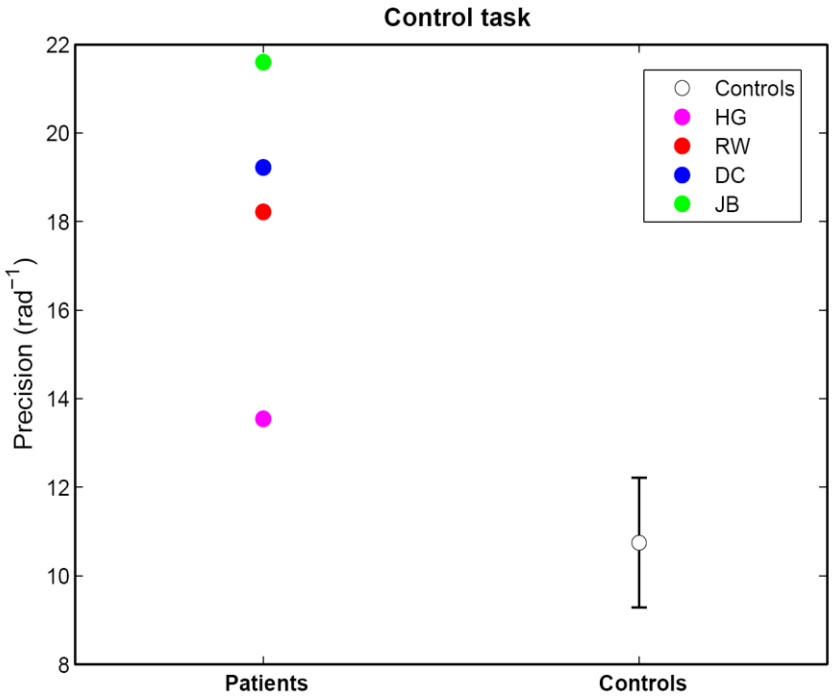


Figure 6.2: Control task results.

Patients and healthy controls were tested on a control task where the orientation of a probe had to be adjusted to match that of a target item which was visible on the screen, rather than memorised.

Patient HG (purple point) performed as well as controls (white point), while patients RW (red point), DC (blue point), and JB (green point) performed even better than healthy controls in this task.

6.3.3 Serial WM precision in MTL lesion patients

WM precision was assessed in MTL lesion patients and healthy controls using a task where one to three items, displayed in sequence, had to be kept in memory for a brief period of time (500-2500ms). Average WM precision across all sequence lengths is presented in **Figure 6.3**.

HG, a patient with highly focal, predominantly left-sided hippocampal damage due to VGKC-associated encephalitis (**Figure 6.1A**), was assessed before treatment with plasma exchange and IVIg, and in three post-treatment follow-up sessions. HG's overall WM precision was lower than that of healthy age-matched controls, but not significantly so (Z-scores; pre-treatment: Z=-1.29, P=0.098; post-treatment average: Z=-1.31, P=0.095; **Figure 6.3**, purple point). When examining each sequence length separately, HG's memory for one item was not significantly different to controls (Z=-0.55, P=0.29), but WM precision deteriorated steeply as more items were added and it was significantly lower than in controls for two (Z=-2.01, P=0.022) and three items (Z=-1.76, P=0.039) in the sequence.

RW, a patient with the same underlying condition resulting in highly focal bilateral hippocampal damage (**Figure 6.1B**), had lower WM precision than healthy controls, but the comparison was not statistically significant overall (Z-score; Z=-0.90, P=0.18; **Figure 6.3**, red point). When studied at each sequence length, RW's WM precision was unimpaired for a single item when compared to controls (Z=-0.64, P=0.26), and lower than in controls for two (Z=-1.01, P=0.16) and three items (Z=-0.94, P=0.17), but these comparisons were not statistically significant.

DC, who had extensive bilateral temporal lobe damage due to HSV encephalitis (**Figure 6.1C**), was grossly impaired in the sequential WM task. His WM precision was significantly lower than that of older healthy controls (Z-score; Z=-2.50, P=0.006). Remarkably, WM precision even for a single item was lower than the value predicted by chance (**Figure 6.4**). It is noteworthy that this patient performed at chance level in the WM task (**Figure 6.3**, blue

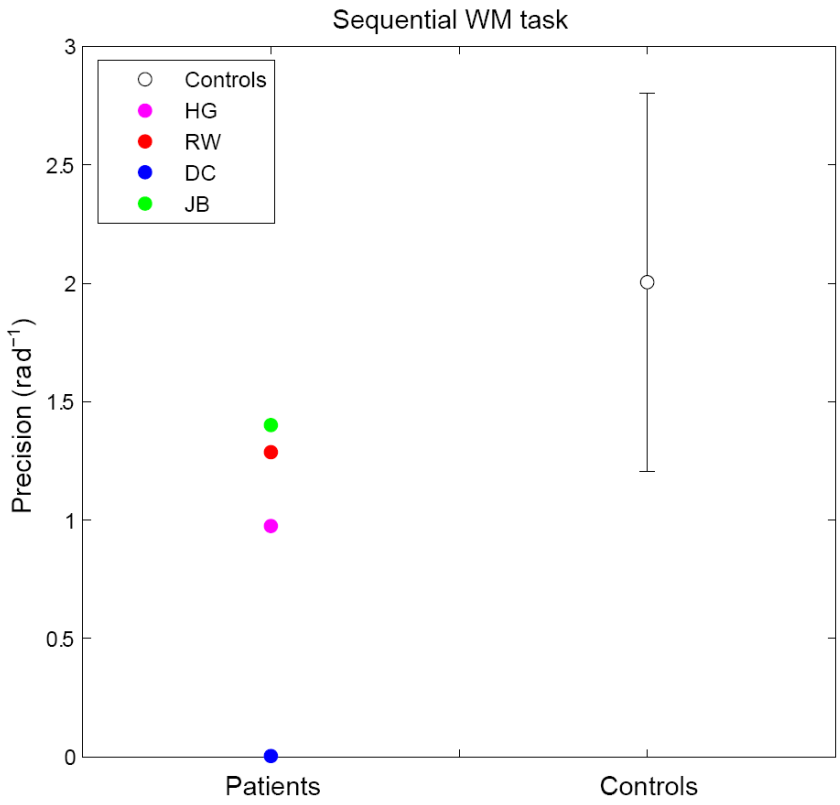


Figure 6.3: Overall WM precision of MTL patients and healthy controls on the sequential WM task for one to three items.

In HG and RW, the two patients with focal hippocampal lesions secondary to VGKC-associated encephalitis, average WM for one to three sequentially presented items was lower than in controls, but this comparison was not statistically significant. Performance of patient DC, who had extensive bilateral temporal damage due to HSV encephalitis, was at chance level. Average WM precision of patient JB, a patient with an extensive right temporal lesion, was not significantly different to controls. Error bars represent SD in control group.

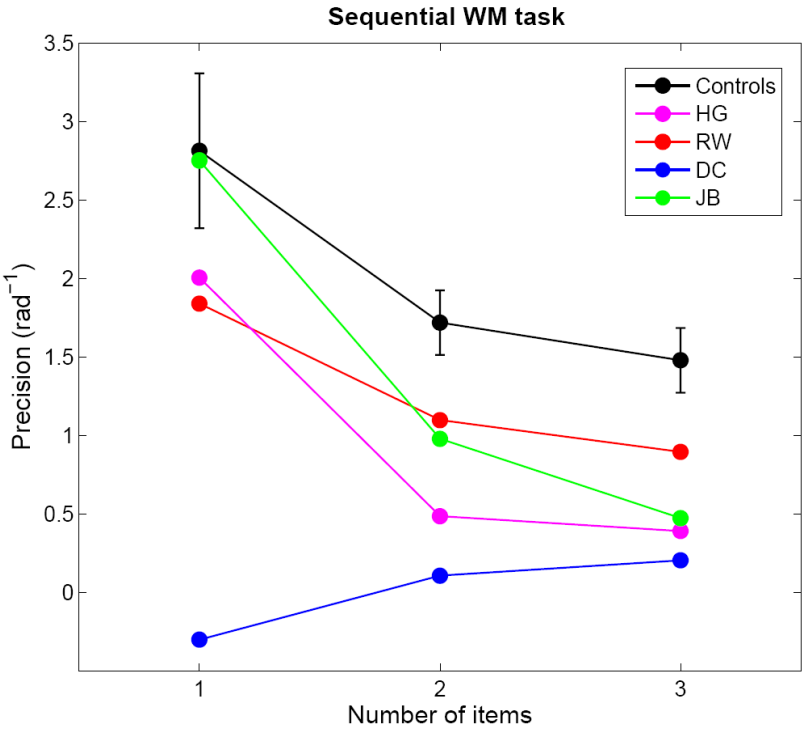


Figure 6.4: WM precision of MTL patients and healthy controls for each sequence length.

In the two patients with highly focal hippocampal lesions due to encephalitis associated with VGKC (HG and RW), WM precision was preserved for a single item, but it was lower than in controls when recalling two or three items. Performance of patient DC, who had extensive bilateral temporal damage due to HSV encephalitis, is at chance, even for a single item. JB, a patient with extensive right temporal damage post HSV encephalitis, had similar WM precision to controls for one item, but WM resolution deteriorated when more items were added to the sequence.

point), despite the fact that he performed better than healthy controls in a similar control task which did not require WM (**Figure 6.2**). WM precision was lower than in healthy controls for all sequence lengths: (one item: Z=-2.1, *P*=0.018; two items: Z=-2.62, *P*=0.004; three items: Z=-2.06, *P*=0.019).

JB, a patient with an extensive lesion in the right temporal lobe following HSV encephalitis (**Figure 6.1D**), performed better than the other focal lesion patients in the sequential WM task. Her WM precision was not significantly lower than in healthy controls overall (Z-score; Z=-0.75, *P*=0. 23; **Figure 6.3**, green point). When examining each sequence length separately, as shown in **Figure 6.4**, this patient's WM precision was very similar to that of healthy controls when remembering a single item (Z=-0.04, *P*=0.48), but it deteriorated steeply when more items had to be memorised, and it was lower than in controls, albeit not significantly, for sequences containing two items (Z=-1.2, *P*=0.16) and lower than in controls, with borderline significance, for three item sequences (Z=-1.63, *P*=0.052; **Figure 6.4**, green points).

6.3.4 A model of potential sources of error

A probabilistic model (Bays et al., 2009) was applied to responses in the sequential WM task, assuming three potential sources of error in the subjects' memory estimates: (1) Gaussian variability of responses centred on the target orientation, (2) a certain probability (with the same Gaussian variability attached to it) of responding to one of the non-target orientations, due to associating erroneously the target colour with the orientation of a non-target item, and (3) a probability of responding randomly. Each of these parameters was computed for each subject and each number of items in the sequence, and they were compared between each patient and the control group.

The results of this analysis should be interpreted with caution, as maximum likelihood estimation of the model parameters was based on a small amount of noisy data in patients. Note that the results were rather variable: for example, in **Figure 6.5A**, the concentration parameter estimates in patients RW (in red)

and DC (in blue) do not reduce monotonically with increasing number of items as expected, and as noted in controls (in black). Z-scores of the concentration parameter for each patient are given on **Table 6.2**. The concentration parameter values are similar between each of the patients and controls (**Table 6.2**; **Figure 6.5A**), but the Z-scores are difficult to interpret as parameter estimates were rather noisy.

Responses of patients HG (VGCK-associated encephalitis) and DC (HSV encephalitis) were less likely to cluster around the target orientation than those of controls (**Table 6.2**; **Figure 6.5B**, purple and blue datapoints, respectively). Patients RW (focal bitemporal lesions following VGCK-associated encephalitis) and JB (extensive right sided HSV encephalitis temporal lesion) had similar values in this parameter when compared to controls (RW: **Table 6.2**; **Figure 6.5B**, red and green datapoints, respectively). However, in the case of patient RW, note that although the probability of target responses for two items was very high (**Figure 6.5B**, second red datapoint), the corresponding concentration parameter estimate was low (**Figure 6.5A**, second red datapoint), suggesting that the target responses probability value might be unreliable in this case.

The probability of responding using a non-target orientation was generally higher in patients HG, RW and DC than in controls, but this was significant only in the case of RW for three-item sequences (**Table 6.2**; **Figure 6.5C**). In patient JB, the probability of non-target responses in three-item sequences was lower than in controls (**Table 6.2**), but note that the corresponding concentration parameter is also low (**Figure 6.5A**, in green), which makes the non-target parameter value difficult to interpret.

Finally, the probability of responding at a random orientation (**Figure 6.5A**), was higher in patients HG and DC when compared to controls, as well as in RW for one-item only, while in patient JB this parameter was similar to controls (**Table 6.2**).

In summary, the results of this model analysis are noisy and should be interpreted with caution. Random responses, due to simple guessing seem to

		Model Parameter Z-scores			
Patient	**Number of items**	**Concentration (κ)**	**Target responses (PT)**	**Non-target responses (PNT)**	**Uniform responses (PU)**
HG	1	0.48	-1.10		1.10
	2	1.16	**-4.34****	0.53	**7.88****
	3	-0.24	**-3.54****	0.77	**3.72****
RW	1	0.25	**-1.89***		**1.89***
	2	-1.45	0.91	-0.85	-0.77
	3	0.98	-1.28	**2.17***	0.25
DC	1	0.32	**-6.18****		**6.18****
	2	**4.88****	**-4.37****	0.54	**7.93****
	3	-0.86	**-3.39****	1.61	**3.05***
JB	1	-0.81	0.41		-0.41
	2	-1.44	0.78	-0.62	-0.80
	3	-1.54	1.00	-1.26	-0.45

Table 6.2: Z-scores of model parameter estimates for each patient in comparison to controls.

Each patient's individual results are expressed in units of standard deviation of the control group. Significant results in bold and marked by asterisks. *P<0.05; **P<0.001.

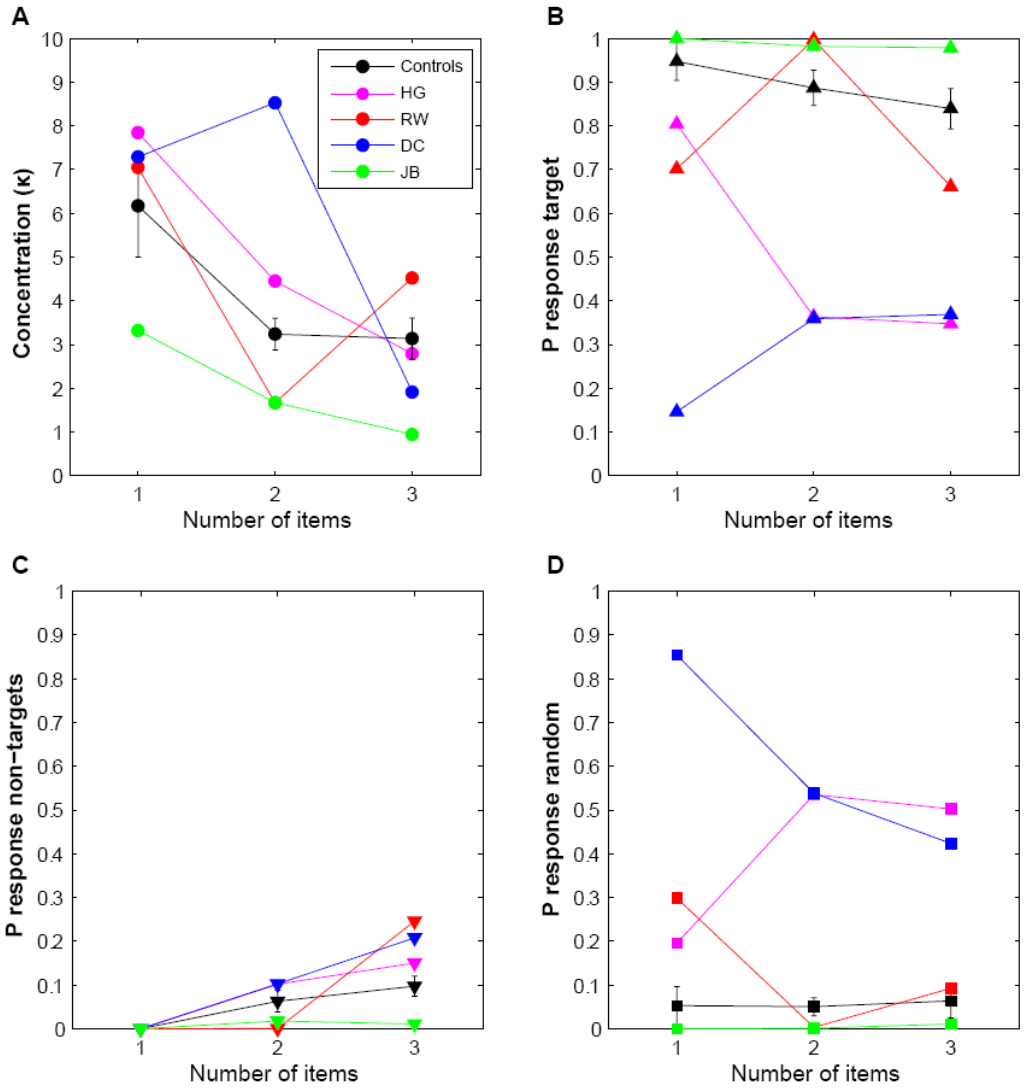


Figure 6.5: A probabilistic model accounting for loss in WM precision in each patient and in healthy controls.

Model parameter values are compared between healthy controls (in black), a patient with focal MTL damage secondary to VGCK-associated encephalitis (HG, in purple), a patient with focal bitemporal lesions due to the same condition (RW, in red) a patient with extensive bilateral temporal damage following HSV encephalitis (DC, in blue), and a patient with a large right-sided temporal damage due to HSV. **(A)** Concentration parameter describing the width of distribution (variability) of non-random responses. **(B)** Probability of responses centred on the target orientation. **(C)** Probability of responses centred on the orientation of a non-target. **(D)** Probability of random responses.

explain a large proportion of errors at least in patients HG and DC. With this in mind, it is interesting to note that in the case of patients with predominantly left sided (HG) or bilateral (DC, RW) temporal lesions, there was a suggestion that misbinding of the target colour with the orientation of a non-target item might have contributed to loss of precision, at least in three-item sequences, albeit these results were not significant. Remarkably, however, there was no suggestion of such illusory conjunctions in a patient with an extensive right temporal lesion, according to the analysis presented here. Some of the limitations of this approach as used here are further explained in this Chapter's Discussion.

6.3.5 Nearest neighbour analysis

Errors due to misreporting the orientation of a non-target item, instead of that of a target, were examined more directly in HG and RW, the two patients with VGCK-antibody associated encephalitis, using the 'nearest neighbour' procedure introduced by Pertzov et al., (2013). In this analysis, when the reported orientation was distant from the target orientation and closer to that of a non-target item, that item was treated as if it was the target. This analysis aimed to find whether by doing so it was possible to minimise or eliminate error when non-target responses were accounted for. Indeed, controlling for non-target responses in this way greatly diminished the patients' impairment when two items were present (HG vs. controls: $Z=0.7$, $P=0.76$; RW vs. controls: $Z=0.3$, $P=0.62$), and it completely eliminated the deficit in three-item sequences (HG vs. controls: $Z=0.28$, $P=0.61$; RW vs. controls: $Z=0.7$, $P=0.76$). Therefore, non-target responses in patients HG and RW accounted for a significant proportion of error.

6.3.6 Predictive cueing in MTL lesion patients

Patients HG and RW were also tested in a version of the sequential WM task in which one of the items was cued predictively, by being probed more frequently

than other items in the sequence. WM precision for the cued item was compared to that for the other, less task-relevant ('uncued') objects.

In controls, the cued item was remembered with significantly higher precision than the uncued items (paired *t*-test: $t_{(8)}$=3.2, *P*=0.012; Figure 6.5). Similarly, for patient HG, WM precision for the cued object (1.61) was almost double that of the other items (0.86). HG's WM precision was not significantly lower than in controls for either the cued (Z=-1.31, *P*=0.095), or uncued items (Z=-0.63, *P*=0.26; **Figure 6.5**).

The effect of predictive cueing on WM precision was even more marked in patient RW, representing a more than fivefold increase in WM precision for the cued item. Accordingly, WM precision in this patient was significantly lower than that of controls for the uncued items (Z=-1.24, *P*=0.011), but not for the cued item (Z=-1.46, *P*=0.072; **Figure 6.5**).

In conclusion, the effect of predictive cueing was preserved in both patients with focal hippocampal lesions due to VGKC-associated encephalitis.

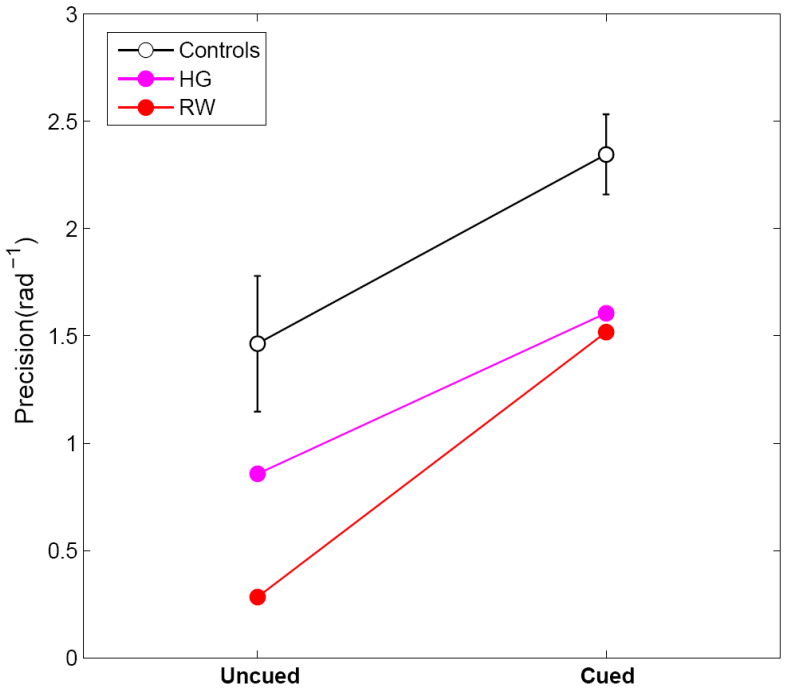


Figure 6.5: Effect of predictive cueing on WM precision in MTL patients and healthy controls.

WM precision is enhanced for the cued items when compared to the remaining, uncued ones, in both patients with focal hippocampal lesions, and in healthy controls.

6.4 Discussion

In this Chapter, WM precision was studied in two patients with focal MTL lesions due to VGCK-associated encephalitis (HG and RW), in two patients with more extensive temporal lobe damage following HSV encephalitis (DC and JB) and in a group of healthy control subjects. WM precision in this group was examined using a modified version of the sequential WM task introduced in Chapter 2. One, two or three coloured bars were presented in sequence at the same location, and subjects were asked to reproduce the orientation of one of these items from memory using a dial (Gorgoraptis et al., 2011). WM precision for sequences containing two or more items was lower in patients (albeit not significantly so in RW and JB), despite intact performance on a control task which did not require memory. This is in keeping with significant WM impairment secondary to MTL damage, even for only two items, well below what is thought of by some authors as the WM capacity limit of three or four items (Zhang and Luck, 2008).

In previous studies examining the role of MTL in WM, memory of the tested object's location was required to perform the task correctly (Ranganath and Blumenfeld, 2005; Cashdollar et al., 2011). Given the well-recognised role of the MTL, and particularly of the hippocampus, in spatial processing and orientation (Burgess et al., 2002; O'Keefe, 2004; Hartley et al., 2007; Bird and Burgess, 2008), it could be hypothesised that the WM deficit following lesions in the MTL might be selective to memory for object location in space. In the current study, all items were presented at the same location, in sequence, therefore remembering where they were situated was not necessary in order to carry out the task. Hence, as demonstrated here, the WM deficit in MTL lesion patients is not necessarily confined to memory for location, but it also relates to WM for non-spatial features.

Is there a cognitive process within WM for which the MTL is essential? One possibility is that the MTL operates as an integrator of information (Marr,

1971), associating, or binding together, different visual features, such as colour, shape and location, to create and maintain a complete visual object within WM (Wheeler and Treisman, 2002). Similar views also pertain to the concept of relational memory (Eichenbaum, 2006; Konkel and Cohen, 2009). The task used in the current Chapter required not only precise WM of each object's orientation but also accurate association of that orientation with the correct item's colour. Therefore, there are at least two potential sources of error: loss of WM precision might have been due to inaccuracy in remembering the correct orientation value, or due to erroneous association of the accurate target item's orientation with one of the other (non-target) items' colour.

Importantly, despite considerable impairment in VWM precision, patients' performance was intact on standard measures of WM – digit span and Corsi spatial span. One possible explanation is that the sequential precision task might be more sensitive than these standard WM tests. Alternatively, this discrepancy might reflect different task requirements: in particular, the sequential precision task used here requires subjects to remember associations between colour and orientation. However, intact memory for associations is not necessary for either digit span or Corsi task. Therefore, the discrepancy between the results from standard WM tests and the VWM precision task could be in keeping with a role of the MTL in visual feature binding.

WM precision of DC, the patient with extensive bilateral lesions secondary to HSV encephalitis, was at chance even for a single item. Therefore, in this patient, loss of WM precision cannot be attributed to misbinding between features of different objects, as WM resolution was severely impaired even when only one item had to be remembered. It is difficult to interpret the results from this patient in relation to the role of the MTL, as damage due to HSV in his case extended well beyond that area, to affect the right temporal lobe almost in its entirety, a large portion of the contralateral temporal lobe, and even parts of the right inferior frontal and parietal lobes. Although similar HSV encephalitis patients have been studied extensively in the past in an effort to understand the role of the MTL in memory (Squire and Alvarez, 1995; Olson et al., 2006a; Ezzyat and Olson, 2008; Jeneson et al., 2010), the case of

DC illustrates the limitations in the use of widespread brain lesions to model more confined brain areas.

In contrast, WM precision for a single item was preserved in the remaining three patients: both HG and RW, who had highly focal hippocampal lesions due to VGCK-associated encephalitis, and JB, who had an extensive, predominantly right-sided temporal lesion following HSV encephalitis, were able to recall one item with similar resolution to that of healthy controls. However, it should be noted here that patients RW and JB were both younger (63 and 59 years old, respectively) compared to controls (69±6.1 years), and given the well known effect of age on WM (Salthouse and Babcock, 1991), this age difference may have contributed to the lack of a statistically significant difference in WM precision for one item between patients and controls.

Could incorrect association of visual features account for the loss in WM precision when these patients had to remember two or three items? To address this question, I used a generative model which considers the distribution of responses taking into account variability in subject's responses to the target orientation, a certain probability of responding using the orientation of a non-target, and random error (Bays et al., 2009). For three-item sequences, the results from this analysis suggested that patient RW showed a higher probability of responding using a non-target orientation when compared to controls. Although this result would be in keeping with the hypothesised role of the MTL in feature binding in WM, it should be noted that the random (uniform) component of the model was much more significantly higher in patients HG and RW when compared to controls, and the probability of non-target responses was not significantly higher in patients HG, DC and JB than in controls. It is also important to emphasize that, while this model has performed consistently when applied on a considerably larger datasets (Bays et al., 2009; Gorgoraptis et al., 2011), results should be treated with caution when based on a limited amount of noisy data, as is the case here. The local maxima problem is one example of the computational limitations when maximum likelihood estimation is used to evaluate multiple parameters from limited data (Myung, 2003).

A recent study, employing the same sequential WM task used here, introduced an alternative, more direct analysis to examine the contribution of non-target responses (Pertzov et al., 2013). On each trial, when the reported orientation was distant from the target orientation and closer to that of another item from the display, the most similar item was treated as if it were the target item (Pertzov et al., 2013). When applied to the data from the two VGCK-associated encephalitis studied here, this 'nearest neighbour' analysis showed that a large proportion of the patients' responses could be attributed to misbinding, and that this type of error accounted for a large part of the difference in WM resolution when compared with controls. This 'nearest neighbour' analysis does not require a large amount of data to produce meaningful results, and in the context of a small amount of noisy data, as in these limited patient studies, it might be more appropriate than the three-component model which was also used here. Therefore, the 'nearest neighbour' analysis provided more convincing evidence on the crucial role of MTL in binding together different visual features to form objects within WM.

The recent study by Pertzov et al., (2013) on a considerably larger group of seven VGCK-associated encephalitis patients, including the two presented in this Chapter, provided a more definitive answer on the role of MTL in WM binding. In addition to the sequential task presented here, the authors used a new task, where one to three unique fractal shapes were displayed simultaneously, at different locations on a screen. Participants were then presented with a two alternative forced choice of one of the fractal shapes and a foil, and were asked to place the correct item on its original location by memory. There was no difference in WM precision for one item between the group of seven patients and controls, but patients' WM resolution was significantly lower than in controls for two or three items. The number of target items placed at, or very near, the location of a non-target item was significantly higher in patients than in controls, in keeping with failure of effective binding between location and object identity within WM in this group of patients with focal MTL damage (Pertzov et al., 2013).

These results converge with an independent line of research regarding MTL dysfunction. A recent study found that pre-symptomatic individuals at risk of developing familial Alzheimer's disease had intact performance when required to maintain isolated features in WM, however they were impaired when the task required retaining bound features over brief periods of time (Parra et al., 2010). Indeed, the MTL is one of the first structures to be affected in this disease, with hippocampal volume loss occurring as early as in the pre-symptomatic stage (Fox et al., 1996; Jack et al., 1999; Chan et al., 2001, 2003).

The role of the MTL in binding together discrete elements in memory is congruent with the relational theory of memory (Eichenbaum, 2006; Konkel and Cohen, 2009). This hypothesis, originally postulated in relation to LTM, considers the hippocampus as the neural structure responsible for maintaining links relating together separate aspects of memory. The results presented here take this concept further, suggesting that the MTL is not exclusively involved in object-location binding (Olson et al., 2006b; Van Asselen et al., 2009) or in forming associations between different objects (Piekema et al., 2010) but it also contributes to a wider range of associative processes such as binding of non-spatial features within an object.

In keeping with this broad involvement of the MTL in associative processes, a previous study demonstrated that visual search in amnesic patients with hippocampal lesions did not benefit from implicit contextual cueing (Chun and Phelps, 1999). In Chapter 3, I argued that directing attention to an item through predictive cueing enhances its WM precision in part through strengthening binding between its visual features. In the current Chapter, I examined the effect of predictive cueing in the two VGCK-associated encephalitis patients, HG and RW. The positive effect of cueing on WM precision was present in both patients, suggesting that this particular form of cueing enhances attention and WM independently of the MTL.

The results from focal lesion patients presented in the current Chapter support the view that MTL is necessary for WM, and demonstrate for the first time that this area might be involved in non-spatial WM. Taken together with more

recent evidence from a larger group of VGCK-associated encephalitis patients, these results reinforce and expand the importance of the MTL for a wide range of associative processes, including visual feature binding in WM.

Chapter 7

General Discussion

In this thesis, I investigated visual working memory (VWM) and its attentional control in health, and examined how these processes were affected by focal brain lesions and modulated by a dopamine agonist in selected patient populations. In the current chapter, I discuss how these studies contributed to previous work on the field, I consider some of the limitations of my work and I propose future research directions.

7.1 Visual working memory updating across time

A new approach to measuring VWM recently prompted reconsideration of the cognitive properties of memory for visual objects across brief intervals (Wilken and Ma, 2004; Bays and Husain, 2008; Bays et al., 2009). Instead of regarding VWM as an all-or-none event, whereby an object is either stored perfectly in memory, or not remembered at all, these authors quantified *how precisely* we remember objects and their visual features. A long-standing thesis posits that VWM is limited by the number of objects it can hold - usually estimated to about four (Luck and Vogel, 1997; Cowan, 2001). Measuring VWM precision led to a radically different conclusion: rather than supporting an item-limit in VWM, results from these studies were more in keeping with a limited VWM resource, allocated flexibly between objects according to attentional priority (Bays and Husain, 2008).

However, the way this memory resource is updated *across time*, for example when different objects are viewed in sequence, had not been studied previously using WM precision. This is an important and ecologically relevant question: in a highly dynamic, perpetually changing visual world, information is often presented to the visual system in sequence, through body and eye movements and alterations in the environment.

In Chapter 2, a new task was introduced which measured VWM precision for sequences of simple visual objects. In this task, a variable number of coloured bars, each with a different colour and orientation, were presented sequentially on each trial, and participants were asked to adjust the orientation of one of these items from memory. Examining WM precision as a function of order in the sequence, I found a significant recency effect, with the last object being remembered more precisely than previous items (**Figure 2.2**).

Similar serial order effects, including one-item recency and no primacy, have been previously observed in VWM (Phillips and Christie, 1977). However, the magnitude of recency and primacy effects have been shown previously to depend both on temporal properties of the task, including the retention interval (Wright et al., 1985), and on the mode of probing - for example testing by object identity produced different serial order effects than probing by serial order (Avons, 1998; Smyth et al., 2005). In future, it would be interesting to characterise serial order effects using a precision measure in different modes of testing, for example to compare probing by a visual feature (for example, probing by the items' colour, as in my task) versus testing memory based on serial order.

Examining VWM precision in sequences, I observed that as the total number of items in memory increased, the proportion of resources dedicated to each item declined, degrading the fidelity of storage (**Figure 2.3**). Crucially, WM resolution decreased smoothly as total number of items increased, and this loss of fidelity affected every item in the sequence (**Figure 2.2**); even adding a single item to a previous object held in memory was sufficient to produce a significant drop in mean precision. Furthermore, even for the least well-remembered

objects in sequences of six items, WM precision was better than chance (**Figure 2.2**). These results cannot be accounted for by a 'slot' model of WM, in which WM is quantised and limited to about four items (Pashler, 1988; Luck and Vogel, 1997; Cowan, 2001), but they could be explained adequately by a limited memory resource, a proportion of which is allocated to each item as the total number of items increases. This resource model of VWM was proposed previously for simultaneously-presented objects (Bays and Husain, 2008; Bays et al., 2009), and the results presented in Chapter 2 demonstrated for the first time that it can also explain parsimoniously WM for sequentially presented items.

Therefore, results from multiple tasks based on precision offer support to a resource model in WM across time and space. However, precision does not directly translate to the amount of memory resource allocated to an item. For example, adding memory precision values for multiple objects kept in memory at any one time would not lead to an appropriate estimate of the total amount of information held in memory. Further theoretical work is needed in order to establish whether it is possible to obtain such an additive measure of memory resource through appropriate mathematical transformations based on memory precision. Concepts from information theory, such as mutual information (Shannon and Weaver, 1948), might prove useful in moving from measures of memory resolution, to estimates of the amount of information available in memory.

In the serial task introduced in Chapter 2, with each additional item in the sequence, VWM resources already allocated to previous objects had to be redistributed to accommodate both new and previous items. A critical question was how this redistribution affected precision in the sequence, both on average and for each serial position. Direct comparison between the same number of items presented simultaneously or sequentially showed that items were recalled with significantly lower precision when presented sequentially, in keeping with previous studies (Lecerf and De Ribaupierre, 2005; Allen et al., 2006b; Blalock and Clegg, 2010). Critically, however, I found that the last item in the sequence was remembered with similar precision to an object in an array

of the same number of simultaneously presented items (**Figure 2.3**). Thus, while memory precision for the last item was simply determined by the total number of objects, just as in simultaneous presentation, this was not the case for previous items, precision for which was also limited by some additional source of error, which I sought to determine.

When items were presented sequentially at different locations, precision was again lower for earlier items and memory resolution for the last item was similar to that for an item in an array of the same number of objects (**Figure 2.8**), suggesting that spatial overwriting was not responsible for loss of precision in sequential presentation. The possibility that temporal decay might have accounted for these results was also excluded (**Figure 2.4**).

Therefore what might have resulted to loss of precision for earlier items above and beyond their 'fair share' of memory resource? To answer this question, I applied a probabilistic model (**Figure 2.5**) to the distribution of recall errors that was previously developed for simultaneous presentation (Bays et al., 2009, 2011b), and took into account a certain probability of responding with the remembered orientation of a *non-target*, due to associating incorrectly visual features of different objects, as one of the potential sources of error. This analysis revealed that errors due to misbinding between the colour of a target item and the orientation of a non-target were significantly higher for sequences than in simultaneous presentation (**Figure 2.6C**). Furthermore, these errors were more common for objects earlier in the sequence than for the last item (**Figure 2.7C**), even when the locations of misbound objects did not overlap (**Figure 2.9C**). These binding failures for earlier items in the sequence were in keeping with previous results (Allen et al., 2006b), and with the general concept that attention is necessary for successful feature integration (Treisman and Gelade, 1980). Additionally, my results demonstrated that both spatial and non-spatial attention were required for successful feature binding.

The occurrence of misbinding errors in the data presented in Chapter 2 was remarkably high; for example, for the middle item in 5-item sequences, subjects responded with a non-target orientation in as much as 50% of the cases. The

simple stimuli –coloured bars– used in these experiments were characterised by a high degree of visual similarity, and it seems plausible that this might have led to such a high frequency of misbinding. One could hypothesise that misbinding might occur less commonly with real-world objects, which are often much more complex. It would be interesting to test this hypothesis empirically, for example by examining misbinding while varying item similarity parametrically, or by comparing between simple, abstract items such as those used here and more realistic, complex objects.

Chapter 2 focused on WM for static orientation; interestingly, a subsequent study testing orientation for moving patterns has shown very similar results (Zokaei et al., 2011). Future work should investigate whether these results extend to other visual dimensions. Additionally, it would be interesting to test WM precision for multiple visual dimensions in a single sequential task, as Bays et al. (2011b) did for simultaneously presented items. By examining whether errors between feature dimensions are correlated, this approach could further clarify the issue of feature binding in sequences.

7.2 Effects of goal-directed attention

As we saw in Chapter 1 (section 1.4), the contents of VWM are controlled by processes commonly associated with goal-directed attention (Rock and Gutman, 1981; Smyth and Scholey, 1994; Smyth, 1996; Awh et al., 1998, 2006; Awh and Jonides, 2001; Zanto and Gazzaley, 2009; Rutman et al., 2010). Note that the term attention is used here rather loosely, to include a multitude of potentially dissociable processes which lead to prioritisation of specific visual information. These processes can be highly dynamic – goal-directed modulation of VWM takes place even in retrospect, after encoding is completed (Griffin and Nobre, 2003; Lepsien and Nobre, 2007; Makovski and Jiang, 2007; Makovski et al., 2008; Astle et al., 2009, 2012; Sligte et al., 2010; Lepsien et al., 2011; Pertzov et al., 2012a). However, the role of goal-directed control in determining VWM

precision across time, for sequentially presented items, had not been studied before.

In Chapter 3, I examined how memory precision was affected by the relative behavioural relevance of each of the objects in a sequence. Task-relevance of items presented in sequence was manipulated by modulating how frequently each of them was probed. In a first experiment, this difference in task-relevance was relative, meaning that non-cued items were still tested, albeit in a smaller proportion of the trials. VWM precision for cued and non-cued items was compared with a baseline neutral condition, where all items were equally task-relevant. I found that cueing enhanced WM precision significantly for more task-relevant objects, but with a corresponding reduction in memory resolution for the remaining items (**Figure 3.1A**). Critically, both the beneficial effect of cueing on memory for the task relevant item, and the detrimental effect on other items were present at all serial orders throughout the sequence (**Figure 3.1B**). These results could be well accounted for by a flexible memory resource, which can be dynamically redistributed according to an item's behavioural priority, not only in space (Bays and Husain, 2008), but also across time.

To examine the cognitive mechanisms underlying the allocation and redistribution of VWM resources according to task-relevance, I applied to the distribution of responses for each condition the same probabilistic model which was used in the previous chapter (**Figure 2.5;** Bays and Husain, 2008; Bays et al., 2009). This analysis revealed that a significant proportion of the gain in precision for the cued items could be explained by a reduction of erroneous responses to non-targets, suggesting that feature binding was more effective for more task-relevant –and therefore better attended– items (**Figure 3.2**). Conversely, for the remaining items in the sequence, which were less task-relevant, reduced VWM precision could not be explained by non-target responses, but by an increase in random responses (**Figure 3.2**), possibly suggesting incomplete encoding of these items.

Therefore, goal-directed processes appeared to have affected VWM for sequentially presented items by two distinct mechanisms: enhancement of feature integration for better attended objects, and incomplete encoding of individual features of 'uncued' items, which received less attention. This behavioural dissociation is in keeping EEG and fMRI results suggesting that enhancement of task-relevant information and suppression of distracting, irrelevant stimuli are dissociable also neurally (Gazzaley et al., 2005a, 2005b, 2008).

The improvement in binding within VWM for sequentially presented items which receive enhanced goal directed attention, as demonstrated here, is in keeping with the general framework proposed by Wheeler and Treisman (2002), according to which feature integration requires attention. Also in agreement with this framework, previous studies have shown selective impairment of feature binding in WM when attention was engaged elsewhere (Elsley and Parmentier, 2009; Fougnie and Marois, 2009; Brown and Brockmole, 2010). In contrast, other authors have found that exogenous spatial cueing did not impair maintenance of feature binding (Gajewski and Brockmole, 2006). A further study found that attentional distraction did not influence memory for colour-shape conjunctions more than for individual features, as long as the items were simultaneously presented, but binding was selectively impaired in a task using sequential presentation (Allen et al., 2006b). This might suggest that the results from previous studies examining attentional effects on VWM in simultaneous presentation cannot be necessarily extrapolated to sequences, therefore further work is needed to characterise the role of attentional modulation of memory across time.

It is important to note that the majority of the above studies have examined the effects of stimulus-driven, rather than goal-directed, attention, or have used concurrent tasks directing attentional resources away from the memory task. In contrast, the studies presented in Chapter 3 of this thesis examine goal-directed filtering in WM. As the effects of these different modes of attention on VWM might be dissociable, in future work, it would be interesting to investigate the individual contributions of top-down and bottom-up attention

on VWM precision and feature integration within VWM in sequential and simultaneous presentation. For example, by varying both task-relevance and visual salience, future studies could examine the effects of each mode of attention on VWM precision for individual features and their conjunctions.

An interesting further question was addressed in Chapter 3: is the ability to allocate memory resources flexibly across time according to task-relevance unlimited? If this was the case, one would expect memory precision for a task-relevant object to be unaffected by the presence of task-irrelevant items in a sequence. I attempted to answer this question in a second experiment presented in Chapter 3. In this task, an item of a given colour was tested on all trials, with 100% validity. Therefore, all other items in the sequence were never probed, and were entirely task-irrelevant. WM precision was measured in the presence of such distracting items presented in sequence, and compared with a condition where a single (task-relevant) item was shown, and also with a baseline condition where all items were equally task-relevant.

I found that although the presence of task-irrelevant items in the sequence did not impair VWM precision overall (**Figure 3.3B**), the first item in the sequence was remembered less precisely when followed by three subsequent distractors, when compared to an item followed by a matched blank delay (**Figure 3.3B**). Therefore, subjects were capable of filtering out previous items, or one and two subsequent distractors, but this filtering ability was limited: three subsequent task-irrelevant items were sufficient to decrease memory resolution for a task-relevant object.

Previous studies have used neural markers of individuals' attentional ability to filter out irrelevant stimuli, and examined the relationship of such measures with VWM capacity. Using contralateral delay activity, an EEG measure of top-down attentional filtering, Vogel et al. (2005) found that high WM capacity individuals are much more efficient at selecting and maintaining only the task-relevant items in VWM. In contrast, low capacity individuals unselectively encoded and maintained information about both relevant and irrelevant items (Vogel et al., 2005).

In Chapter 3, I used a behavioural index of filtering ability (Paragraph 3.3.2). This filtering index measured how WM precision for each individual was affected by the presence of distracting, task-irrelevant items as opposed to a condition where distractors were absent. I did not find a significant correlation between this filtering index and VWM precision, but this topic warrants further investigation. Specifically, it would be useful to examine in future whether individual differences in established measures of top-down attentional filtering, such as contralateral delay activity on EEG, correlate with the behavioural index of filtering ability introduced here.

7.3 Insights from visual neglect

Chapters 2 and 3 examined VWM precision across time and its modulation by goal-directed attention in healthy subjects. Moving a step further, Chapter 4 investigated how these processes may be affected by visual neglect (Heilman and Valenstein, 1979; Mesulam, 1981, 1999; Stone and Greenwood, 1991; Driver and Mattingley, 1998; Parton et al., 2004) in a group of patients with focal lesions in the right cerebral hemisphere. Attentional deficits, including impairment in goal-directed attention, as well as complex deficits in VWM in neglect patients, including impairments in transaccadic memory, spatial memory and non-lateralised spatial memory, have been recognised as important components of visual neglect (Heilman and Watson, 2001; Husain and Rorden, 2003; Buxbaum et al., 2004; Corbetta and Shulman, 2011).

However, it was not clear previously whether *non-spatial* VWM might also contribute to the syndrome. Using a change detection paradigm, one study found that VWM for spatial information, but not for object identity, was impaired in patients with right posterior parietal damage and neglect (Pisella et al., 2004). Nevertheless, it is possible that a continuous measure of VWM such as precision might be more sensitive in detecting non-spatial deficits than a change detection task which measures WM in binary fashion (for a review of the divergent results produced by these techniques, see Paragraph 1.2).

Furthermore, previous studies demonstrated impairments in the temporal dynamics of attention in neglect patients, such as a protracted attentional blink (Husain et al., 1997) and deficits in sustained attention (Hjaltason et al., 1996; Robertson et al., 1997). However, VWM updating across time, and its goal-directed attentional modulation had not been studied before in this patient population.

To examine these critical questions, in Chapter 4, I used modified versions of the sequential tasks introduced in Chapters 2 and 3. I examined memory precision for 1 to 3 sequentially presented items in a group of patients with visual neglect following right hemisphere stroke, and compared their performance with that of right-hemisphere stroke patients without clinically detectable neglect, and with age matched healthy volunteers. VWM precision for the tested feature, orientation, was profoundly impaired in neglect patients, even for a single item, when compared to healthy controls or stroke patients without clinically identifiable neglect. Stroke patients without neglect also performed significantly worse than healthy age-matched controls; however this impairment was mild, in contrast to the striking, profound WM deficit affecting the neglect group (**Figure 4.2**).

These results could not be explained by pure motor or perceptual impairments, as patients performed well in a task controlling for these components of the sequential task (**Figure 4.1**). Both in the WM and in the control task, patients responded by rotating a probe on the screen using a dial,in the first case from memory, and in the second comparing with a visual target which was always present on the screen. However, it is interesting to note that neglect patients were profoundly impaired in the WM task even for a single item (**Figure 4.2**) when they did not have constant visual feedback on the target orientation. Therefore, impairment in the sequential task for one item, albeit not purely perceptual, might be a result of constructional and / or representational deficits which are accentuated when constant visual feedback on the target orientation is absent. This hypothesis would be in keeping with known deficits in mental rotation, mental imagery and constructional ability in patients with right parietal lesions and neglect (Gainotti et al., 1977; Ratcliff, 1979; Hier et al.,

1983). Comparing between active rotation using a dial –which has a constructional and mental rotation element– as in the task presented in Chapter 4, with a two-alternative forced choice task, in which the constructional element would be removed, might elucidate this issue further.

In Paragraph 4.4.3 I described an interesting perseverative behaviour of a proportion of neglect patients when using the response dial. These patients tended to rotate the probe multiple times before deciding on a response. This was observed qualitatively but unfortunately not studied quantitatively. A further insight on the nature of the profound WM deficit of neglect patients on the sequential WM task might be provided by studying this more systematically. This might lead to interesting insights into the relationship of constructional abilities with mental representation within WM and how a breakdown in the interaction of these cognitive areas might lead to behavioural deficits in neglect patients.

Another possibility is that the sequential WM task results might be explained in part by impairment in temporal dynamics of attention. Indeed, a protracted attentional blink (AB) has been demonstrated in neglect, whereby the physiological impairment in the ability to detect a second stimulus following an attended target, normally for 180-270ms (Raymond et al., 1992), is prolonged up to 1200ms in neglect patients (Husain et al., 1997). However, the timescale of stimulus presentation in the task used in Chapter 4 was considerably slower than even the remarkably protracted AB noted in neglect patients, allowing 2000ms for visual processing of each target. Therefore, these results are in keeping with a profound deficit of non-spatial WM in neglect, although it is not impossible that a protracted AB might have contributed to impaired performance.

In a further task, voluntary attention was manipulated by predictive cueing, in a similar way to Experiment 1 in Chapter 3. While WM precision for cued items of any order in the sequence improved in stroke patients without neglect, in a similar way to healthy controls, remarkably, VWM in neglect patients did not improve with predictive cueing (**Figure 4.5**). This impairment in

reallocating attentional resources voluntarily across time in neglect is also in keeping with previously recognised deficits in detection of behaviourally relevant stimuli, which need not be lateralised, in neglect (Husain et al., 1997; Samuelsson et al., 1998; Robertson, 2001; Husain and Rorden, 2003; Malhotra et al., 2009). However, the profound impairment for a single item in the WM task where no cueing was present (**Figure 4.2**) precludes interpretation of the absence of cueing effect in this group.

In a carefully designed study, Bays et al. (2010) tracked the eye movements of neglect patient in a visual search task, while systematically manipulating both task-relevance and visual salience of the presented stimuli. They demonstrated that both goal-directed and stimulus-driven attention contribute to target selection in a biased competition in which the priority of contralesional targets is undervalued. Furthermore, they were able to ameliorate this spatial bias in goal-directed search by modifying the spatial distribution of stimulus salience (Bays et al., 2010). An interesting further direction might consist in manipulating goal-directed and stimulus-driven attention in a similar way, but across time, rather than space, to examine how abnormal temporal dynamics of attention and WM in neglect patients might be affected by such manipulations.

Neglect is not a simple deficit – rather, it consists of a combination of spatially lateralised and non-lateralised component cognitive deficits (Husain and Rorden, 2003; Buxbaum et al., 2004; Verdon et al., 2010), and the extent of impairment in each of these cognitive components might not be the same in every patient. Lesion studies on some of the component deficits of neglect support the hypothesis that damage to different parts of a complex network produces different combinations of cognitive deficits (Husain et al., 2000; Committeri et al., 2007; Bays et al., 2010; Verdon et al., 2010). In Chapter 4, I presented the results a Voxel-based Lesion-Symptom Mapping (VLSM) study aiming to identify damaged brain areas associated with loss of WM precision or insensitivity to predictive cueing. This analysis was carried out in the entire group of patients with right hemisphere stroke, taking into account their performance in standard visual search tasks.

VWM precision was determined by lesions in the right inferior frontal gyrus and insula, as well as in subcortical structures, including the globus pallidus, putamen and caudate (**Figure 4.8**). The involvement of the inferior frontal gyrus in VWM is consistent with the results of several neuroimaging studies which showed evidence of VWM related activity in the inferior temporal cortex (Courtney et al., 1997; Sala et al., 2003; Rämä and Courtney, 2005), and particularly object-selective activity (Druzgal and D'Esposito, 2003; Ranganath et al., 2004a, 2004b). The involvement of the basal ganglia, and particularly of the globus pallidus, is also in keeping with neuroimaging results both in healthy subjects (McNab and Klingberg, 2007), and in focal lesion patients (Voytek and Knight, 2010). The relationship between neural activity in the basal ganglia and that in the prefrontal cortex in supporting WM processes merits further investigation. Examination of the functional and structural connectivity between these regions during WM tasks in healthy individuals and focal lesion patients using MRI analysis techniques such as dynamic causal modelling (DCM) and diffusion tensor imaging (DTI) might help in elucidating the interplay between these regions in WM processes.

Insensitivity to cueing was associated with lesions in a different set of regions, not overlapping with those associated with WM precision. Specifically, cueing was determined by lesions in the angular gyrus of the right inferior parietal lobule, an area in the right premotor cortex in proximity to the frontal eye field (FEF), and white matter areas, several of which may overlap with the superior longitudinal fasciculus (SLF) (**Figure 4.8**). The right inferior parietal lobule (IPL) is commonly lesioned in neglect (Vallar and Perani, 1986; Heilman and Watson, 2001; Mort et al., 2003), and it has been implicated in spatial perception, spatial attention and action (Corbetta and Shulman, 2002; Rizzolatti and Matelli, 2003; Husain and Nachev, 2007; Vandenberghe et al., 2012). The result that lesions in the angular gyrus cause insensitivity to predictive cueing is interesting, as previous fMRI studies have linked top-down attentional spatial selection to more posterior parietal areas, namely the intraparietal sulcus within the dorsal posterior parietal cortex, rather than to

the angular gyrus and IPL (Corbetta et al., 2000; Corbetta and Shulman, 2002).

Critically, however, the IPL is also active in a range of non-spatial tasks (Husain and Nachev, 2007), which, importantly, include non-spatial, sequential selective attention tasks (Coull and Frith, 1998; Wojciulik and Kanwisher, 1999; Marois et al., 2000). The IPL has been shown to be part of several fronto-parietal networks (Corbetta and Shulman, 2002; Husain and Nachev, 2007; Catani and Thiebaut de Schotten, 2008a). Furthermore, fMRI studies have suggested that this area is implicated in storage of locations and objects within WM (Todd and Marois, 2004, 2005; Xu and Chun, 2006; McNab and Klingberg, 2007), a result which is in keeping with recordings from the homologous region LIP in the monkey (Constantinidis and Steinmetz, 1996; Pesaran et al., 2002). The results from the lesion analysis presented in Chapter 4 suggest that the role of the IPL might extend beyond simple storage to goal-directed selection within WM. This aspect of the IPL merits further investigation. Larger studies in patients with highly focal lesions of the IPL, as well as carefully designed fMRI studies using tasks which can distinguish WM storage from goal-directed selection, might help in pursuing this question further.

7.4 Dopaminergic modulation of visual neglect

As mentioned in the previous section, neglect can be seen as a syndrome consisting of several component deficits (Heilman and Valenstein, 1979; Mesulam, 1999; Husain and Rorden, 2003; Hillis, 2006; Bartolomeo, 2007). Such cognitive components include impairments in VWM (Wojciulik et al., 2001; Pisella et al., 2004; Mannan et al., 2005; Ferber and Danckert, 2006; Parton et al., 2006; also see Chapter 4 in this thesis), selective and sustained attention (Posner et al., 1984; Robertson et al., 1997, 1998). The study presented in Chapter 5 tested the hypothesis that visual neglect could be ameliorated by targeted pharmacological modification of one or more of these component deficits.

The pivotal and multifaceted role of dopamine in WM processes has been outlined in Chapter 1 (Paragraph 1.6.2), including the discrete effects of D_1 versus D_2 receptor agonist activity (Sawaguchi et al., 1990; Schneider et al., 1994; Müller et al., 1998). In addition to its role in working memory, new findings suggest that frontal D_1 receptor activity can have long-range, modulatory effects on visual areas subserving attention (Noudoost and Moore, 2011). Furthermore, dopaminergic neuronal networks have a well-recognised role in alerting or allocating attention to unexpected sensory cues based on the behavioural relevance of the stimulus (Bromberg-Martin et al., 2010).

A compelling hypothesis based on these observations is that a dopamine agonist with high affinity to D_1 receptors might ameliorate neglect in stroke patients by modulating attention and/or working memory. Rotigotine was selected as a good candidate for such pharmacological modulation as it has high affinity for the D_1 receptor compared to many other licensed dopamine agonists (Jenner, 2005; Naidu and Chaudhuri, 2007). However it should be noted that rotigotine is not selective to the D_1 receptor, but it also has D_2 and D_3 receptor agonist actions (Belluzzi et al., 1994; Jenner, 2005; Naidu and Chaudhuri, 2007). Therefore, the effect of rotigotine studied in Chapter 5 may also have been mediated, at least in part, by D_2 and/or D_3 agonist activity. In future studies it would be interesting to examine the effects of a highly selective D_1 receptor agonist in neglect, and compare those with the effects of D_2/D_3 agonists.

In Chapter 5 I presented a double-blind, randomised, placebo controlled trial of the dopamine agonist rotigotine in 16 patients with hemispatial neglect and unilateral weakness following right hemisphere stroke. A replicated ABA N-of-1 randomised design was used. Each patient's performance was measured in three phases, each consisting of several assessment sessions: before treatment (**phase A1**), while receiving transdermal rotigotine (**phase B**) and after discontinuation of the drug (**phase A2**). Crucially, the exact duration of each phase was randomised across patients. Performance on rotigotine was compared with the pre-treatment baseline and post-treatment follow-up phases. Crucially, this design allows robust evaluation of the effectiveness of an

intervention in small sample sizes, theoretically even in single subjects (Edgington and Onghena, 2007).

The choice of this design was based on two main considerations. First, as discussed in Paragraph 1.6.2, the effects of dopaminergic drugs on cognition, including WM, are highly variable between individuals, depending on their baseline performance (Kimberg et al., 1997, 2001; Mattay et al., 2000; Kimberg and D'Esposito, 2003; Gibbs and D'Esposito, 2005). Therefore, a design giving the possibility to examine drug effects in small subgroups or even in individual patients was more appropriate than a more commonly used clinical trial design with separate placebo and drug groups, as the latter would only demonstrate group effects, potentially concealing beneficial effects in some subjects and negative effects in others. Second, N-of-1 randomised designs provide more statistical power in small sample sizes (Edgington and Onghena, 2007), such as the group of 16 patients available in this study.

Treatment with rotigotine was associated with significant improvement in visual search, as quantified by the Mesulam shape cancellation task in the group of all 16 patients (**Figure 5.3**). The effect size was considerable, representing a 12.8% increase in the number of targets found on the left in the actual treatment allocation in comparison to all possible permutations of the data. This result compares favourably with the effects of most other neuromodulatory agents established in the clinical treatment of cognitive deficits, which overall are typically very modest (Husain and Mehta, 2011).

However, response to treatment was variable between individuals, with some patients demonstrating considerable improvement on visual search on rotigotine, and others showing little or no benefit (**Figure 5.6c**). Importantly, this variability did not appear to depend on baseline visual search performance (**Figure 5.6c**), perhaps contrary to what might be expected based on previous studies (Kimberg et al., 1997, 2001; Mattay et al., 2000; Kimberg and D'Esposito, 2003; Gibbs and D'Esposito, 2005). Furthermore, subgroup analysis suggested that response to the drug was not determined either by the relative preservation of the right prefrontal lobe, as beneficial effects on visual search

were noted both in the subgroup with minimal and in that with extensive prefrontal involvement (**Figure 5.6c**).

The role of damage in certain brain regions in determining response to rotigotine was explored further using non-parametric mapping lesion analysis. The superior prefrontal area indicated by this analysis (**Figure 5.7**) shows substantial overlap with the right Frontal Eye Field (FEF – Brodmann area 8), which has a well-known role in visual search and attentional shifting (Gitelman et al., 2002; Moore and Fallah, 2004). The more ventral and rostral temporal area identified is in close proximity to the parahippocampal gyrus, which has critical role in neglect (Mort et al., 2003). Finally, the white matter areas shown in **Figure 5.7** could be in keeping with parts of the superior longitudinal fasciculus (Catani and Thiebaut de Schotten, 2008b; Thiebaut de Schotten et al., 2008), which has been implicated in spatial awareness (Thiebaut de Schotten et al., 2005) and neglect (Bartolomeo et al., 2007; Urbanski et al., 2008). It is important to emphasise that this approach requires a considerably larger sample size to produce reliable results (Medina et al., 2010), and therefore the conclusions from it should be treated with caution.

Therefore, in the current study it has not been possible to identify a factor which might predict treatment response reliably. This remains an important question, as identifying such a predictor not only might help in understanding better the mechanism underlying the action of rotigotine in neglect, but it would also be clinically valuable, as it would aid patient selection, leading to targeted treatment of individuals that are expected to respond favourably. Potential directions for future research that might identify such predictors could include analysis of genetic factors that influence the metabolism of dopamine, such as polymorphisms in the Catechol-O-Methyltransferase (COMT) gene (Mattay et al., 2000; Apud et al., 2006; Roussos et al., 2009), and/or use of Positron Emission Tomography (PET) imaging to quantify dopamine synthesis at baseline (Cools et al., 2008).

Chapter 5 assessed the effectiveness of rotigotine in ameliorating spatial bias in neglect, but also examined possible cognitive mechanisms which might have

mediated this effect, including measures of spatial WM and selective attention. Rotigotine was not associated with improvement of spatial working memory, examined either indirectly, by measuring the number of revisits in the touchscreen cancellation task (Parton et al., 2006), or directly, with a vertical variant of the Corsi spatial memory task (Malhotra et al., 2005). Therefore, the hypothesis that rotigotine might improve performance on cancellation tasks by enhancing working memory for the location of previously cancelled targets, in keeping with the known role of D_1 dopamine receptor activity in spatial working memory (Funahashi and Kubota, 1994; Castner et al., 2000; Castner and Goldman-Rakic, 2004), was not substantiated. However, it is possible that these measures of WM were not as sensitive as precision measures which were introduced after the protocol for the rotigotine study was established. In further studies, it would be useful to examine dopaminergic modulation of WM using measures of precision, both in healthy individuals and in patients with neglect.

The effect rotigotine on goal-directed and stimulus-driven attention was measured in a dedicated task in which participants detected targets among of distractors randomly presented to the ipsilesional and contralesional visual fields, in sequence. Targets could be of low or high visual salience (**Figure 5.8**). Interestingly, responses to *less salient (*but equally *task-relevant)* targets relative to the more salient ones became faster on the left with rotigotine. This result may be in keeping with more effective voluntary allocation of selective attention to the task-relevant visual targets, and less involuntary attentional capture, driven by stimulus salience, on rotigotine. Therefore, it is possible that rotigotine improved performance on the Mesulam shape cancellation task by enhancing selective attention to the targets, while reducing involuntary attentional capture by the distractors. This result is in keeping with the known role of dopamine in attention switching, arousal to behaviourally relevant stimuli and goal-directed behaviour (Bromberg-Martin et al., 2010; Cools, 2011).

Interestingly, the significant treatment effect observed on the Mesulam task was not seen on two similar visual search tests (Bells and touchscreen invisible

cancellation tasks). Taken together with the specific enhancement of responses to less salient targets in the selective attention task, this discrepancy might be due to the characteristics of each of these visual search tasks. In contrast to the abstract shapes used as targets and distractors in the Mesulam test, targets in the Bells task are highly salient object silhouettes, therefore it is conceivable that improvement on this task through further enhancement of visual salience was not possible due to a ceiling effect. On the other hand, the touchscreen invisible cancellation task (in which no visible mark appears on the screen when a target is identified) may depend heavily on a WM component to determine which targets have been already cancelled to prevent 'revisiting' of targets that have been already cancelled. As shown in the vertical Corsi task, treatment with rotigotine was not associated with an improvement in WM, therefore this might have been the limiting factor in preventing improvement in visual search on the invisible cancellation task.

L-dopa as an adjuvant of physiotherapy has been demonstrated to improve motor function in stroke patients with unilateral weakness (Scheidtmann et al., 2001). In the current study, there was no significant effect of rotigotine treatment on motor performance. However, the study was not designed to assess drug effects prospectively, and the amount of physiotherapy received by each patient was not controlled, therefore although an effect of rotigotine alone on motor performance was not demonstrated, it remains an open question whether this drug may benefit motor rehabilitation when used as adjuvant of physiotherapy. Indeed, given the well-recognised role of dopamine in complex reinforcement learning (Dayan and Balleine, 2002; Wise, 2004), a possible synergistic role of dopamine agonists in novel rehabilitative approaches that aim to improve spatial awareness in neglect (Parton et al., 2004) also presents itself as an important question for future research.

In Chapter 5, I presented the first successful randomised double-blind placebo controlled study of the dopamine agonist rotigotine in a group of stroke patients with hemispatial neglect and unilateral weakness. Rotigotine was associated with significant improvement in visual search, and this effect might have been mediated by an enhancement of selective, goal-directed attention.

Larger trials should confirm whether this treatment may be practical for widespread clinical use in visual neglect following stroke, or indicate predictive markers of treatment response.

7.5 Insights from MTL lesion patients

Studies of patients with focal lesions of the medial temporal lobe (MTL), with Scoville and Milner's patient HM as an archetypical example (Scoville and Milner, 1957), have been instrumental in establishing the role of that area in long-term memory (LTM) processes (Milner, 1970; Squire and Zola-Morgan, 1991; Burgess et al., 2002; Simons and Spiers, 2003; Squire et al., 2004; Bird and Burgess, 2008). However, the role of the MTL in supporting WM functions has been more controversial. According to some views, medial temporal (MTL) structures, including the perirhinal, parahippocampal, entorhinal areas and hippocampus, are vital for LTM, but not involved in WM (Squire and Zola-Morgan, 1991; Squire, 1992; Alvarez et al., 1994). In contrast, evidence from lesion studies in monkeys and humans, suggested that intact function in these areas is necessary in order to maintain representations of novel or complex objects even across short delays (Murray and Mishkin, 1986; Meunier et al., 1993; Eacott et al., 1994; Hannula et al., 2006; Olson et al., 2006a, 2006b; Ezzyat and Olson, 2008; Finke et al., 2008).

In Chapter 6, I studied WM precision in two patients with extensive lesions involving the MTL following HSV encephalitis, but also in two patients with a recently recognized condition associated with much more focal medial temporal lobe involvement due to autoimmune limbic encephalitis associated with antibodies to components of the voltage-gated potassium channel (VGKC) complex (Vincent et al., 2004, 2011). Crucially, several lines of evidence suggest that VGKC-associated encephalitis is highly selective to limbic structures, including the hippocampus, and to a lesser extent, the amygdala (Ances et al., 2005; Harrower et al., 2006; Khan et al., 2009; Herranz-Pérez et al., 2010). Owing to this anatomical selectivity, the study of patients with VGKC-

associated encephalitis could offer new insights on the role of the hippocampus in cognition, including its involvement in VWM.

Using a modified version of the sequential WM task introduced in Chapter 2, I found that VWM precision for the orientation of sequentially presented coloured bars was impaired, despite intact performance on a control task which did not require memory, and on standard measures of verbal and spatial WM (digit span and Corsi spatial span).

One hypothesis which might explain this discrepancy between the sequential precision task and the standard memory tests could relate to a potential role of the MTL in visual feature binding. Indeed the sequential precision task required subjects to remember associations between colour and orientation, while intact memory for associations was not necessary for either digit span or Corsi task. Such a role for the MTL would be theoretically plausible (Eichenbaum, 2006; Konkel and Cohen, 2009), and in keeping with previous imaging results implicating this region in feature binding information in VWM (Piekema et al., 2006; Hannula and Ranganath, 2008).

As previously, I examined potential sources of loss of WM precision using a generative model which considers the distribution of responses taking into account variability in subject's responses to the target orientation, a certain probability of responding using the orientation of a non-target, and random error (Bays et al., 2009). This analysis it suggested that non-target responses in three-item sequences were significantly elevated for one patient with VGKC-associated encephalitis, but this was not the case in any of the other patients. Additionally, an increase in the random (uniform) component of the model accounted for a much higher proportion of variability in patients than non-target responses. In any case, results from this analysis should be treated with caution as they are based on a limited amount of noisy data.

A more recent study on a more extensive group of VGKC-associated encephalitis patients provided a more definitive answer on the role of MTL in WM binding, demonstrating failure of effective binding between location and object identity within WM in this group of patients (Pertzov et al., 2013). These

results are in keeping with previous imaging studies implicating the MTL in object-location binding (Piekema et al., 2006; Hannula and Ranganath, 2008). Interestingly, a further study demonstrated fMRI activation in the MTL during object-location binding, as well as in associations between different objects but not in binding between non-spatial features within objects (Piekema et al., 2010). These results call for further exploration of the role of the MTL in non-spatial feature integration within VWM. Future studies on patients with highly focal MTL lesions, such as those resulting from VGKC-associated encephalitis, should measure directly impairments in binding of location with other visual features versus binding between non-spatial features of objects in VWM.

7.6 Conclusions

In this thesis, I attempted to encompass the problem of VWM updating across time and its goal-directed attentional control from multiple perspectives.

Using precision as an index of WM in healthy individuals provided new insights on how WM resources can be flexibly reallocated across time. By manipulating task-relevance of visual objects across time, I explored the physiological capability and limitations of VWM systems in redistributing memory resources dynamically across time according to behavioural relevance.

Studying how these physiological processes were affected by focal brain lesions in carefully selected patient populations offers the opportunity to gain more insight into the neural correlates of VWM and goal-directed attention. What is more, it can lead to a better understanding of the role of these cognitive processes in complex clinical syndromes such as visual neglect. In Chapter 4, I found for the first time a profound non-spatial impairment in WM and its voluntary attentional control in neglect, and studied the lesional correlates of each of these cognitive deficits. The role of the MTL in VWM across time was examined in Chapter 6 in individual patients with focal lesions due to VGCK-associated encephalitis or HSV encephalitis.

A more detailed understanding of the cognitive components of complex clinical syndromes, such as visual neglect, may open pathways to targeted treatment. In turn, the study of pharmacological modulation of cognition in such patient populations may lead to better understanding of the underlying cognitive function and dysfunction. In Chapter 5 I showed that the dopamine agonist rotigotine was associated with significant improvement in visual search in a group of patients with visual neglect following stroke, and I proposed a potential mechanism of this effect through enhancement of selective, goal-directed attention.

This thesis attempted to exploit the exciting synergy between basic and clinical research in cognitive neuroscience. In this regard, I hope it may serve as a starting point for further work aiming to understand cognition and ameliorate cognitive dysfunction.

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