Neural substrates supporting the influence of working memory contents on visual attention

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I, José Miguel Pinto Cardoso de Bourbon Teles confirm that the contents of this thesis represent my own original work. Anything that is derived from other sources is appropriately referenced.

Abstract

The present thesis investigates the neural mechanisms supporting working memory (WM) guidance of visual attention, focusing on the role of the thalamus. Chapter 1 is a review of the relevant literature and sets-up the specific research aims. Chapters 2 and 3 explore the role of the thalamus on guidance of attention by WM contents. Stroke patients with focal-brain lesions performed a WM-guided search task. In valid conditions, the colour of the search target was pre-cued by the WM cue while on neutral conditions there was no cue prior to search. In invalid conditions, the WM cue specified the colour of a search distracter and the target appeared elsewhere. First, it was hypothesized that lesions to the thalamus could lead to deficits in attentional control (e.g. failing to separate irrelevant memory contents with relevant target information and leading to increased capture from WM-like distracters during invalid search conditions). An alternative hypothesis was that the thalamus may support the capture of attention by WM contents, hence thalamic patients would display little bias of attention from the WM contents, despite those contents are being maintained in memory. It was found that patients with focal-thalamic lesions especially in the ventrolateral nucleus, showed no search benefit from the valid cues on search as opposed to a control group of patients with lesions outside the thalamus and non-stroke patients. In the invalid condition, thalamic patients showed no capture by the irrelevant search item that matched the WM cue, whereas a group of healthy age-match controls exhibited the normal effect of capture by irrelevant contents held in WM. These observations suggest that lesions to the ventrolateral nucleus of the thalamus impair the capture of attention from WM contents. In Chapter 4, I aimed to establish the role of cortical structures that are known to be structurally connected with the ventrolateral nucleus of the thalamus (i.e. superior frontal gyrus) in WM guidance of attention. To do this, I investigated the effects of transcranial direct current stimulation (tDCS) of the dorsal frontal cortex in WM guidance of attention under distinct WM loads. I found that despite the effect of WM guidance of attention decreasing as WM load increased, frontal-tDCS modulated WM guidance in these conditions. We suggest that the dorsal frontal cortex forms part of a network

alongside the thalamus in supporting WM guidance of attention. Finally, I conducted a functional Magnetic Resonance Imaging (fMRI) experiment (Chapter 5) with healthy volunteers to test the hypothesis that the thalamus plays a role in WM guidance when learning of abstract cue-target feature associations needs to take place for guidance of behaviour to emerge. I used four Japanese ideograms as WM cues, each associated with the colour surrounding the sought after target in the subsequent search display (valid trials). In the neutral condition, four different Japanese ideograms were presented that did not predict the colour of the target. Hence, for WM to guide attention the association between the abstract cue and the colour that surrounded the search target needed to be learned. I found that responses in the thalamus and the frontoparietal cortex displayed sensitivity to the predictiveness of the ideogram cues as WM guidance of attention emerged during learning. The findings reported in this thesis demonstrate the pivotal role of the thalamus in WM guidance of attention.

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Table of Contents

List of Figures

List of Tables

Chapter 1: General Introduction

Attention can be defined as the process that enables us to concentrate neural resources and select a particular target stimulus while ignoring or suppressing other irrelevant information (Desimone, 1996). Working memory (WM) is the mechanism by which individuals are able to retain in mind relevant information for the task at hand (Baddeley, 2003). Working memory is not the same as visual short-term memory (VSTM) in the sense that the information that is in WM may be manipulated, rather than merely maintained in VSTM, to become readily available for goal-directed behaviour.

Perhaps the main difference between attention and WM lies in the fact that during attention the allocation of resources is driven towards a stimulus that is present in the external environment whereas during WM stimulus information is being mentally represented. Until recently, human brain imaging research assessed both cognitive functions separately and found that brain regions of the prefrontal cortex (PFC) are consistently activated during WM paradigms (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Curtis & D'Esposito, 2003; Owen, 1997); while the superior parietal lobe (SPL) and the precuneus are largely activated during attention paradigms (Behrmann, Geng, & Shomstein, 2004; Corbetta & Shulman, 2002; Giesbrecht, Woldorff, Song, & Mangun, 2003; Liu, Slotnick, Serences, & Yantis, 2003).

However, human brain imaging work also clearly indicates that a subset of brain regions located in the frontal and parietal cortex are consistently activated both during WM (Passingham & Sakai, 2004; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002) and attention paradigms (Corbetta & Shulman, 2002). The large overlap in brain areas involved in attention and working memory suggest strong reciprocal links between the two cognitive functions**.** A similar pattern is found in single cell recording studies in monkeys using paradigms requiring shifting attention to a pre-cued location or delayed match to sample WM tests that involve sustained remembering of a visual

object: in both cases activity in the prefrontal cortex is observed (Wilson, Scalaidhe, & Goldman-Rakic, 1993).

1.1. Commonalities between working memory (WM) and visual attention

WM has been investigated by assessing the neural activity that correlates with the performance across three distinct phases of a delay match to sample task, namely, encoding, delay, and test (Pessoa et al., 2002). Pessoa and colleagues (2002) used functional MRI to show that activity in the occipital cortex during the encoding phase was associated with successful performance, whereas successful performance during the delay period was associated with activity in dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF) and intraparietal sulcus (IPS); and the anterior prefrontal cortex during the memory test (Pessoa et al., 2002). The DLPFC is thought to be an important region for WM (Curtis & D' Esposito, 2003). Lesions to the principal sulcus of the DLPFC lead to impairments in oculomotor delayed-response task (Funahashi, Bruce, & Goldman-Rakic, 1993). It has been argued that the DLPFC may serve a 'control' function in WM, and that DLPFC activity can be a source of top-down biasing control over posterior parietal regions that store the representations (Curtis & D' Esposito, 2003).

But activity in frontoparietal cortex does not seem specific to WM tasks. Imaging studies of visual attention have observed overlapping activation in frontal (e.g. FEF, DLPFC), parietal (e.g. IPS) and extrastriate occipital areas (Corbetta & Shulman, 2002). Attention driven by goals, is mediated by the dorsal attentional network which is involved in voluntary (top-down) orienting of attention towards relevant targets and shows increased activity with the presentation of cues that specify relevant location information (Corbetta & Shulman, 2002) or relevant feature information (e.g. colour) (Egner, Monti, Trittschuh, Wieneke, Hirsch, & Mesulam, 2008). This pattern of activations in frontal and parietal cortex is found both when participants covertly (without eye movements) and overtly (with eye movements) attend to relevant information (Astafiev, Shulman, Stanley, Snyder, Van Essen, & Corbetta, 2003; Corbetta, Akbudak, Conturo, Snyder, Ollinger, Drury, Linenweber,

Peterson, Raichle, Van Essen, & Shulman, 1998; Corbetta, Miezin, Shulman, & Petersen, 1993; Corbetta et al., 2002; Egner et al., 2008).

The fact that overlapping brain areas are present during WM and attention tasks suggests that the two concepts might reflect the same cognitive function. For example, in a typical delayed match to sample paradigm the process of committing a sample to WM must require some form of attention towards the sample information. The difference with attention directed externally to a stimulus lies on the fact that during WM the stimulus in not present out there, however, this does not mean that a form of 'internal' attention is not conferred towards it (Olivers, 2008). Likewise, during goal-driven attention the process of attending to a cued location in anticipation of a subsequent search target (Corbetta & Shulman, 2002) might also in parallel require some degree of WM for location information. This suggests that WM and attention may engage similar processing mechanisms.

In keeping with this proposal, it has been suggested that the active maintenance of spatial information is accompanied by focal shifts of spatial attention to memorized locations (Awh & Jonides, 2001; Awh, Jonides, & Reuter-Lorenz, 1998). To test these predictions, Awh et al (1998), exposed participants to a cue (a letter) in a specific location to keep in memory and five seconds later a memory test with another letter (probe) appeared and participants had to indicate whether or not it was in the same location as the original memory cue. Between the presentation of the cue and memory test (i.e. during the retention interval), participants made a key response to indicate the shape of a character like-letter that appeared in the visual screen. In some trials the character like letter appeared in the same location of the memory cue and in other trials in non-memorized locations. When the character like letter appeared in the same location of the memory cue key responses were faster in comparison to when the character like letter appeared in a different location (Awh et al., 1998). This suggests that spatial attention is directed towards locations held in working memory.

Further studies demonstrate that both WM and attention functions share the same capacity limitations. It has been shown that human participants can only retain in WM a maximum of four items (Cowan, 2001). Similarly, visual attention paradigms have shown that I can only attentionally track the trajectory of four items at a time (Cavanagh & Alvarez, 2005; Pylyshyn & Storm, 1988). At the beginning of each trial, flashing cues would mark some items as targets for tracking and then cued and non-cued items moved randomly during 7-15s. Note that all the items had the same features (colour and shape). Tracking performance was measured at the end of the trial by probing a single item: participants had to report whether or not it was a pre-cued item. Most participants were able to keep track of as many as 4 or 5 targets (Cavanagh & Alvarez, 2005; Pylyshyn et al., 1988).

In agreement with the above behavioural studies on the capacity limits of WM and attention, functional MRI studies also show a linear increase in activation of the posterior parietal cortex when the number of items to be tracked increases (Culham, Cavanagh, & Kanwisher, 2001) and a linear increase in the activation of the same areas as the number of items to be retained in visual short-term memory increases (Todd & Marois, 2004). The similarity in the number of items that can be held in WM and attentively tracked has led researchers to suggest that these two abilities rely on a common capacity-limited process (Cavanagh & Alvarez, 2005). Thus, the above findings suggest that capacity limitations in WM and attention are constrained by processing limitations in the same neural regions.

Taken together, the above behavioural and imaging studies show clearly that WM and attention might have more in common than previously thought. Below, I review further literature on the interplay between WM and attention, that is, on how the contents of WM can be used to guide attention.

1.2. The interaction between WM and visual attention

It is now well established that selection of a stimulus amongst different competitors can be influenced by previous information that is held WM (Downing, 2000; Huang & Pashler, 2007; Soto, Heinke, Humphreys, & Blanco, 2005; Soto, Hodsoll, Rotshtein, & Humphreys, 2008a; Soto, Humphreys, & Rotshtein, 2007b). For example, the search for a particular music CD in a shell filled with a lot of CDs can be influenced by an 'online' memory of the features of the CD cover (such as colour and shape drawings) that one seeks to find. According to the biased competition model of visual selection (Desimone & Duncan, 1995), top-down feedback from information held in WM plays a critical role in biasing the competition for selection amongst different items in the visual environment. Early evidence for this model came from single cell recordings of inferotemporal cortex (IT) while monkeys performed a delay match to sample task (Chelazzi, Miller, Duncan, & Desimone, 1993). Cues were carefully selected to include a "good" stimulus that elicited strong cell response and a "poor" stimulus that elicited little or no cell response. After a delay, both the good and poor stimulus were presented as choice stimulus and the monkey made a saccade to the target stimulus that matched the cue. During the delay period, the recorded IT cell had sustained delay-related activity for which the good cue evoked higher cell response in comparison to the poor cue. Subsequently, the choice array was presented and the initial cell response (first 200ms) was the same independently of whether the target was the good or the poor stimulus. However, just before saccade onset the cell response changed in a way that if the target was the good stimulus the response remained high but if the target was the poor stimulus the response to the good distracter stimulus was suppressed. This shows that inferior temporal cortex has a critical role in biasing the competition for selection of stimulus that are behaviourally relevant (Chelazzi et al., 1993).

A subsequent study used single cell recordings in the prefrontal cortex (PFC) and also inferotemporal cortex (IT) in monkeys as they performed a delay match to sample task. (Miller, Erickson, & Desimone, 1996). A sample stimulus was presented, which was followed by a delay and

a visual array containing five test stimuli, one of them matching the sample. Monkeys had to release a lever when the matching stimulus appeared. Recordings showed that PFC neurons had higher sample delay related activity and match enhancement relative to IT neurons consistent with a role of PF neurons in WM. On the other hand, IT neurons were more responsive to the presentation of the visual stimulus. This study suggests that PFC neurons contain neural signals that correlate with maintenance of sample information and an evaluation of whether test stimuli match it or not. According to the biased competition model, the PFC plays a primary role in working memory tasks and may be a source of top-down feedback inputs to the IT cortex, biasing activity in favour of stimulus that are behaviourally relevant (Miller et al., 1996).

1.2.1. Behavioural evidence for an automatic interplay between WM and attention

Pashler and Shiu (1999) demonstrated that creating a mental image of an irrelevant object (i.e. a tiger) interfered with the detection of a target digit presented in a rapid serial visual presentation when the object associated with the mental image reappeared in the rapid visual stream just before the target digit (Pashler & Shiu, 1999). The presence of the imagined item was detected by observers, and impaired the detection of the subsequent target digit in the sequence of events. The results illustrate that participants could not avoid but to attend to the object that was being mentally represented.

In Downing's study (2000), participants were presented with a face cue to hold in memory. Simultaneously, a pair of faces were presented on the right and left side of a fixation dot. One of the faces was a memory-matching face. Participants performed a discrimination task on a small bracket (the target) appearing at the location of one of the two faces. A memory test was presented at the end to ensure the cue face was held in WM. Search responses to the target stimulus were faster when presented in the same location as the memory-matching face relative to when it was presented at the location of the non-matching face. The results illustrate that attention was shifted to the location of the face held in WM and facilitated processing of target stimulus at that location.

The cueing effect was disrupted when participants were instructed to merely attend to the cue face. This study suggests that attention is biased towards items matching WM representations (Downing, 2000).

Soto and colleagues (2007b) presented participants with an object to either hold in memory or to merely attend (Figure 1). The main target object was a tilted line that appeared in a subsequent search display amongst a vertical distracter line. In valid trials, the tilted target line was presented inside the cued object held in WM. In invalid trials, the object held in WM reappeared in the search display and contained a distracter vertical line and the search target appeared elsewhere. On neutral trials, there would be no relation between the object held in WM and the search display. By the end of each search trial, there followed a memory test that involved the presentation of a single item which observers had to match (in colour and shape) to the memory cue (Figure 1). Memory scores were high, showing that participants were able to commit the cues into WM. It was verified that search for the target was slower in invalid compared to neutral or valid trials. This same effect did not occurred when participants merely attended to the cues but were not required to keep the cues in WM throughout the trials (Soto et al., 2008a; Soto et al., 2007b). However, the increased interference of the distracters in invalid WM trials occurred even when the participants knew that the WM item would always be invalid and had no incentive to attend to the items matching the WM cue. Soto et al., 2005, included for the first time conditions where the WM content was always detrimental (e.g. invalid) for search and compared performance against a neutral condition (Figure 1). Search for the target was slower in invalid compared to neutral trials. Again, the cueing effect only occurred when the cue was held in WM and not when participants were merely attending to it (Soto et al., 2005). Taken together, the evidence indicates that the contents of WM guide attention in a rather automatic and involuntary way.

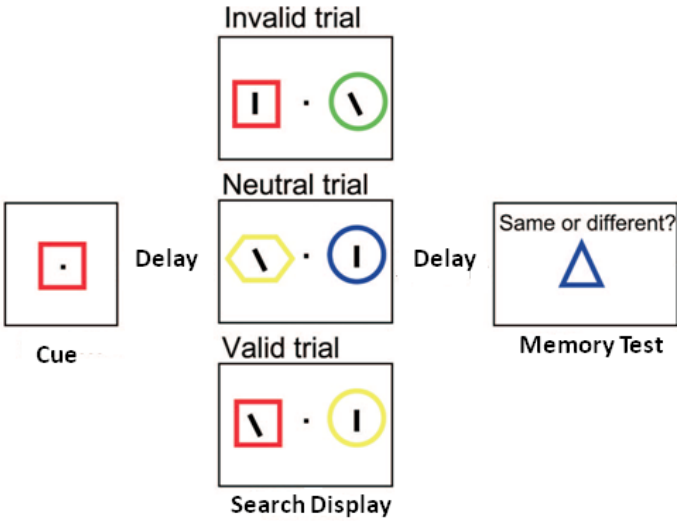

Figure 1. Behavioural paradigm depicting different cued conditions: valid, neutral and invalid (Reproduced with permission from Soto et al., 2007b).

There are however limits in the influence of WM on attention. For example, Soto & Humphreys (2008b) presented participants with either one or two items to keep in WM and then required participants to search for a tilted target line amongst different distracter lines (as in Figure 1). It was observed that under stressing memory conditions (i.e. when holding 2 items vs. 1 item in WM) the effects of WM guidance on selection decreased. The authors suggested that under high WM load conditions there is higher competition between items for neural representations, reducing the effect of WM on attention (see also Bays & Husain, 2008; Soto, Greene, Chaudhary, & Rotshtein, 2012a).

Research from Lavie and colleagues (Lavie & de Fockert, 2005; Lavie, Hirst, de Fockert, & Viding, 2004) also suggest that WM is important for control of goal-directed behaviour during search and as such reducing the availability of WM resources (by loading WM in a simultaneous, yet unrelated task) reduces the efficiency of focusing attention in relevant information with greater interference from distracters. In keeping with this proposal, behavioural experiments of selective attention showed that interference of flanking distracting letters over detection of centrally displayed target letters increased significantly under conditions of high WM load (i.e. when participants had to rehearse a set of six digits) in comparison with low WM load (i.e. when there

was only one digit to rehearse) during search attention (Lavie et al., 2004).

Downing and Dodds (2004) presented participants with two items to keep in WM. Participants received instructions that one item specified the target of the search (i.e. the search template) while the second item was irrelevant for search but had to be maintained for a subsequent memory test. When the second item reappeared in the search display as a distracter it had no influence on search attention as measured by reaction times (RTs) and accuracy to the target discrimination. Nevertheless, accuracy in the memory test was high (Downing & Dodds, 2004). These results support the important principle that information is fractioned in different WM systems: accessory memory items may be retained in WM but in a state that limits their influence on visual attention but still can be used for later recognition memory processes; items that are represented as search templates in WM have an prominent influence on the deployment on attention (see also Olivers, Peters, Houtkamp, & Roelfsema, 2011).

The above experiments (Downing, 2000; Soto et al., 2005; Soto et al., 2007b) illustrate that visual WM cues guide our attention. However, attention can also be guided by verbal WM. In Soto & Humphreys study (2007a), participants were presented with a verbal cue (e.g. “Red Square”) or visual cue and where required to search for a tilted target line amongst different distracter vertical lines (as in Figure 1). Participants were instructed to merely attend or hold the cue in WM in different experiments and the cue was always invalid (i.e. containing a distracter) when it reappeared in the search display. When the verbal cue matched a search distracter (invalid condition) performance was impaired relative to neutral condition without matching between the cue and search. The cueing effect was absent when the cue was merely attended. This experiment demonstrated that encoding of verbal information can guide attention automatically as much as visual information does (Soto & Humphreys, 2007a).

A related experiment by Huang & Pashler (2007) further assessed the effects of verbal WM cues on attention. Participants retained in memory a cue white word. This was followed by a display

of three background words with a superimposed green digit. Participants were instructed to remember the digits. One of the three background words (critical word) was semantically related to the cue word. For example, the cue word might have been “boat” and the critical word “ship”. Afterwards, a memory test followed and participants reported whether a test word matched or not the cue word. Finally, participants reported which digit was stored in memory. There was a tendency for participants to report more digits that were inside the background word associated with the cue word. This shows that when participants where retaining the verbal cue in working memory there was a tendency for attention to be drawn towards the background word that bears a semantic relationship with the WM representation (Huang & Pashler, 2007).

Together, these studies demonstrate that WM representations either visual (Downing, 2000; Soto et al., 2005; Soto et al., 2007b) or conceptual (Huang & Pashler, 2007; Soto & Humphreys, 2007a) can have a strong influence on attention.

1.2.2. Brain Imaging evidence for the interplay between WM and attention

Although not as extensive as the brain imaging work on goal-directed attentional cueing (Corbetta et al., 1998; Corbetta & Shulman, 2002), there has been recent functional imaging research dedicated to assess the neural regions that support the interaction between WM and visual attention. Interestingly, the neural regions that activate in paradigms assessing the interaction between WM and attention area not quite the same as previously found for goal-directed attentional cueing (Corbetta et al., 1998; Corbetta & Shulman, 2002) or WM paradigms alone (Pessoa et al., 2002).

Soto and colleagues (2007b), assessed performance of a group of healthy participants in the WM guidance of attention paradigm depicted in Figure 1, and found evidence of two different networks responding (i) to the reappearance of a memory stimulus in the visual display independently of its relevant for the search target goal and (ii) to the validity of the contents held

in memory for the search goals (i.e. valid relative to invalid trials). More specifically, activity in regions of the superior frontal gyrus (SFG) in the vicinity of the frontal eye fields, the lingual gyrus (Ling G), and the bilateral parahippocampal gyrus (PHG) increased with reappearance of the WM cue during search (in both valid and invalid trials) (Figures 2A and 2B) relative to the neutral condition where the memory cue did not reappear during search (Figure 2B). Interestingly, this effect was only present when participants were required to keep the cue in WM. In the priming condition (mere-repeat condition), when participants simply needed to attend to the cue but not keep the cue in memory these regions showed decreased activity with reappearance of the cue in the search array (Figure 2B). The results suggest that these areas are sensitive to the reappearance of the WM cue independently of their relevance for search (in valid but also invalid conditions) (Soto et al., 2008a; Soto et al., 2007b). On the other hand, responses in the bilateral anterior PFC and bilateral thalamic nuclei was higher in valid than in the invalid condition (Figures 2C and 2D). This network was only present when the cue was held in WM but not in the priming, mere-repetition condition (Figure 2D). It was suggested that a frontothalamic network is involved in monitoring the validity of the WM cue when it reappears in the search display (Soto et al., 2008a; Soto et al., 2007b). More recent experiments have shown evidence of the same frontothalamic activation during WM guidance of attention driven by abstract/semantic cues in WM (i.e. colour words and emotional faces) (Grecucci, Soto, Rumiati, Humphreys, & Rotshtein, 2010; Soto, Rotshtein, Hodsoll, Mevorach, & Humphreys, 2012b).

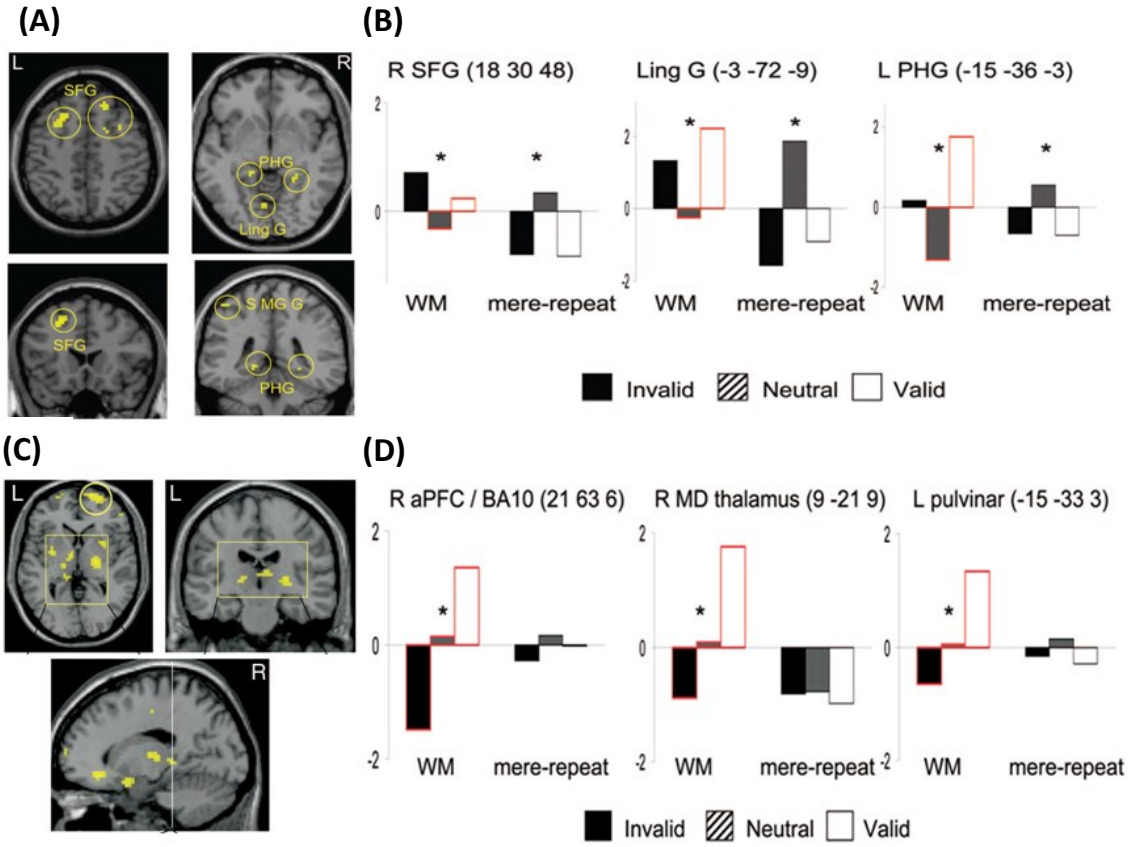

Figure 2. Neural correlates of WM guidance of visual attention (A) Brain regions that show increased responses to the reappearance of the cues (valid and invalid) relative to the neutral condition when the cues were maintained in WM. The same brain regions display decreased response to the reappearance of the cues relative to the neutral baseline when the cue is merely repeated (B) Graphs depicting the estimated response (arbitrary units) of the three brain regions in the different conditions (C) Brain regions that show increase responses to the reappearance of valid cues and decrease responses to the reappearance of invalid cues during the WM condition (D) Graphs depicting the estimated responses of the three brain regions in the different conditions (Reproduced with permission from Soto et al., 2007b).

In summary, recent neuroimaging studies suggest that attentional guidance by WM contents engages a network including prefrontal areas and, superior frontal gyrus (SFG) and the thalamus (Grecucci et al., 2010; Soto et al., 2008a; Soto et al., 2007b; Soto et al., 2012b) which may influence in a top-down manner responses to critical stimuli in early visual areas. The view that PFC plays a key role in controlling the top-down, working memory biasing of sensory processing (Miller et al., 1996) has been recently confirmed by a repetitive transcranial magnetic stimulation (rTMS) study using a memory paradigm in which participants had to remember stimulus properties of a cue for a subsequent delayed recognition test. It was found that memory accuracy decreased

following disruption by rTMS of the inferior frontal junction (IFJ) relative to sham rTMS. Event related potentials recorded from extrastriate cortex (i.e. the P1 waveform) while participants were engaged in the experimental task revealed that the P1 potential was impaired following rTMS to the IFG (relative to sham rTMS), suggesting that IFJ is a frontal source of top-down biasing of early sensory processing in occipital cortex that is critical for WM performance (Zanto, Rubens, Bollinger, & Gazzaley, 2010; Zanto, Rubens, Thangavel, & Gazzaley, 2011).

1.3. Role of the thalamus in memory and attention

So far, I reviewed existing research on the importance of the frontoparietal network in goal-directed attention and WM. In the current thesis, I am particularly interested in characterising the role of the thalamus in the interplay between WM and attention. However, very little is known about the functional roles of the thalamus in cognition, particularly in attention and WM. Before going into the specific aims and hypothesis, here, I review what is known about the anatomy and function of different thalamic nuclei in attention and WM.

1.3.1. Anatomy of the thalamus

Investigations on the anatomy of the thalamus have shown it is composed by distinct nuclei that connect to very specific regions of the cerebral cortex (Johansen-Berg, Behrens, Sillery, Ciccarelli, Thompson, Smith, & Matthews, 2005; Sherman & Guillery, 2002) (Figure 3). The cerebral cortex also sends information back to the thalamus, which then sends this information to other cortical brain regions (Johansen-Berg et al., 2005). Therefore, the thalamus is a highly dynamic subcortical region with established reciprocal connections with most cortical regions of the brain.

Early studies on the anatomy of the thalamus were made with monkeys using connection-tracing techniques (Rausell & Jones, 1991). For example, the anterograde tracing method uses injections of fluorescent dyes into the monkey thalamus that would then be absorbed by the cell bodies of the neurons and travel alongside the axon terminal into the target synaptic field. In this

way markers are created that allow visualisation of the regions of the brain to which neurons project to (Rausell & Jones, 1991). The anatomy of the monkey thalamus was then based on its connectivity profile with the cerebral cortex.

Similarly, anatomical parcellations of the human thalamus into different subdivisions have also been based on connectivity patterns with different cortical brain regions by using diffusion-tensor imaging (DTI) and probabilistic tractography (Figure 3; Johansen-Berg et al., 2005). This technique obtains a connectivity index along a white matter pathway linking two regions. Johansen-Berg et al. (2005) classified thalamic voxels based on the cortical regions with which they show the highest connection probability and parcelated distinct connectivity-defined regions (CDRs) that where hypothesized to correspond to distinct thalamic nuclei. Figure 3 shows the major thalamic nuclei (Figure 3A) coloured according to their major cortical connection site (Figures 3B and 3C). It was also found that some thalamus divisions projected to multiple adjacent cortical regions. For example, prefrontal cortex connections where not only primarily based on the mediodorsal nucleus (MD) but also extended to a secondary region located within a sub-region anatomically corresponding to the ventrolateral nucleus (Johansen-Berg et al., 2005).

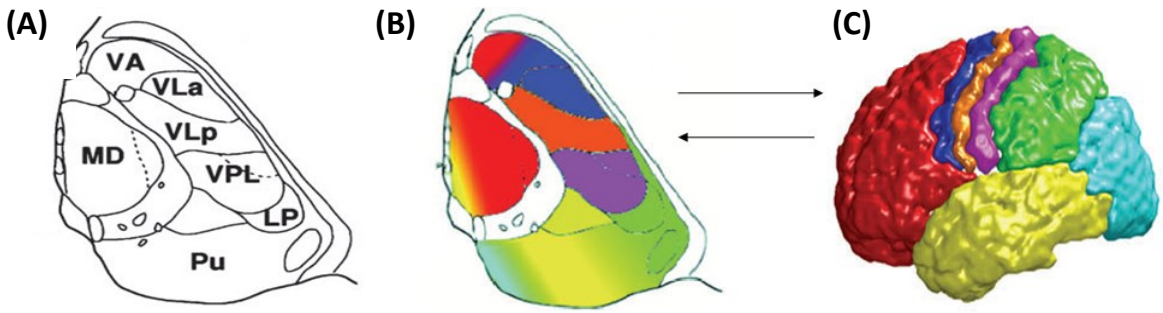

Figure 3. Anatomy of the human thalamus (A) Thalamic subdivisions: MD = medial dorsal, Pu = pulvinar, LP = lateral posterior, VPL = ventral posterolateral, VLp = ventral lateral posterior, VLa = ventral lateral anterior, VA = ventral anterior (B) The thalamic maps were coloured according to their probability of connections to cortical regions (C) Cortical subdivisions: Red = prefrontal, Blue = premotor, Orange = primary motor, Magenta = somatosensory, Green = posterior parietal, Cyan = occipital, Yellow = temporal (Reproduced with permission from Johansen-Berg et al., 2005).

1.3.2. Functions of thalamic nuclei

Evidence from neuro-stimulation experiments in patients during stereotaxic thalamic operations have shown that the ventrolateral (VL) nucleus and the pulvinar (Pulv) are important for verbal WM and speech (Johnson & Ojemann, 2000). For example, left VL thalamic stimulation influenced speech articulation and, stimulation of the left anterior pulvinar impaired the ability to name objects (Johnson & Ojemann, 2000). Stimulation of the same left VL nucleus of patients also affected verbal short-term memory. When patients where stimulated during presentation of verbal material, recall performance was high (Johnson & Ojemann, 2000), however, when the stimulation was made at the time of recall then performance decreased. Similar effects were found following, stimulation of the left pulvinar (Johnson & Ojemann, 2000). The above studies suggest that the VL and pulvinar nucleus of the thalamus may be important for the online maintenance of verbal information possibly by means of subvocal rehearsal strategies (Baddeley, 2003; Smith, Jonides, Marshuetz, & Koeppe, 1998).

Portas and colleagues (1998) discovered that the VL thalamic nucleus had an important role in mediating the interaction between attention and arousal. Participants performance in an attention task (i.e. to locate a digit superimposed in a row with several distracters) was assessed under 3 different levels of arousal: normal arousal (i.e. awake after normal nigh of sleep); high arousal (i.e. following administration of caffeine) and low arousal (i.e. under sleep deprivation). Performance on the attention task during a state of low arousal correlated with increase activation of the VL thalamus relative to normal and high levels of arousal. No other regions showed different levels of activation as a function of arousal and no effects of arousal on thalamus responses were found during passive viewing conditions (Portas, Rees, Howseman, Josephs, Turner, & Frith, 1998). The VL nucleus of the thalamus might be an important region for regulating the necessary levels of arousal and alertness that are required for performance of cognitively demanding tasks such as those requiring the interplay between WM and attention.

Evidence from human and monkey studies suggest that different nucleus of the thalamus (VL, MD, Pulv) are important for controlling attention and the orienting of eye movements. Using micro-stimulation, Berman and Wurtz (2010) identified a subset of pulvinar neurons called relay neurons that projected to the medial-temporal (MT) cortex. Wurtz et al. (2011) also showed that responses in pulvinar neurons increased when the animal was about to make a saccadic eye movement to a visual stimuli and also when attention was directed to the stimuli located in the neuron's receptive field (Wurtz et al., 2011). It was thought that pulvinar activity in anticipation of visual stimulus reflects preparatory, attention related signals (Wurtz, McAlonan, Cavanaugh, & Berman, 2011).

The monkey medial-dorsal nucleus of the thalamus (MD) is also important for saccades. Recordings of FEF neurons while monkeys performed a simple fixation to target saccade task showed that some of these neurons had a shift of activity from the current receptive field (RF) to the future RF just before the time of saccade and the neuron then responded to the target stimulus. When the relay MD nucleus was inactivated (using muscimol) the main effect was a 70% decrease in the ability of the FEF neuron to shift its activity across current and future RFs. This shows that the MD thalamus controls the generation of saccades in the FEF (Sommer & Wurtz, 2006). Further experiments, recorded distinct neuronal activity in the MD thalamus and prefrontal cortex during memory-guided saccade tasks (e.g. visual cue appears on a side of the screen and instructs monkeys to produce a saccade to the location where the cue had been) (Tanaka & Kunimatsu, 2011; Watanabe & Funahashi, 2004; Watanabe, Takeda, & Funahashi, 2009). For example, during a 3 second delay of a memory-guided saccade task, MD activity was found to be earlier than in the prefrontal cortex, suggesting that the MD thalamus may provide motor information about forthcoming saccades to the cortex (Tanaka & Kunimatsu, 2011; Watanabe & Funahashi, 2004; Watanabe et al., 2009). Similarly, recordings of neurons in the monkey ventro-anterior (VA) and VL nucleus of the thalamus during a memory-guided saccadic task (Tanaka, 2007) showed that VL neurons exhibit significant increase in activity with delay, whereas neurons in the VA exhibit a weak

transient increase in activity during delay that often decayed before saccade initiation (Tanaka, 2007). Because the VL also connects to the FEF (Mesulam, 1990), the VL might also control the production of saccades in the FEF (Sommer & Wurtz, 2006). Therefore, these thalamic nuclei (MD, VA and VL) appear to respond during the delay period of memory-guided saccade tasks which suggests that they carry preparatory related signals that are relayed to cortical regions (such as the FEF) for the generation of saccadic eye movements (Tanaka & Kunimatsu, 2011).

An interference study showed that inactivation of the VL nucleus of the thalamus (using muscimol) delayed the generation/latency of memory-guided saccades in monkeys (Tanaka, 2006). Moreover, inactivating the VL also decreased the accuracy of saccades; that is, the distance between target and saccade endpoints increased significantly (Tanaka, 2006).

Similarly to the monkey thalamus, the human thalamus may also be involved in the regulation of saccades (Bellebaum, Daum, Koch, Schwarz, & Hoffmann, 2005; Kronenbuerger, Gonzalez, Liu, Moro, Steinbach, Lozano, Hodaie, Dostrovsky, Sharpe, & Hutchison, 2010).

The idea that the thalamus monitors eye movements through relay signals to cortical areas has been supported by human studies that suggest it plays a role in spatial updating of eye movements. Using a double-step saccade paradigm (Bellebaum et al., 2005) two targets were presented only briefly and human participants had to make two successive saccades in the absence of the targets. Accuracy for the second saccade (but not the first) decreased with focal lesions in either the MD or VL thalamus suggesting the thalamus is important for spatial updating and monitoring of eye movements (Bellebaum et al., 2005).

Furthermore, evidence from deep brain stimulation (DBS) studies of the VL thalamus in Parkinson's patients showed that DBS impaired the generation of visually-guided saccades (Kronenbuerger et al., 2010). Patients were instructed to focus attention on a fixation point and look to a visual target on the right or left side of the visual field. Saccade accuracy decreased in both patients and control group when DBS was applied contra-laterally to the target's location. The

authors suggested that DBS affected critical cortico-thalamic circuits that connect the VL with the FEF and are important for visually-guided saccades (Kronenbuerger et al., 2010).

Recent investigations in humans suggest that the thalamus is also important for controlling the orienting of attention while separating irrelevant distracter information from relevant target information (Snow, Allen, Rafal, & Humphreys, 2009). The pulvinar is a dynamic area whose dorsal parts connect to frontal cortices (FEF, DLPC) and parietal cortices (posterior parietal cortex and parietal eye fields), while the ventral pulvinar projects to visual areas (occipital and temporal) (Saalmann & Kastner, 2009, 2011; Shipp, 2003, 2004).

Snow and colleagues (2009) found that, relative to controls, patients with unilateral ventral pulvinar lesions were impaired in filtering irrelevant information but only when the target was presented in the context of salient distracters (i.e. of high luminance). Moreover, this deficit was higher in the contralateral side of space relative to the pulvinar's lesion. When the target contrast increased (high luminance) relative to distracters (low luminance) then performance was re-established, that is, detection and response to the target became faster (Snow et al., 2009).

In a different study, Ward and colleagues (2002) verified that a patient with unilateral pulvinar lesion had difficulties in separating target from nearby distracters in the contralateral side. These difficulties related to the binding of feature information as a result of deficit in target localization. For example, the colour of a target located in the contralateral lower left quadrant would be easily confused with the colour of a nearby distracter. The authors suggested that the human pulvinar along with the parietal cortex seems to be part of a distributed network for controlling spatial attention and binding of feature information (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Ward, Danziger, Owen, & Rafal, 2002).

Finally, it has been shown that other thalamic nuclei such as the lateral geniculate nucleus (LGN) is also relevant for goal-directed attention. Investigations in humans and monkeys showed that when the observer attends to visual cues, LGN responses increase in anticipation of the

forthcoming target stimulus and also in response to its presentation (O'Connor, Fukui, Pinsk, & Kastner, 2002). When the target stimulus appears inside the receptive fields (RF) of LGN neurons, these show increase activation relative to when the target stimulus is located outside the RF of the LGN neuron (Crick, 1984; McAlonan, Cavanaugh, & Wurtz, 2008; O´Connor et al., 2002; Saalmann & Kastner, 2009, 2011).

Overall, the above literature illustrates that the thalamus is important for distinct cognitive operations including: verbal WM (Johnson & Ojemann, 2000), controlling orienting of attention with saccades (Bellebaum et al., 2005; Kronenbuerger et al., 2010; Sommer & Wurtz, 2006; Tanaka, 2006; Tanaka, 2007; Tanaka & Kunimatsu, 2011; Wurtz et al., 2011), goal-directed attention (McAlonan et al., 2008; O'Connor et al., 2002) and the orienting of attention to visual targets while filtering salient irrelevant distracters (Snow et al., 2009).

1.4. Aims and Hypothesis

To date, fMRI studies have mainly focused on the importance of the frontoparietal network in goal-directed attention (Corbetta et al., 1998; Corbetta & Shulman, 2002). Recent fMRI evidence has however shown that other regions outside the frontoparietal cortex, for example, subcortical regions such as the thalamus or the hippocampus may be essential for attention control by the contents of WM (Grecucci et al., 2010; Soto et al., 2008a; Soto et al., 2007b; Soto et al., 2012b). However, fMRI techniques are correlational by nature and it is difficult to determine whether the thalamus is causally involved in WM guidance of visual attention. Moreover, it can be difficult to use fMRI evidence to infer the specific function of the activated area in relation to the behaviour.

In the current thesis, I aim to significantly go beyond previous correlational fMRI research on WM/Attention interactions (Grecucci et al., 2010; Soto et al., 2008a; Soto et al., 2007b; Soto et al., 2012b) to characterise the role of the thalamus in this interaction and to provide causal evidence for this role. To do this, I assessed the performance of patients with focal thalamic lesions in multiple

tasks conditions requiring interplay between WM and attention (Chapters 2 and 3) and their performance was compared relative to a group of stroke patients with lesions outside the thalamus.

I predicted that lesions to the thalamus ought to lead to deficits of WM guidance of attention. One hypothesis is that, thalamic patients may show deficits in separating/filtering irrelevant distracter from relevant information in WM to guide selection, so attention would be more captured by WM-like distracters (when memory information specifies distracter information and hence needs to be separated from the relevant information that specifies the target). This hypothesis is based on evidence that the thalamus may be involved in the filtering of salient distracters (Snow et al., 2009), and on fMRI evidence from Soto and colleagues that the thalamus may be involved in monitoring the relevance of the contents held in memory for current selection goals (i.e. whether the current memory content overlaps with a target or a distracter) (Soto et al., 2007b; Soto et al., 2012b).

An alternative hypothesis is that, thalamic patients may actually display reduced or attenuated biases of attention from information that is held in WM. Firstly, patients might fail to represent the verbal cues in their WM (Johnson & Ojemann, 2000). In addition to that, it is possible that verbal cues may be maintained in WM in thalamic patients but in a state which does not trigger top-down modulation of visual attention. According to this view, the thalamus might form part of a network that promotes top-down control of attention (e.g. by the contents of WM). As reviewed above, frontal regions such as SFG and PFC are interconnected with thalamic nuclei (VL, MD and Pulv) (Mesulam, 1990; Shipp, 2003, 2004; Sommer & Wurtz, 2006) and are known to play a role on the over direction of attention (Sommer & Wurtz, 2006; Tanaka & Kunimatsu, 2011). Also, the pulvinar is linked to parietal regions involved in WM and attention (Corbetta & Shulman, 2002; Todd & Marois, 2004) and feeds back to visual regions; the pulvinar is also in a good position to control attention by the contents held in WM. Thus, thalamic stroke may lead to disruption of thalamo-cortical circuits that are critical for promoting top-down orienting of attention by WM contents.

In line with this idea, I conducted a transcranial direct current stimulation (tDCS) study of the dorsal frontal cortex (Chapter 4) to characterise the role of cortical regions (e.g. SFG) that are known to be structurally connected with the thalamus in WM guidance of attention. I stimulated the left dorsal frontal cortex (and targeted the stimulating electrode so it was closer to the SFG) of healthy volunteers and assessed performance in a WM guidance of attention task under high and low WM load conditions (i.e. remembering 1, 2 or 3 cues). I predicted that tDCS stimulation to the dorsal frontal cortex ought to modulate WM guidance of attention particularly under conditions where WM is stressed. I hypothesized that if the dorsal frontal cortex (e.g. SFG) is important for WM guidance of visual attention, then stimulating this area should influence the maintenance and use of information in WM to control attention even under high loads (when holding 2 and 3 cues in WM). Our interest in studying the role of the dorsal frontal cortex (e.g. SFG) on the interplay between WM and attention is based not only on the fact that it is structurally connected to the thalamus (Mesulam, 1990; Shipp, 2003, 2004; Sommer & Wurtz, 2006) but also upon prior fMRI data from Soto and colleagues (2007b) that the SFG may display sensitivity to the reappearance of cued information during search.

In a final set of functional MRI experiments (Chapter 5), I assessed the role of the thalamus in memory-guidance of attention in task contexts that involved learning of abstract cue- target feature associations to facilitate the guidance of attention. Chapters 2 and 3 investigated the role of the thalamus in guiding attention from verbal coloured cues that involved a well-established and consolidated correspondence with the search items. Chapter 5 tested the hypothesis that the thalamus role in attentional guidance may also generalise to circumstances in which the validity of the cues for attention needs to be learned. Furthermore, the use of functional MRI in Chapter 5 allowed the assessment of the role of the thalamus in memory-guidance of attention as part of a broader cortico-subcortical network, which could not be addressed in the lesion-studies in Chapters 2 and 3.

Chapter 2: A Lesion-Symptom Mapping Study

2.1. Experiment 1: Voxel-based Lesion Symptom Mapping (VLSM)

I tested thalamic patients with focal brain lesions in distinct thalamic nuclei comprising the anterior VL thalamus, the medial dorsal nucleus and the pulvinar (Pulv) (see Table 1 for description). I assessed the hypothesis that patients with focal-brain lesions in specific thalamic nuclei would show different effects of WM guidance of attention in comparison with a control group of patients with lesions in regions outside the thalamus (see Table 2) and in comparison with a control group of non-stroke patients. The first hypothesis I tested was whether relative to the control groups, thalamic patients would show deficits in separating irrelevant distracter from relevant information in WM to guide selection, so attention would be more captured by WM-like distracters. The other hypothesis I tested was whether relative to the control groups, thalamic patients would show reduced or attenuated biases of attention from information that is held in WM. I also performed voxel-based Lesion Symptom Mapping (VLSM) analysis to assess the anatomical brain lesions that were associated with deficit in the WM/attention paradigm.

2.1.1. Methods

Patients

Patients were recruited from the Stroke Unit of Charing Cross Hospital. Previous to the experiments, patients were provided with an information sheet about the purpose of the study. I also used the Buckles test to assess patients capacity to consent (Buckles, Powlishta, Palmer, Coats, Hosto, Buckley, & Morris, 2003). The study was approved by the West London Research Ethics committee. Patients with a history of dementia and marked visual impairment, as per clinical notes, were not tested.

A group of 6 patients with thalamic lesions due to stroke (Table 1), 18 patients with lesions outside the thalamus (Table 2) and 22 non-stroke patients took part. The group of non-stroke patients were admitted to the stroke units suspected of having a stroke but no stroke was detected

following detailed examination. Clinical conditions of admission included sudden loss of vision (one or both eyes), dizziness, severe headache, weakness in the face and arm especially on one side, problems in balance and coordination of movements and, difficulties speaking.

The lesions of the thalamic patients were confirmed by an experienced neurologist and comprised the left anterior VL thalamus (patients VL1, VL2 and VL3), right and left pulvinar (Pulv1 & Pulv2) and medio-dorsal thalamus (MD). Patients VL1, VL2 and Pulv1 were initially tested in their acute stage in Experiment 1. Patient Pulv1 received no further testing whereas patients VL1 and VL2 received further testing up to 1 year following stroke. VL3 was tested five years after stroke and Pulv2 and MD were tested 3 and 10 months, respectively, after stroke. All of them suffered from ischemic stroke (see Table 1).

Patients	Sex/Age	Main Lesion Site	Time of Testing
VL1	Male/74	Left anterior ventrolateral thalamus	A and C
VL2	Female/59	Left anterior ventrolateral thalamus	A and C
VL3	Male/70	Left anterior ventrolateral thalamus	C
Pulv1	Male/80	Right Pulvinar	A
Pulv2	Male/68	Left Pulvinar	C
MD	Male/78	Right Medial Dorsal Thalamus	C

Table 1. Thalamic patients demographic description: Sex, Age, Main Lesion Site and Time of Testing/Stage (A = Acute, C = Chronic).

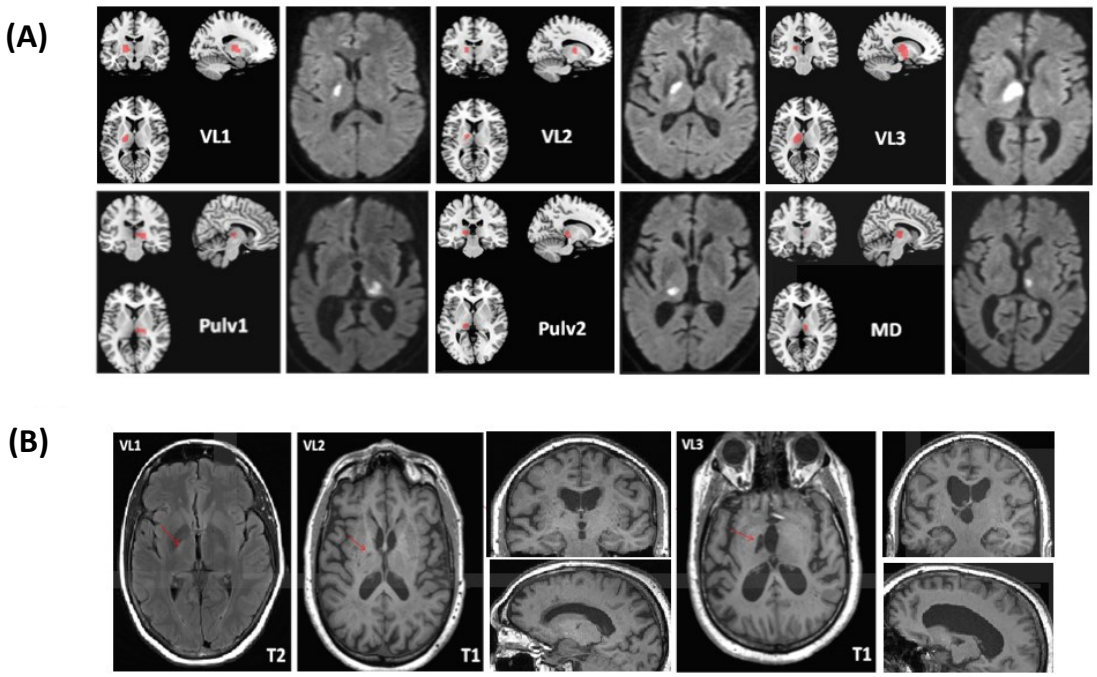

Figure 4. MRI Images of thalamic patients (A) Axial, Coronal and Sagittal views of the lesion mapping and DWI images highlighting the thalamic lesion in the acute stage (B) High-resolution structural MRI of the VL patients acquired during the chronic stage following stroke. For patient VL1, I present the T2 rather than T1. I note that patient VL2 also had a small lesion in the left pallidum.

Patients	Sex/Age	Main Lesion Site	Time of Testing
1	Female/70	Left parietal córtex	A
2	Male/74	Occipital, temporal and cerebellum	A
3*	Male/58	Left white matter	A
4	Male/70	Left occipital lobe	A
5	Male/28	Midbrain	A
6*	Male/66	Right precentral gyrus	A
7	Male/59	Right corona radiata	A
8**	Male/59	Left striatum and insular cortex, left parietal cortex and basal ganglia	A
9	Female/66	Left temporal lobe	A
10	Male/55	Mature right cerebellum	C
11	Male/64	Tiny infarcts left white matter	A
12	Male/58	Mature left insular cortex	C
13	Male/74	Left insular cortex, caudate nucleus and lentiform nucleus	A
14	Male/51	Left striatum	A
15	Male/70	Right frontal and parietal	A
16	Male/82	Right hippocampus	A
17	Male/68	Mature right inferior frontal cortex	C
18	Male/79	Right postcentral gyrus	A

Table 2. Control group of patients with lesion outside the thalamus demographic description: Sex, Age, Main Lesion Site and Time of Testing/Stage (A = Acute, C = Chronic). Most patients had ischemic stroke except * who was haemorrhagic and ** who was both ischemic and haemorrhagic. See appendix I for MRI lesions.

Experimental Tasks and Procedure

All tasks were programmed using E-Prime v2.0 (Psychology Software Tools Inc., Pittsburgh, USA; www.pstnet.com/eprime.cfm).

Memory test: I included a recognition test (Figure 5A) in order to gauge the patient's ability to keep the cues in memory. Each trial of the recognition test started with the word "Remember". Once the patient was ready the experimenter pressed a key to start the trial. There followed a delay of 2 sec with a blank screen, which was followed by a verbal cue in the form of a colour word (RED, GREEN, BLUE, YELLOW or PINK) for 3 sec. Following a delay of 2 sec, with a blank screen, the patients received a memory test. Here, a coloured circle appeared and patients were asked to report whether or not the colour word (cue) matched the circle's colour. Patients gave their responses aloud, which were then recorded by the experimenter by pressing a different button for 'same' and 'different' responses.

WM guidance of attention task: The task had two conditions depending on the validity of the memory cue: valid and neutral (Figure 5B). Each trial started with the presentation of the word "Valid" or "Neutral" as a reminder that the subsequent cue would be valid or not. The experimenter then started the proper trial via button press. Following a fixation dot for 1000 ms, in valid trials, a verbal cue in the form of word cues (RED, GREEN, BLUE, YELLOW or PINK) was presented for 3000 ms. On neutral trials, patients were presented with the word "NO CUE" during 3000 ms. After presentation of the cue, following a 2000 ms delay with a blank screen, patients were presented with a search display containing four circles. Three of the circles had a gap either on the top-right or the bottom-left and the critical target of search had two vertical gaps, one on the top and one on the bottom. The task was to specify if the target circle was on the right or left side of the visual field, by pressing "m" for right and "n" for left. Patients had unlimited time of response to the target circle. In valid trials patients were instructed and encouraged to keep the cue in memory as it would specify the colour of the search target (Figure 5B). Each stroke patient performed one block of 40

trials (20 valid and 20 neutral) with the exception of thalamic patient VL3 (Table 1) who performed 4 blocks of 40 trials. Valid and neutral trials were randomly presented.

WM guidance of attention task including a memory test: Patients Pulv2 and MD performed the same task but including a memory test for the initial cue at the end of each valid search trial. This was due to time constraints in testing these patients, who were recruited in the chronic stage and I wanted to make sure from the beginning that these patients attempted to commit the cue in working memory throughout the trials. By including a memory test at the end of each valid trial I can firmly establish whether or not the reduction of validity cueing effects on search may be the result of poor memory processing.

The WM guidance of attention paradigm with memory test was similar to the one depicted in Figure 5B with the exception that at the end of each valid trial, a memory test appeared and patients had to report whether the single memory item (i.e. in form of a colour word) matched or not the previous cue by responding aloud "same" or "different". The experimenter then pressed a response key ("s" for same and "d" for different"). Patients had unlimited time to respond in the memory test. Patients Pulv2 and MD performed a total of 2 blocks of 60 trials (30 valid and 30 neutral). Valid and neutral trials were randomly presented.

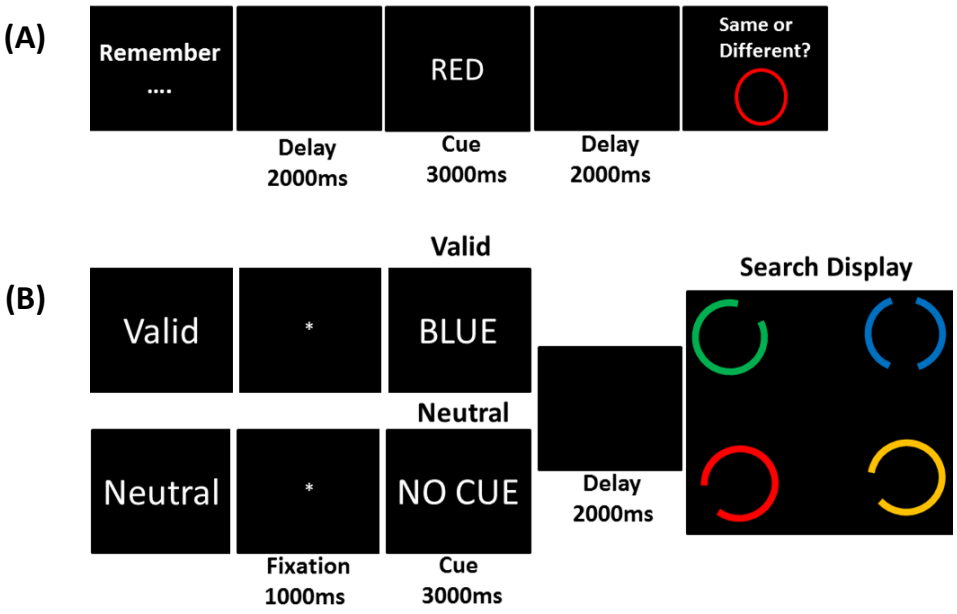

Figure 5. Example of display sequences (A) Delayed recognition trial. Patients were required to remember the cue (in form of a colour word) and following a 2 sec delay period with a blank screen to indicate whether the coloured outline circle matched or not the colour word (cue) (B) Memory-guided search task. In valid trials a coloured word pre-cued the colour of the circle containing the search target (i.e. circle containing two vertical gaps). In neutral trials no cue was presented.

Imaging Pre-processing

Brain scans: I used diffusion weighted imaging (DWI) and T2 scans for each patient. Diffusion weighted imaging is a MRI technique which is sensitive to the diffusion of water molecules (Hagmann, Jonasson, Maeder, Thiran, Wedeen, & Meuli, 2006). In DWI each voxel has a signal intensity that reflects the rate diffusion of water molecules in that particular location (Tonarelli, 2012). The diffusion rate of water molecules vary from voxel to voxel and are highly dependent on its cellular environment. Brain regions of ischemic stroke are characterized by reduced water diffusion (particularly in the first 0-6 days) as a result of reduced blood flow (Tonarelli, 2012) and can be detected in DWI images as hyperintense, bright areas during the acute/early stages of a stroke. With increased recovery time following stroke, diffusion of water also increases and consequently there is a reduction in DWI signal in the affected area such that if a patient is scanned 2 months after stroke it becomes very difficult to detect a lesion when using a DWI scan (Tonarelli,

2012). Considering that patients were initially tested in the acute stage, I selected individual DWI scans for our VLSM analysis (see below). However, I also confirmed the lesion in the chronic stage by using high resolution structural T1 imaging.

I also used T2 scans which are typically used to detect chronic stroke (it is also used to detect acute stroke but is not as powerful as the DWI). On a T2-weighted scan, water and fluid in tissues appear bright and because damaged brain tissue tends to produce edema (i.e. abnormal accumulation of fluid beneath the skin that results in swelling), this makes T2-weighted sequence very sensitive for detecting differences between normal and abnormal tissue (Chavhan, Babyn, Thomas, Shroff, & Haacke, 2009).

Lesion Mapping: The lesions for each patient were located and confirmed by a consultant neurologist. The lesions were highlighted in the DWI images by using custom-made Matlab program which produced a mask of the lesion for each patient. For patients who had an acute lesion I used the DWI scans to map the lesions, however in patients with a case of an old lesion I also used the T2 scans, as these have better resolution to detect mature infarcts. For illustration of patients MRI images go to appendix I in the end of the thesis.

Co-registration: the source DWI image and the lesion mask were then registered to the patient T2 image.

Reorientation: at this point each individual patient brain image was reoriented so that its spatial position (pitch of the head, roll of the head etc.) matches as close as possible to the standard MNI template.

Normalization: Because human brains differ in size and shape, the normalization step is critical to register all the scans to a common template, so that a given brain location in one individual scan corresponds to the same location in another individual's brain scan. This is critical in order to perform statistical analyses (i.e. VLSM). Here, brain images from each patient were transferred to

the standard MNI-whole brain high-resolution template.

Voxel-based lesion-symptom mapping analysis

Following image pre-processing, I performed VLSM analyses to assess the relationship between behavioural deficits in our stroke patients and lesion sites (Bates, Wilson, Saygin, Dick, Sereno, Knight, & Dronkers, 2003). Here, I used a Student's t test to quantify in a voxel-by-voxel basis the differences in search behaviour between patients with or without lesion in given voxel locations. Search behaviour was indexed here by the validity effect, that is, the difference in RTs between neutral trials and valid trials: Neutral search RT – Valid search RT. Statistical tests were whole-brain corrected for multiple comparisons using False Discovery Rate (FDR).

2.1.2. Results

Group Analysis

Performance in the valid vs. neutral conditions was assessed across the three different groups: thalamic patients (n=6), non-stroke patients (n=22) and patients with lesions outside the thalamus (n= 18) by performing independent sample t-tests of the cueing effect (Neutral RT – Valid RT). The results showed that the thalamic group of patients have a lower cueing validity effect relative to the control group of patients with lesions outside the thalamus ($t(22) = -3.5$, $p= 0.002$) and control group of non-stroke patients ($t(26) = -3.4$, $p= 0.002$). This is depicted below in Figure 6.

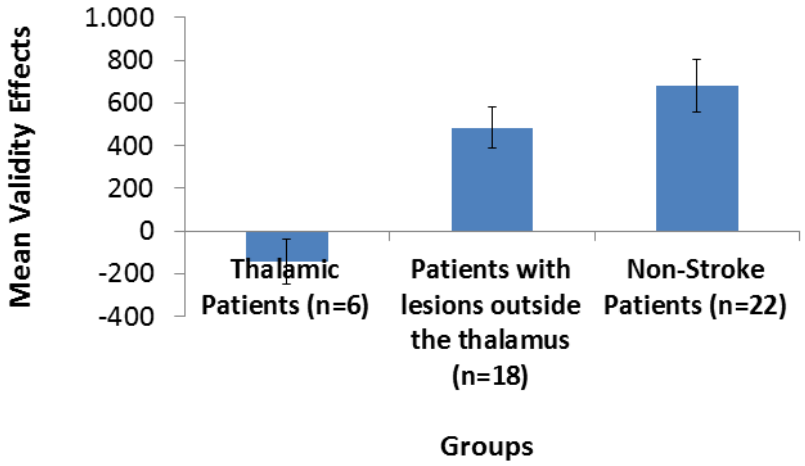

Figure 6. Validity effects (Neutral RT – Valid RT) across the different groups of patients. Error bars depict the standard error of the mean (SEM).

VLSM results

I then performed VLSM analysis to further corroborate the above finding. Critically, the VLSM analysis identified significant overlap in the left anterior VL nucleus of the thalamus ($t = -3.51$; $p < 0.05$, FDR corrected for multiple comparisons) associated with a lack of validity effects (Figure 7A). Numerical means showed faster median search RTs in the neutral condition relative to the valid condition for patients VL1 and VL2 (Figure 8A). Patient VL3 Search RTs were faster in valid relative to neutral condition (Figure 8A) but the cueing effect was lower in comparison to patients with lesions outside the thalamus (Figure 7B). The analysis shows that the anterior VL nucleus of the thalamus is the area associated with highest deficit of WM cueing.

Assessing each thalamic patient performance against the control sample

There were significant differences between the size of the validity effect (Neutral RT – Valid RT) of the patients with lesions outside the thalamus and the validity effect of patient VL1 ($t(17) = 11.9$, $p < 0.0001$), VL2 ($t(17) = 6.7$, $p < 0.0001$), VL3 ($t(17) = 4.3$, $p < 0.0001$), Pulv1 ($t(17) = 6.1$, $p < 0.0001$), Pulv2 ($t(17) = 5.4$, $p < 0.0001$) and MD ($t(17) = 5.1$, $p < 0.0001$). Validity effects of the group of non-stroke patients also differed relative to the validity effects of patients VL1 ($t(21) = 10.9$, $p < 0.0001$), VL2 ($t(21) = 6.8$, $p < 0.0001$), VL3 ($t(21) = 4.9$, $p < 0.0001$), Pulv1 ($t(21) = 6.3$, $p < 0.0001$),

Pulv2 (t (21) = 5.8, p < 0.0001) and MD (t (21) = 5.6, p < 0.0001) (Figure 7B).

Overall, the above results show that the validity effects of individual thalamic patients were lower relative to the validity effects of the controls groups. This is depicted below in Figure 7B.

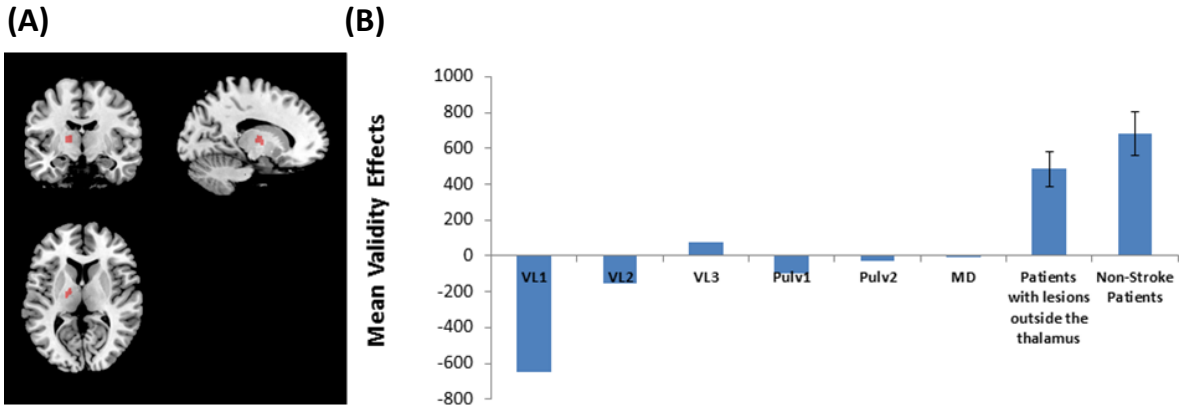

Figure 7. (A) VLSM analysis displaying patients lesions overlap in the anterior VL nucleus of the left thalamus (n=3) (B) Differences in the mean validity effects between each individual thalamic patient and the control groups of patients with lesions outside the thalamus and non-stroke patients (error bars depict SEM).

Individual univariate analysis of search performance

Patients VL1 and VL2 displayed a negative validity effect as well as Pulv1 (although at a lower extent). The remaining thalamic patients (VL3, Pulv2 and MD) seem to have a validity effect close to zero consistent with no cueing effect (Figure 7B). I then performed univariate statistical analysis on each individual patients RT data to assess the significance of the validity effect on an individual basis. On this univariate analysis of variance (ANOVA) each individual trial RT is treated as independent observations (Balani, Soto, & Humphreys, 2009). Analyses in all experiments were made for correct responses only. I analysed the effect of validity (valid, neutral) on the median search RTs. The results confirmed that in patients VL1 and VL2 the effect of validity was 'reversed', such that median search RTs were faster in neutral relative to valid conditions (see Table 3 for a summary of the results from the univariate analyses). Patient VL3 displays faster median search RTs on valid relative to neutral condition (Table 3 and Figure 8A). Nonetheless, the validity effect in this

patient is lower in comparison to control groups (Figure 7B).

				Median Search RTs (ms)	
Patients	F	Df	P	Neutral	Valid
VL1	18.7	1,36	0.0001	833.5	1482
VL2	4.76	1,36	0.036	883	1038
VL3	11.76	1,156	0.001	726.5	651
Pulv1	1.43	1,36	0.24	971	1069
Pulv2	0.47	1,94	0.49	1019	1047
MD	0.53	1,99	0.46	917	922

Table 3. Summary of results from univariate statistical analysis

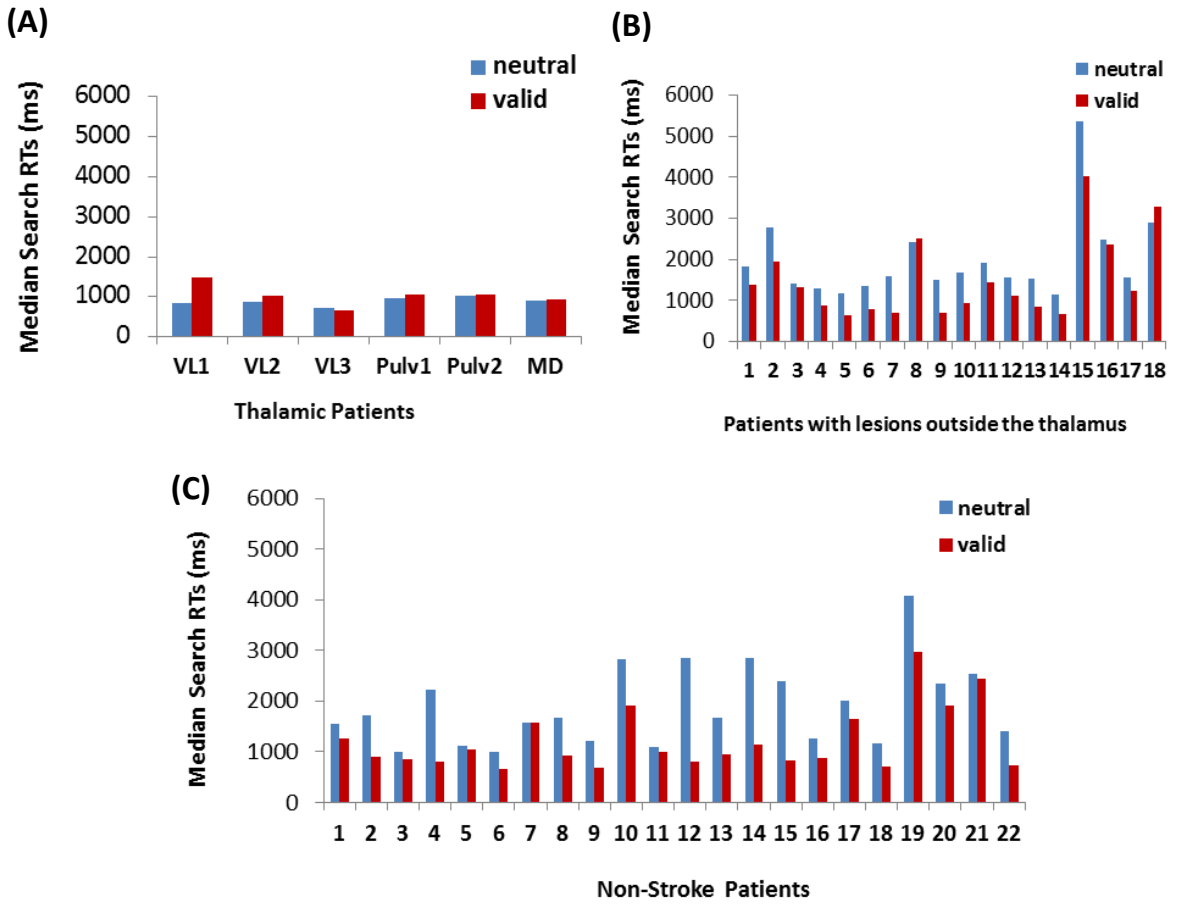

Figure 8. (A) Median search RTs as a function of validity (neutral, valid) in the thalamic group (B) in the control group of patients with lesions outside the thalamus (C) in the neurological patients without stroke.

Memory performance

I compared memory performance across the different groups by means of independent sample t-test analyses. Memory data is illustrated in Figure 9A. There were no differences in mean memory accuracy between the group of thalamic patients vs. group of patients with lesions outside the thalamus (t (22) = -0.25, p= 0.8) and group of non-stroke patients (t (26) = 0.08, p= 0.9) (Figure 9A). Overall, thalamic patients had high memory scores (94, 6%) as well as patients with lesions outside the thalamus (95.5%) and the non-stroke patients (94.3%). Thalamic patients individual memory scores were high (VL1 = 100%; VL2 = 100%; VL3 = 100%; Pulv 1 = 100%; Pulv2 = 82%; MD = 86%) (Figure 9B).

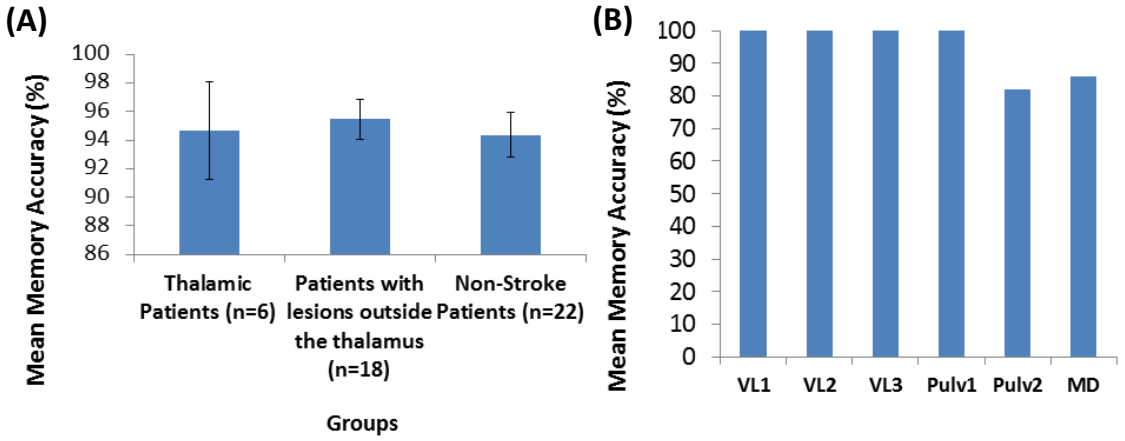

Figure 9. (A) Percentage of correct memory responses for each of the thalamic patients and each of the control groups (error bars depict SEM) (B) Thalamic patients individual memory scores.

2.1.3. Discussion

The results show that the validity effects in thalamic patients were lower relative to the validity effects of control group of patients with lesions outside the thalamus and control group of non-stroke patients. As opposed to thalamic patients, both controls groups show faster Search RTs in valid relative to neutral trials. Thalamic patients search accuracy was perfect in both valid and neutral conditions. Memory scores were also very high. This shows that patients responded effectively to the search targets and were able to commit the cues in memory. Pulv1, Pulv2 and MD patients had close search RTs between valid and neutral conditions. Even when trained and

instructed to use the memory cue to guide attention patients were unable to do so. These results show that lesions to the thalamus impaired WM guidance of visual attention.

Critically, we identified three critical thalamic patients whose focal-brain lesions overlapped in a region corresponding to the more anterior part of the VL nucleus of the thalamus and which was associated with the highest deficit in using of the verbal cues to guide search attention. Patients VL1, VL2 had a 'reversed' memory guidance effect with significantly faster search RTs in neutral compared to valid trials. The same effect was not found however in patient VL3, who showed a validity effect in the 'normal' direction, however, the size of this validity effect was considerably reduced relative to the control groups. I note that patients VL1 and VL2 were tested in the acute stroke phase in the present Experiment 1 (and more chronically up to 1 year later in subsequent experiments reported in this thesis), while patient VL3 took part in the first Experiment five-years after stroke. Hence, due to the longer recovery period in VL3, it is likely that brain compensatory mechanisms may have operated to regain some of the functional loss in this patient. Such compensatory mechanisms in patient VL3 may have well operated in intact brain areas such as the frontoparietal network that are relevant for attention control (Corbetta & Shulman, 2002; Egner et al., 2008). I reiterate however that the size of the cueing effect on search was significantly weakened in VL3 relative to the controls. These findings indicate the importance of the more VL regions of the thalamus in WM guidance of attention.

Strikingly, despite exhibiting no cueing effects during search, thalamic patients overall search RTs were faster in comparison to the control groups of patients. That thalamic patients responded very fast and accurately to the location of search target, could reflect a "survival mechanism" for overcompensating the fact that patients failed to comply with the main task demands of integrating the WM cue with the search target.

As noted, impaired memory guidance in the thalamic group could not easily be accounted for by poor memory since patients performance in the delayed recognition memory tests were high

and did not differed significantly from performance of both control groups. Note that thalamic patients VL1, VL2, VL3 and Pulv1 performed the memory test separately from the visual search task. Because of this it may be argued that patients did not attempt to strongly commit the cue to memory during the search trials despite being instructed to do so and despite knowing that it was relevant to find the search target. I address this issue in the following Chapter 3 which contains further experiments in these patients (VL1, VL2 and VL3) in paradigms that integrated both search and memory tasks.

Patients Pulv2 and MD did perform the memory tests integrated with the search task, and while I recognize that their memory scores tended to be lower relative to VL patients, this could have been because the memory test was preceded by a search display which could have interference with the precision of memory representations. Nonetheless, memory scores were high and, more critically, because analysis for search RTs was made for correct responses only during the later memory test then poor valid cueing effects in Pulv2 and MD patients cannot be explained by poor processing or commitment of the cues into WM.

In sum, the most remarkable finding of this Chapter was that anterior VL thalamic lesions impaired the guidance of attention by memory contents, in accord with the hypothesis that these thalamic nuclei are pivotal for linking active memory representations to attentional biasing processes. Strikingly, the results indicated that VL lesions reversed the direction of the cueing effect, instead of simply abolishing the standard validity effects, as was the case in the pulvinar and MD patients. The 'reversed' cue validity effect in the VL patients is consonant with the idea that these patients are not biased by the contents held in memory. That search performance in the VL patients was impaired in the presence of valid memory cues is consistent with the view that thalamic insult can trigger inhibition of perceptual representations that match the contents held in memory hence leading to impaired search performance when the memory content overlaps with the search target. I further assessed this idea in Chapter 3.

Chapter 3: Characterization of thalamic deficits in WM guidance of visual attention

3.1. Chapter Introduction

Here, I further assessed the performance of the thalamic patients (n=5; note that patient Pulv1 did not came back to participate in further experiments). In particular, I ran additional experiments in patients VL1 and VL2 to further assess whether these patients would still display deficit of WM guidance of attention in their chronic stage of stroke and to establish that poor cueing effects in these VL patients were not due to an inability to remember the memory cues as they performed the search task. In experiments 3 and 4 I compared VL patients performance against the control groups of patients with lesions outside the thalamus and non-stroke patients. However, note that only the VL patients took part in those experiments (3 and 4) and data that is presented from the control groups corresponds to their performance in original experiment 1.

To examine the hypothesis that poor cueing effects could be due to the fact that thalamic patients inhibit memory information when it reappears in the search display, I incorporated experimental conditions that included memory cues that were always invalid for search, that is, cues that specified the colour of search distracters. Recent research demonstrated that attention is automatically biased to irrelevant stimuli matching the contents of working memory (i.e. even when the memory contents are misleading for search goals; Soto et al., 2005, 2007b). Typically, healthy volunteers show impaired search performance in invalid trials (i.e. when the contents held in memory reappear as a search distracter) compared with a neutral condition (i.e. when the memory content does not reappear in search).

If thalamic patients suppress items in search that match the memory information then performance with invalid cues should be facilitated. Given that invalid cues represent distracter information, the VL patients' attention would be repelled rather than attracted by the memory-matching distracters, hence leading to a facilitation of search performance in the presence of a memory-matching distracter. Chapter 3 reports results consistent with this hypothesis.

3.2. Experiment 2: Neuropsychological assessment

Here, I tested thalamic patients in the Addenbrooke's Cognitive Examination (ACE) to further discard any association with dementia and to get some more insight into the patient's basic executive function, visuospatial abilities and language processing. I also assessed overall measures of WM capacity in the digit span task.

3.2.1. Methods

Patients

Five thalamic patients (VL1, VL2, VL3, Pulv2 and MD) were recruited for neuropsychological assessment.

Procedure

ACE

I applied the ACE to the patients in a small testing room. The ACE is a 100-point-test battery that assesses six cognitive abilities: attention, orientation, memory, verbal fluency, language and visuospatial ability (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). The orientation and attention components are similar to the MMSE (Mini-Mental State Examination) and measure general aspects like general orientation and concentration. For example, participants are asked to say current day, month and season; to repeat words like lemon, key and ball. The memory component evaluates episodic memory (recall of three learned items plus learning of a name and address for a subsequent recall test). The verbal fluency component assesses semantic memory (i.e. participants are asked to name as many animals as possible) and phonological processing (i.e. to name words starting with letter P). The language component is important to evaluate aspects like speech articulation (when participants are asked to repeat words like: hippopotamus', 'eccentricity, 'unintelligible', 'statistician; reading of regular and irregular words) and comprehension (i.e. to

make associations and follow written instructions). Visuospatial testing consists of copying overlapping pentagons, drawing a wire cube and a clock face (Mathuranath et al., 2000). The major difference between the MMSE and ACE lies in that the later added more in depth measurements of memory, language and fluency.

Digit span

I also asked patients to carry out a digit span task to get a measure of patients working memory capacity (Engle, 2002). During the task, the experimenter read out loud a list of random numbers to the patients (one by one, at a constant rate of 1 digit per second) who were then required to repeat them as accurately as possible. The first 8 trials are forward digit condition and patients are asked to repeat the numbers in the same order as the experimenter read to them. Each repeated digit was annotated in the digital span task form. For each trial, a final score of 1 or 0 was given depending on the number of correct responses. More specifically, a final score of 1 was given in trials where patients accurately (i.e. in the same order) repeated the list of numbers read by the experimenter. A final score of 0 was given when patients failed to accurately repeat one or more digits. The last 7 trials corresponded to the backward condition and patients were instructed to repeat the numbers in the backward order as read by the experimenter and again responses were annotated in the digit span form. One block of trials for both forward (8 trials) and backward (7 trials) conditions were completed.

3.2.2. Results and Discussion

Table 4 illustrates the scores of each thalamic patient in the different cognitive domains assessed by the ACE battery and in the digit span task (Table 4). Patients performance in the ACE and in the digit span was high overall. Comparing the scores of thalamic patients with the normative data from age match individuals that is reported online (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006); I found that overall our patients were in the normal range. For example, in the study by Mioshi and colleagues (2006), individuals classified in the dementia group (n=142) had an ACE-R

total score of 65.4 which was not the case in any of our thalamic patients. Overall, performance of our thalamic patients, and in particular patients VL1 and VL2 who showed the highest impairment in WM guidance, was similar to the normative score of 84 observed in a large sample of healthy individuals with similar age to our patients (Mioshi et al., 2006). These results indicate that overall cognitive abilities of thalamic patients appear in the normal range and hence proceeded with further testing in paradigms assessing WM guidance of attention.

Tests	**Addenbrooke's Cognitive Examination (ACE)**						**Digit Span**	
Patients	Attention and Orientation	Memory	Fluency	Language	Visuo-spatial	Total ACE-R score	Forward	Backward
VL1	18/18	23/26	11/14	25/26	16/16	93/100	13/16	12/14
VL2	17/18	21/26	8/14	22/26	15/16	83/100	13/16	8/14
VL3	18/18	16/26	6/14	23/26	16/16	79/100	13/16	8/14
Pulv2	18/18	24/26	11/14	26/26	15/16	94/100	12/16	9/14
MD	18/18	22/26	9/14	24/26	11/16	84/100	11/16	4/14

Table 4. Thalamic patients scores in the Addenbrooke's Cognitive Examination (ACE) and Digit Span test.

3.3. Experiment 3: Re-testing ventrolateral thalamic patients in the more chronic stage

Here, I re-examined patients VL1 and VL2, six and tenth months after Experiment 1. Re-testing the patients in the chronic stage is important considering the nature of the deficit displayed in the acute stage, that is, relative to the control groups, these patients showed a 'reversed' memory guidance effect with significantly faster search RTs in neutral compared to valid trials.

In the present experiment, I used two different delays between presentation of the cue and the search display (short delay - 2000ms; long delay – 6000ms) to assess whether the absence of cueing effect could be improved by allowing the patients more time to use the cue. I hypothesized that longer delays should facilitate patients ability to more effectively consolidate the verbal feature cue in WM and restore memory guidance of attention.

3.3.1. Methods

Patients

Patients with lesions in the anterior VL nucleus of the left thalamus (VL1 and VL2) returned to Charing Cross hospital six and tenth months after the first-testing session in the acute stage.

Experimental Task and Procedure

Patients performed again the same memory test (Figure 5A) and visual search task (Figure 5B) in separate blocks, as in Experiment 1. The memory task contained 12 trials. The visual search task was similar to Experiment 1 (Figure 5B) with the exception that here the delay period between cue and search display was manipulated. There were two different delays (short delay - 2000ms, long delay – 6000 ms) with equal probability of occurrence and randomly selected. Patients completed two blocks of the visual search task each containing 64 trials (32 valid and 32 neutral, randomly presented).

3.3.2. Results

Assessing each thalamic patient performance against the control sample

The size of the validity effect (Neutral RTs – Valid RTs) differed between the control group of patients with lesions outside the thalamus and the two VL patients ($t(17) = 12.4$, $p < 0.0001$ – VL1; $t(17) = 13.3$, $p < 0.0001$ – VL2) (Figure 10). The same pattern of results was found relative to the non-stroke patients ($t(21) = 11.2$, $p < 0.0001$ – VL1; $t(21) = 11.9$, $p < 0.0001$ – VL2). Note once more that controls groups validity effects correspond to performance in original experiment 1. Both control groups have a positive validity effect whereas thalamic patients showed the same ´reversed´ validity effect. This is depicted below in Figure 10.

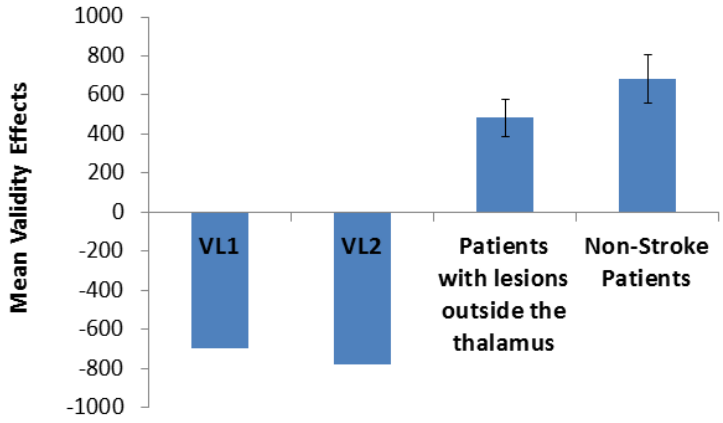

Figure 10. Mean Validity effects (Neutral RT – Valid RT) for each VL patient and for each control group (error bars depict SEM).

Individual univariate analysis of search performance

I conducted a 2 x 2 Univariate ANOVA to assess the effect of validity (valid, neutral) and delay (short delay – 2000ms, long delay – 6000ms) on the median search RTs. An effect of validity was present in a way that patients median search RTs were faster in neutral relative to valid conditions ($F(1, 123) = 63.5$, $p<0.0001$ – VL1; $F(1, 123) = 69$, $p<0.0001$ – VL2) (Figure 11). No effect of delay on patient VL1 was apparent ($F(1, 123) = 1.4$, $p = 0.2$ – VL1). Patient VL2 displayed an effect of delay ($F(1, 123) = 4.2$, $p = 0.041$ – VL2) such that the search RTs for valid and neutral conditions were faster during long delays relative to short delays (Figure 11). There were no significant interactions between validity and delay ($F(1, 123) = 0.9$, $p=0.3$ – VL1; $F(1, 123) = 0.74$, $p=0.4$ – VL2). Search accuracy was very high (VL1: 98% correct in both neutral and valid trials; VL2; Neutral: 98%, Valid: 100%). Memory accuracy was perfect (100%) and demonstrates that patients are able to commit the cues into WM.

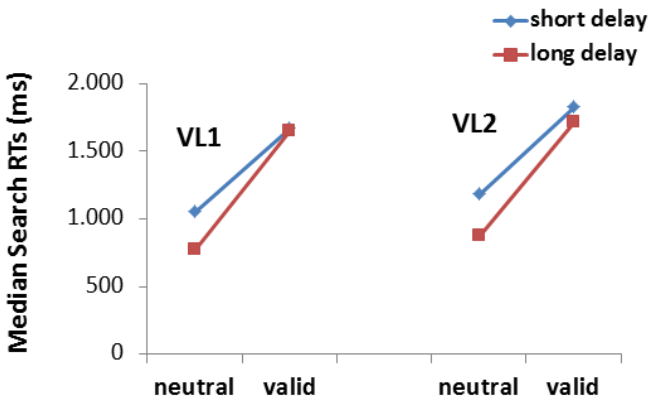

Figure 11. Search RTs as function of validity and cue-search delay in the VL patients.

3.3.3. Discussion

To re-test patients in the same WM guidance of attention paradigm was important to assess whether the deficit in WM guidance found in the acute stage was still present following a period of several months of recovery. I verified that impaired memory guidance was still present with faster search RTs in neutral compared to valid trials, replicating the 'reversed' validity effect found in the acute stage. The result further supports the importance of the more anterior VL regions of the thalamus in WM guidance of attention.

I also found that one of the VL thalamic patients (VL2) showed an effect of delay with faster search RTs during longer delays between cue and search target. Longer delays may lead to stronger preparatory mechanisms that facilitate responses to the search target (Corbetta & Shulman, 2002). However, the effect of delay was not replicated in the other VL patient.

3.4. Experiment 4: Effects of valid cueing with inclusion of subsequent memory test

In the previous experiments, the memory test was performed independently of the search task (i.e. in separate blocks) and subsequently VL patients might have not strongly committed the cue into WM even when they knew that the cue was valid for search. Here, each valid search trial included a memory test following the search response to ensure that patients committed the cue to WM.

3.4.1. Methods

Patients

These were the same as in Experiment 3.

Experimental Task and Procedure

The search task had again two conditions depending on the validity of the cue: valid and neutral, though unlike in Experiment 3, here, a memory test appeared by the end of each valid trial and patients had to report aloud whether the probed item (i.e. a colour word) matched or not the previous cue by responding "same" or "different" (Figure 12). Patients conducted one block of 60 trials (30 valid and 30 neutral, randomly presented) of the task.

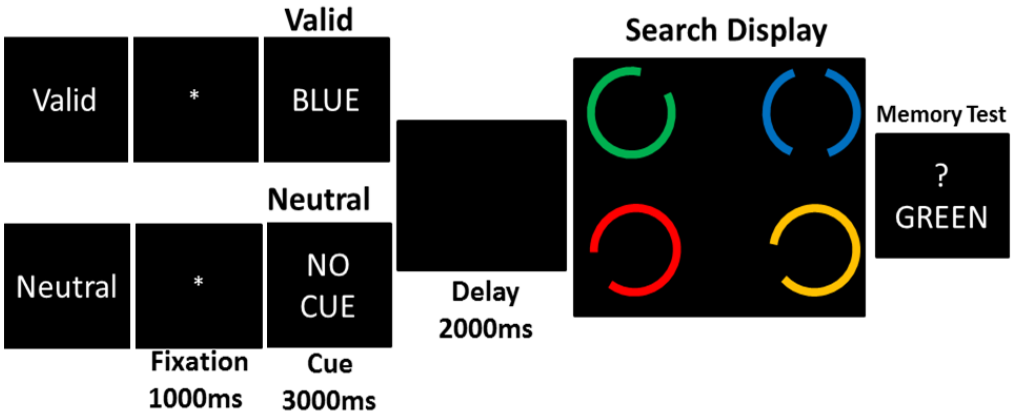

Figure 12. Illustration of trial sequences of display in the valid cueing task with inclusion of subsequent memory test. Note the memory test only appeared in valid trials, in which a colour word was presented to match the cue.

3.4.2 Results

Assessing each thalamic patient performance against the control sample

There was a significant difference in the size of the validity effects between the control group of patients with lesions outside the thalamus and the VL patients ($t(17) = 11.7$, $p < 0.0001$ – VL1; $t(17) = 11.6$, $p < 0.0001$ – VL2) (Figure 13). There were also significant differences between the

size of the validity effect of non-stroke patients and the VL patients (t (21) = 10.7, p < 0.0001 – VL1; t (21) = 10.6, p < 0.0001 – VL2). Once more controls groups validity effects correspond to performance in original experiment 1. The results demonstrate that validity effects are high in the control groups while the VL patients showed the same ´reversed` validity effect. This is depicted below in Figure 13.

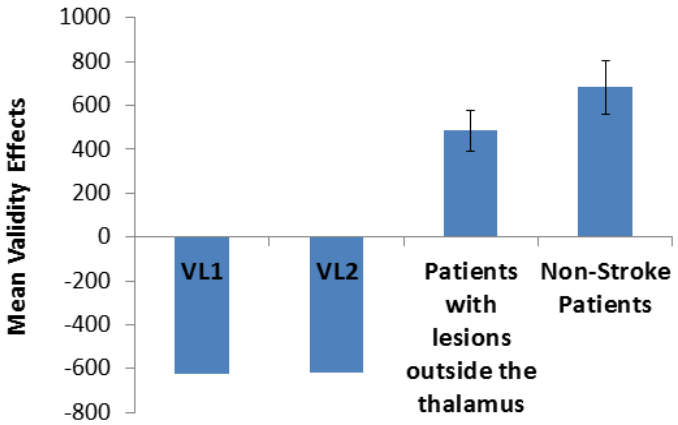

Figure 13. Differences in the size of the validity effects between thalamic patients and control groups (error bars depict SEM).

Individual univariate analysis of search performance

Statistical Univariate ANOVA revealed the same effect of validity on RTs (F (1,55) = 45.7, p<0.0001 – VL1; F (1,54) = 43.6, p<0.0001 – VL2) with faster search RTs on neutral relative to valid trials (Figure 14). Mean search accuracy in both patients was 100%. Mean memory scores were high (VL1 = 100%; VL2= 97%) which demonstrates that patients were able to commit the valid cue to memory.

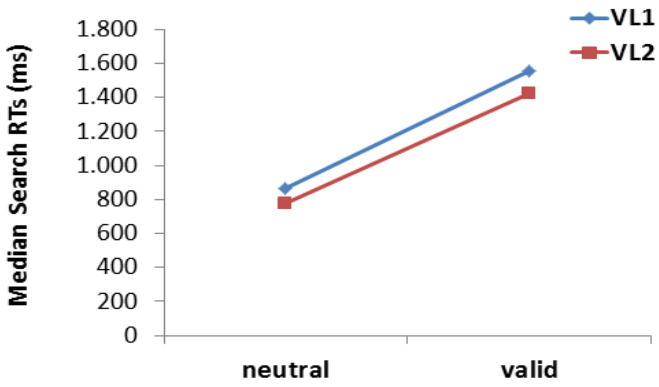

Figure 14. Median Search RTs as a function of validity (neutral, valid) in VL patients.

3.4.3. Discussion

The high level of memory performance shown by the VL patients indicates that they were able to commit the cue in WM. In accordance with previous experiments, thalamic patients VL1 and VL2 show 'reversed' cueing effect with search RTs significantly faster on neutral relative to valid trials. Therefore, the inclusion of a memory test following each valid search trials did not have any effect. Moreover, because analysis of search RTs were made for correct responses only in the later memory test then the above results show that deficits of WM guidance of attention cannot be explained by poor memory processing of the cue.

3.5. Experiment 5: Effects of invalid cueing with no memory test

So far, patients VL1 and VL2 demonstrated 'reversed' effects of memory guidance, as if their attention was driven away from the valid memory-matching information. This is consistent with the hypothesis that the patients inhibited memory-matching items. If patients indeed suppressed any memory matching information then the presence of invalid memory contents (i.e. when the memory item is irrelevant for search and it always specifies a distracter) should lead to facilitation of performance as their attention would be directed away from the distracter. Here, I used memory cues that were always invalid for search. Prior to each trial I cued participants as to whether the upcoming trial cue would be invalid or neutral, and instructed patients about these contingencies.

3.5.1. Methods

Patients

The same thalamic patients VL1 and VL2 returned to participate in the experiment.

Experimental Task and Procedure

Overall, the task was similar to that in Experiment 1 and 3 with the exception that valid trials were replaced by invalid trials. During invalid conditions, a verbal cue in form of a colour word always specified the colour of a search distracter (Figure 15). Patients completed three blocks of the visual search task each containing 40 trials (20 invalid and 20 neutral, randomly presented).

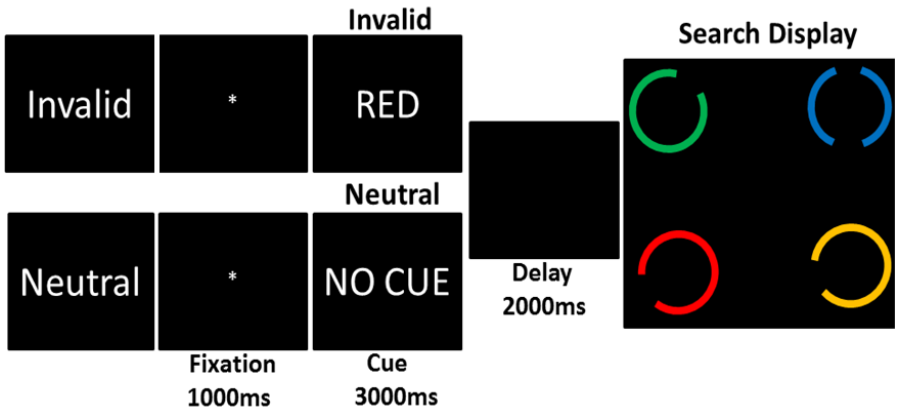

Figure 15. Illustration of trial sequences of display in invalid and neutral conditions.

3.5.2. Results

I conducted Univariate ANOVAs to assess the effect of invalidity (invalid, neutral) on search RTs. An effect of invalidity was observed such that patients search RTs were faster in invalid relative to neutral conditions ($F(1, 117) = 24.8$, $p<0.0001$ - VL1; $F(1, 118) = 17.9$, $p<0.0001$ – VL2) (Figure 16). Mean search accuracy was high (VL1 – Invalid: 100%, Neutral: 98%; VL2 – Invalid and Neutral: 100%).

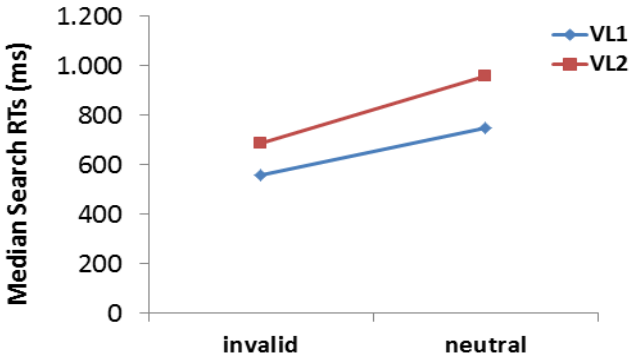

Figure 16. VL patients median search RTs as a function of cue invalidity (invalid, neutral).

3.5.3. Discussion

The results indicate that patients search responses were faster in invalid relative to the neutral conditions. This result suggests that the presence of invalid cues in the search display now facilitated search performance, confirming the presence of 'reversed' cueing effects in these patients. This pattern of results accords with the hypothesis that VL lesions lead to inhibition of any memory-matching information in the search display. Because the memory-matching information in this experiment reappeared as a distracter, its inhibition would lead to attention being directed away of the distracter hence leading to facilitated search performance.

3.6. Experiment 6: Re-testing of thalamic patients in an invalid cueing task with subsequent memory test

Here, I tested thalamic patients in the same invalid and neutral conditions as in previous experiment, but now with inclusion of a memory test to ensure that the cues were held in WM throughout the trials. As noted, the typical finding shown by healthy volunteers in similar paradigms where the memory content is always invalid for search is impaired search performance in invalid trials compared with a neutral condition (Soto et al., 2005, 2007b), which demonstrates an automatic bias of attention by stimuli matching the contents held in memory. I asked whether the VL patients still inhibit memory-matching information that is explicitly committed to WM.

A further distinction from Experiment 5 is that here patients were never informed of whether a following trial would be invalid or neutral (they were never given previous information in form of a word "Invalid" or "Neutral" as in experiment 5). I wanted to establish whether suppression of memory matching information could still occur even when patients cannot anticipate the presence of a forthcoming invalid trial.

I tested VL patients and healthy controls in this experiment, along with the pulvinar patient (Pulv2) and the MD thalamus patient. The inclusion of these patients acted as a further control condition to address that it is the VL patients in particular who show a 'reversed' memory cueing effect.

3.6.1. Methods

Patients

I tested the three patients with lesions in the anterior VL thalamus (VL1, VL2 and VL3) and the two other thalamic patients with lesions in the pulvinar (Pulv2) and medial dorsal nuclei (MD). I also tested a group of 11 age-match healthy controls (8 Males, 3 Females; age range: 45-65).

Experimental Task and Procedure

The current experiment had some differences in relation to Experiment 5 using invalid cueing with no subsequent memory test. Each trial started with a fixation point for 1000 ms, followed by a verbal cue in form of a colour word for 3000ms that could randomly on half of the trials reappear as a distracter in the search display (invalid conditions) while in the other half it did not reappear (neutral conditions) (Figure 17). Therefore, patients would never know whether a given trial would be invalid or neutral. Following the search display, on a trial by trial basis, a memory test was presented and patients had to report aloud whether the single item (in form of a colour word) matched or not the previously displayed verbal cued colour word saying "same" or "different". The experimenter then pressed a response key ("s" for same and "d" for different").

Patients had unlimited time of response in the memory test (Figure 17). Patients conducted training trials until they were ready to start the experimental trials. VL1 and VL2 performed 4 experimental blocks of 40 trials each. VL3 conducted the experiment in three separate days and performed 16 blocks of 40 trials whereas Pulv2 and MD patients performed 3 blocks of 40 trials. Invalid and neutral trials were randomly presented.

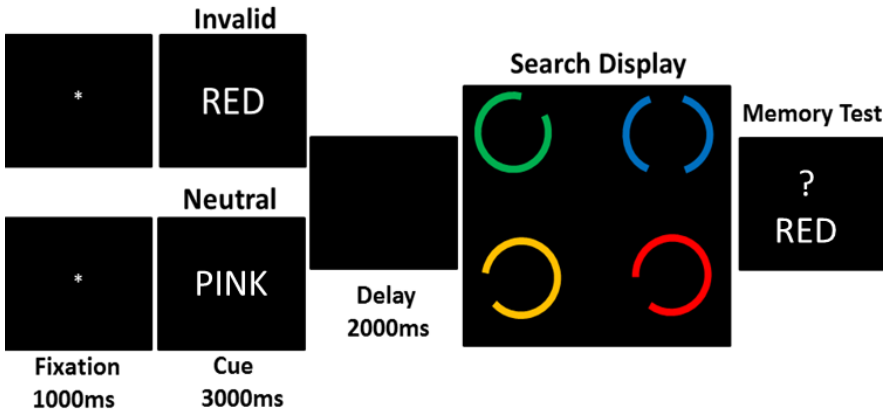

Figure 17. Illustration of the trial sequence of displays for invalid and neutral conditions.

3.6.2. Results

Patients search accuracy was high (VL1 and VL2 = 100% both conditions; VL3 = 99 % both conditions; Pulv2= 100% both conditions; MD = Invalid: 98%, Neutral: 100%) and memory accuracy was also high (Figure 21B). This shows that patients responded effectively to the search targets and were able to commit the cue in memory.

Group analysis

I computed the cueing effect (Invalid Median RT – Neutral Median RT) for the thalamic patients (n=5) and healthy controls (n=11) and then performed an independent sample t-test. The results show that as a group, thalamic patients (n=5) had a lower invalidity cueing effect relative to the control group of healthy controls (n=11) ($t(26) = -3.38$, $p= 0.002$). This is depicted in below in Figure 18.

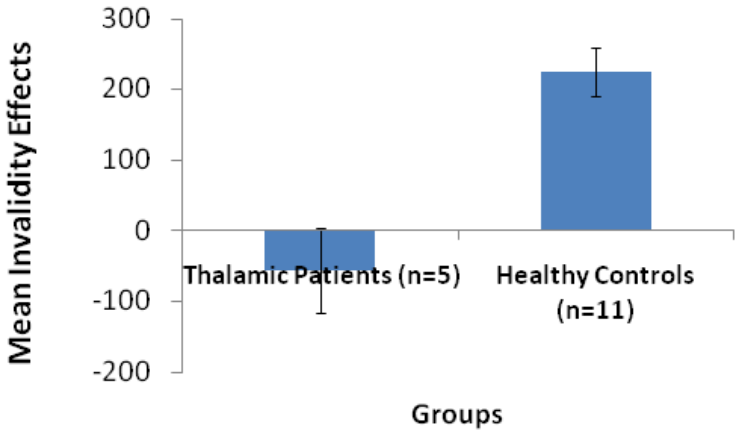

Figure 18. Illustration of the differences in the size of the invalidity effects between the group of thalamic patients and the group of healthy controls (error bars depict SEM).

Assessing each thalamic patient performance against the controls sample

I found significant differences between the size of the invalidity effect in the group of healthy controls and the invalidity effect from each of the thalamic patients VL1 ($t(10) = 14,5$, $p < 0.0001$), VL2 ($t(10) = 9.1$, $p < 0.0001$), VL3 ($t(10) = 6.7$, $p < 0.0001$), Pulv2 ($t(10) = 6.9$, $p < 0.0001$) and MD ($t(10) = 3.9$, $p = 0.003$).

Overall, the above results show that the size of the invalidity effect of individual thalamic patients was lower relative to the invalidity effect of the healthy control group. This is depicted below in Figure 19. I note that patients VL1 and VL2 actually displayed a negative invalidity effect whereas VL3 and Pulv2 patients have an invalidity effect close to zero consistent with lack of cueing effect. Patient MD has a positive invalidity effect however this was still lower in comparison to healthy controls (Figure 19).

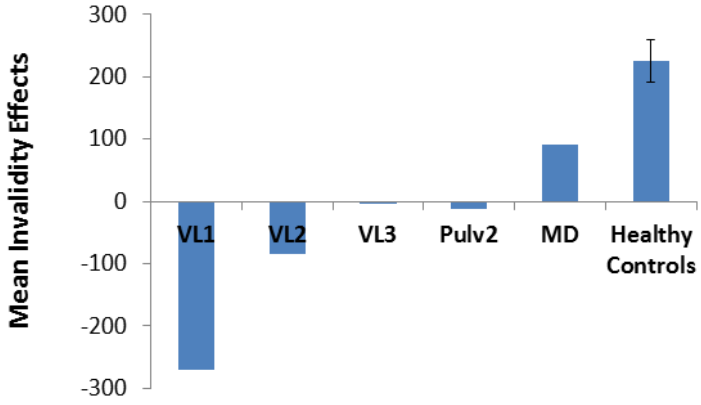

Figure 19. Illustration of the differences in the size of the invalidity effects between individual thalamic patients and healthy controls (error bars depict SEM).

Individual univariate analysis of search performance

These analyses revealed `reversed` effects of cue invalidity in patient VL1 such that search RTs were faster in invalid relative to neutral condition. Patient VL2 showed a similar pattern which approached significance. Patients VL3 and Pulv2, showed no invalidity effects on search RTs (Table 5 and Figure 20A). Finally, patient MD showed an effect of invalidity with slower search RTs in invalid relative to the neural condition (Table 5 and Figure 20A; Figures 20A and 20B illustrate the individual search RTs). Despite this result, I showed before that the effect of invalid cues in patient MD was lower in comparison to controls.

				Median Search RTs (ms)	
Patients	F	Df	P	Invalid	Neutral
VL1	45.5	1,153	0.0001	792.5	1062
VL2	2	1,155	0.16	882.50	967
VL3	0.001	1,618	0.98	1168	1171
Pulv2	0.38	1,100	0.54	943	956
MD	9.6	1,106	0.002	1091	999

Table 5. Summary of results for univariate statistical analysis.

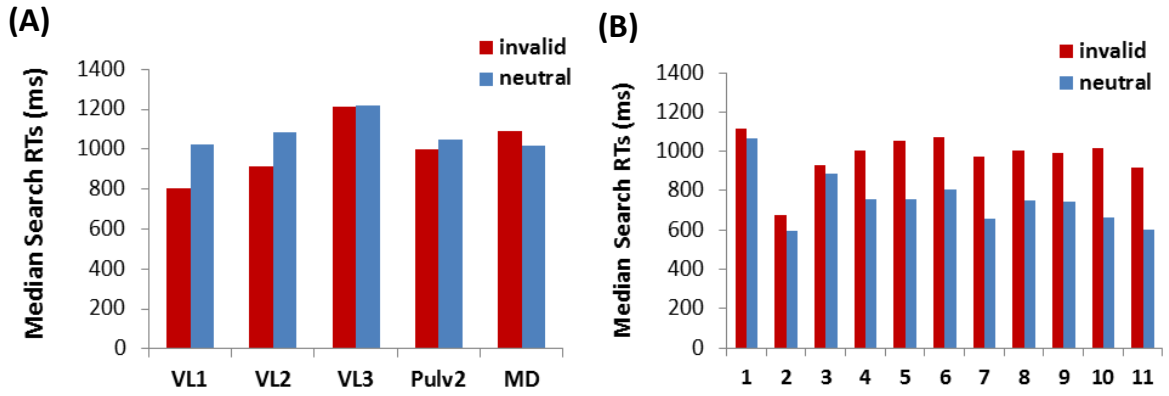

Figure 20. (A) Median Search RTs as a function of cue invalidity in the thalamic group and (B) in the healthy controls.

Memory performance

An independent sample t-test comparing the memory accuracy of thalamic patients and the controls showed that as a group, thalamic patients (n=5) appeared to display lower memory accuracy in comparison to the control group of healthy controls (n=11) (t (14) = -2.6, p= 0.019) (Figure 21A). I note however that the two VL patients showing the 'reversed' invalidity effect had comparable level of memory performance relative to controls while the Pulv2 and MD patients showed the lowest scores (see Figure 21B and Table 6). Critically, we only analysed search trials when the response in the recognition test was correct. Together, these results indicate that impaired memory guidance across the thalamic group cannot be accounted for by poorer memory per se and the 'reversed' invalidity effect shown by the VL patients arose despite the level of memory performance in these patients being near ceiling.

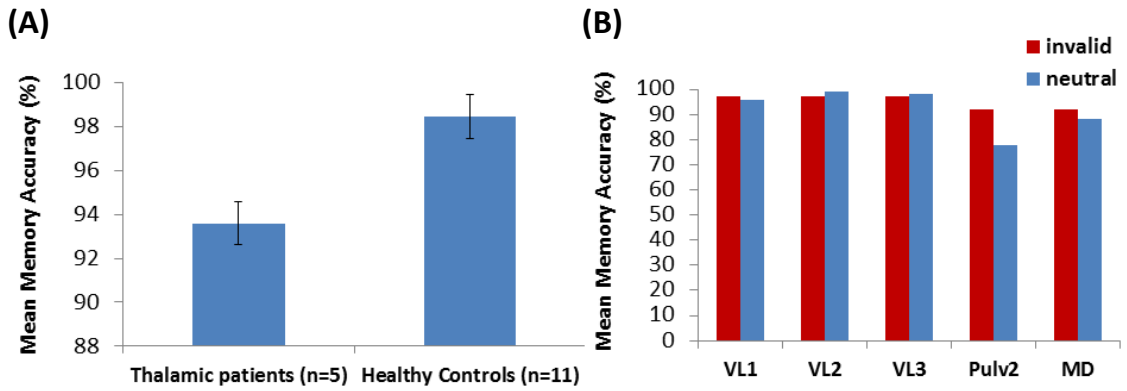

Figure 21. (A) Memory performance of thalamic patients and healthy controls (error bars depict SEM) (B) Mean memory accuracy of individual thalamic patients in invalid and neutral trials.

	Mean Memory Accuracy (%)	
Patients	Invalid	Neutral
VL1	97	96
VL2	97	99
VL3	97	98
Pulv2	92	78
MD	92	88

Table 6. Mean memory accuracy of patients in invalid and neutral trials.

3.6.3. Discussion

In this experiment, the WM cue was irrelevant and even misleading for search as it always specified the colour of a search distracter. Healthy controls showed slower search RTs in the invalid relative to the neutral trials in line with evidence for automatic guidance of attention by the contents of WM (Soto et al., 2005, 2007b). By comparison, the thalamic patients as a group did not show evidence of automatic capture of attention by WM.

Importantly, VL patients (VL1 and VL2) now displayed faster search RTs in invalid relative to neutral conditions – a 'reversed' invalidity effect- replicating here the results from Experiment 5. Further the pattern of memory performance indicates that the 'reversed' effect cannot be accounted for by poor memory skill. These findings strongly suggest that VL patients automatically suppress any memory matching information even when this is explicitly committed to memory.

3.7. General Discussion

Taken together, the psychophysical analysis of the human participants with discrete focal ventrolateral (VL1, VL2 and VL3), pulvinar (Pulv1 and Pulv2) and medial dorsal thalamic lesions (MD) lends strong support to the idea that the thalamus plays a critical role in promoting WM guidance of visual attention.

In valid cueing conditions, I observed that two VL patients (VL1 and VL2) show a 'reversed' effect of the memory cue on attention, with faster search RTs in neutral relative to valid trials. Patient VL3 search RTs were faster in valid relative to neutral trials but the cueing effect was lower in comparison to the control groups suggesting that the thalamic lesion also impaired memory guidance. Note once more that while patients VL1 and VL2 were tested in the acute stroke phase in the first Experiment 1 and then more chronically up to one year later in the subsequent Experiments 3, 4, 5 and 6 patient VL3 took part in the first Experiment five-years after stroke. Hence, due to the longer recovery period in VL3, it is likely that brain compensatory mechanisms may have operated to regain some of the functional loss in this patient. I reiterate however that the size of the cueing effect on search was significantly weakened in VL3 relative to the controls both in the presence of relevant valid cues and also in the presence of consistently invalid WM cues.

The remaining thalamic patients (Pulv1, Pulv2 and MD) show very similar search RTs between valid and neutral trials. A cueing/validity effect close to zero implies that there is no effect of the valid cue on search. In contrast, the control groups show clear cue validity effects on search and hence search RTs are faster in valid relative to neutral conditions.

As noted, the typical finding shown by healthy volunteers in invalid cueing conditions (i.e. where the cue is search-irrelevant and specifies the colour of a search distracter) is slower search performance in invalid trials compared with a neutral condition (Soto et al., 2005, 2007b), which demonstrates an automatic bias of attention by stimuli matching the contents held in memory. VL

thalamic patients VL1 and VL2 showed a 'reversed' invalidity effect with faster search responses in invalid relative to neutral conditions. This demonstrates that both patients either show no capture from the irrelevant WM cue during search or automatically inhibit the influence of the cue on search. Thalamic patients VL3 and Pulv2 showed minimal invalidity effects (non-significant differences between invalid and neutral RTs). The MD patient showed an effect of invalid cueing in the direction of the healthy controls (i.e. RTs Invalid < RTs Neutral) but this effect was smaller in comparison to the control population. This suggests that thalamic lesion in MD also reduced the effect of capture from memory matching information.

The sections below deliver an account of why thalamic patients do not show WM guidance of attention and how they differ from the control population, providing a behavioural and neural perspective.

Thalamic deficit is not due to poor memory encoding /maintenance

One could argue that the inability of thalamic patients to use the WM cue to guide search is due to poor memory encoding. The results go against this idea because of the high patient scores in the memory tests. Moreover, in Experiments 4 and 6, the analysis of search RTs were made for correct responses in the memory test only. Hence that lack of cueing effects cannot be explained by poor memory.

Different neural regions might have been recruited for encoding of the memory cue. Thalamic patients might have used subvocal rehearsal strategies (i.e. verbally rehearsing the name of the cued colour) to maintain the verbal cue 'online' in WM (Baddeley, 2003; Smith et al., 1998). Neural regions correlated with subvocal rehearsal strategies during the maintenance and manipulation of verbal information have been associated with posterior parietal cortex and regions involved in speech production such as Broca's area 44 around the inferior frontal gyrus, and also premotor area and supplementary motor area (Baddeley, 2003; Smith et al., 1998). These areas, which were intact in our patients, may well have been implicated in the maintenance of the cue in

WM.

Thalamic deficit is not due to low alerting or low levels of conscious awareness

The pattern of connectivity between the central thalamus (i.e. the intralaminar nuclei, medial dorsal thalamus, ventral-anterior thalamus, ventral-lateral thalamus, and inferior pulvinar) and the cortex suggest that many neurons within the central thalamus may serve the general purpose of supporting the brain dynamics associated with goal-directed behaviours and conscious awareness (Schiff, 2008). Regions associated with the regulation of arousal are located around the intralaminar (ILN) nuclei and medial thalamus (MD) (Ward, 2011). Lesion studies (Exner, Weniger, & Irle, 2001; Wallesch, Kornhuber, Kunz, & Brunner, 1983) have shown that following central thalamic lesions (ILN and MD) goal-directed behaviour is impaired. This has been attributed to disruption of thalamo-cortical pathways controlling conscious awareness and sensory integration, in particular, disruption of the circuitry involving the central thalamus (ILN and MD thalamus) with the prefrontal cortex and back to the thalamic reticular nucleus (TRN) (Ward, 2011).

Convergent evidence from lesion and neuroimaging studies suggest that the thalamus regulates the demands of effort and vigilance that are required for attention through feedback connections with cortical frontal and parietal regions (Exner et al., 2001; Kinomura, Larsson, Gulyas, & Roland, 1996; Paus, Zatorre, Hofle, Caramanos, Gotman, Petrides, & Evans, 1997; Portas et al., 1998; Schiff, 2008; Wallesch et al., 1983). One such area is the VL nucleus of the thalamus which has been associated with the regulation of arousal necessary to execute attention tasks (Exner et al., 2001; Portas et al., 1998). However, a low level of awareness cannot explain the WM guidance deficit in our thalamic patients because search RTs were fast and similar to the search RTs of the control population which indicates that patients had adequate levels of alertness, vigilance and concentration during performance.

Thalamic lesions may impair the state of memory representations for the control of attention

I propose that our thalamic patients can attend and maintain the cue in WM but they may fail to represent it in a way that facilitates top-down guidance of attention. According to Oberauer (2002), WM representations may be distinguished by their state of accessibility. Representations can be "passively" integrated within a network of long-term memory that can be used for later recall but not for immediate ongoing cognitive processes; or within the central region of direct access which holds a limited amount of information ready to be used for ongoing cognitive processes (Oberauer, 2002). Within the central region of direct access it is the focus of internal attention which can hold a single item at any one time for ongoing relevant processing. I propose that thalamic lesions may lead to poor integration of the WM content with the target in the focus of internal attention, leading to impaired WM guidance.

Different but much related concepts have been given for the different states of WM representations, such as, active and accessory WM states with only the active WM state influencing perception and visual processing (Olivers et al., 2011). It has been shown that in a typical WM guidance of attention paradigm the number of WM items that can influence attention appears to be only one. This item is also known as the search template (Downing & Dodds, 2004; Olivers et al., 2011). Under higher WM load conditions (when participants have to hold multiple items in memory) there is higher competition between neural representations, reducing the effect of WM representations on attention (Bays & Husain, 2008; Soto et al., 2012a; Soto & Humphreys, 2008b).

According to this principle, when a memory item is conferred the state of a search template it gains access to the sensory system through feedback connections from more anterior frontal to more posterior occipito-temporal areas that bias attention toward matching targets (Olivers et al., 2011; Soto et al., 2012a).

Therefore, the absence of cueing effects on search in our thalamic patients could be the result of a poor integration of the memory cue in the central region of direct access in WM and the focus of internal attention, therefore limiting the influence of the cue on attention during the search. However, the cue is still held in memory perhaps in a more passive state outside the WM zone of direct access, as indicated by the high memory scores.

Thalamic lesions may influence WM guidance by impairing mechanisms of goal-directed attention and eye movements

My main hypothesis establishes that thalamic patients fail to represent the memory cue in the focus of WM and hence fail to integrate the cue information with the processes that guide search to the target. Patients VL1 and VL2 actually showed 'reversed' cueing effect (from valid and also from invalid cues), which suggests that, in their particular case, attention towards memory matching information is inhibited or suppressed. In the remaining thalamic patients with lesions in the ventrolateral (VL3), pulvinar (Pulv2) and medial dorsal nuclei (MD) the memory cueing effect was merely reduced relative to the controls.

How can the 'reversed' memory-validity effect occur in patients VL1 and VL2?

As noted, the impaired use of the memory cues cannot be explained by poor ability to retain the cue information in memory. That VL patients showed improved search performance in the presence of a search distracter matching the memory cue also indicates that the memory presentation was indeed held 'online' so that attention could be directed away from the memory-matching distracter and so improve performance. The memory data therefore suggest that VL thalamic lesions impair how memory information is used to control attention. Earlier, I proposed that VL patients may fail to represent the memory contents in a state that promotes top-down guidance of attention. The presence of 'reversed' validity effects suggests that VL lesions can trigger inhibition of matching signals between the contents held in memory and the incoming perceptual

input, such that attention is directed away from memory-matching stimuli (see below).

Thalamic lesions might have disrupted key cortico-thalamic circuits that are critical for the control of saccades during attention tasks (Sommer & Wurtz, 2006; Tanaka & Kunimatsu, 2011). The VL nucleus of the thalamus projects to the FEF (Mesulam, 1990) and evidence from both monkey (Tanaka, 2006; Tanaka, 2007; Tanaka & Kunimatsu, 2011) and human studies (Bellebaum et al., 2005; Kronenbuerger et al., 2010) suggest that the VL nucleus of the thalamus controls the production of saccades in regions of the cortex (e.g. FEF). In the fMRI study by Soto and colleagues (2007b) WM guidance of attention correlated with activity in a network comprising the MD, VL and the pulvinar nucleus of the thalamus and the SFG around the FEF. The thalamus while controlling the allocation of attention according to the validity of the cue might have recruited the SFG for directing of covert attention and saccades towards relevant information held in WM. Thus, disruption of VL-FEF circuitry (Kronenbuerger et al., 2010; Mesulam, 1990; Tanaka & Kunimatsu, 2011) in thalamic patients VL1 and VL2 might have produced inhibition in the over direction of attention towards matching information held in WM. This means therefore that there follow costs in performance during valid conditions (when attention should be directed towards relevant memory matching information) and performance improvements during invalid conditions (when the memory matching information was irrelevant for search and therefore it needed to be ignored).

Furthermore, anterior VL nuclei also forms part of a network comprising the hippocampus, fornix, mammillary bodies, retrosplenial and posterior cingulate cortex that support for recollective aspects of memory (i.e. ability to recall previous events vividly) rather than familiarity-based aspects of memory (Aggleton, Mara, Vann, Wright, Tsanov, & Erichsen, 2010; Vann, Aggleton, & Maguire, 2009). Disruption of this circuit as a result of thalamic stroke may impair the ability of patients to represent the memory input in a “vivid” state so it can be used to control attention.

In sum, VL lesions can lead to widespread damage of attention circuits (connecting with regions in superior frontal and PFC) and memory circuits (connecting with regions of the

hippocampus, mammillary bodies, posterior cingulate) that are critical for memory-based control of selection. This should explain why VL patients display higher deficits of WM cueing in comparison to thalamic patients with damage in distinct nuclei.

Patient VL3 may also have disrupted this circuitry but did not show inhibition of attention towards matching memory items. However, as noted, VL3 took part in the first Experiment five-years after stroke. Hence, due to the longer recovery period in VL3, it is likely that brain compensatory mechanisms may have operated to regain some of the functional loss.

In addition, I found that pulvinar lesions reduced the influence of memory contents on attention. Evidence from both neuroimaging (i.e. fMRI) and lesion studies support a prominent pulvinar's role in control processes of filtering distracter information and there is also evidence of a role of the pulvinar in the deployment of attention (Snow et al., 2009; Strumpf, Mangun, Boehler, Stoppel, Schoenfeld, Heinze, & Hopf, 2013; Ward et al., 2002). Even though our study was not specifically devised to test this idea, the results are consistent with a pulvinar role in the orientation of attention, namely, from the contents held in memory. A filtering account would have predicted here that pulvinar patients ought to show exacerbated distraction by the stimulus matching irrelevant contents held in memory. As noted, the pulvinar is strongly linked to parietal regions (Shipp, 2003, 2004) involved in WM and attention (Corbetta & Shulman, 2002; Todd & Marois, 2004) and feeds-back to visual regions; hence the pulvinar is in a good position to control attention by the contents held in WM. Damage to pulvinar nuclei in patients Pulv1 and Pulv2 may have disrupted related thalamo-cortical circuits that are critical for promoting top-down orienting of attention by the contents of WM.

Taken together, the findings provide novel causal evidence that the thalamus, in particular its anterior VL part, serves the general purpose of guiding attention from information held in WM.

Chapter 4: The role of the dorsal frontal cortex on the interplay between WM and attention: a transcranial direct current stimulation (tDCS) study

4.1. Chapter Introduction

Previous research has shown that the dorsal frontal cortex (e.g. SFG, FEF, DLPFC) in humans is important for goal-directed attention, as part of a frontoparietal network. For example, the FEF along with the intraparietal sulcus (IPS) shows increased response with the presentation of spatial cues that specify the location of a subsequent target (Corbetta et al., 1998; Corbetta & Shulman, 2002).

More recently, the role of the SFG (an integral part of the dorsal frontal cortex) has been attributed to automatic WM guidance of attention. As reviewed earlier, fMRI work by Soto and colleagues (2007b) showed that the SFG displayed sensitivity to the reappearance of WM information during search even when the WM content provided no relevant information to find the search target. Disruption of the SFG by means of rTMS impaired guidance of attention from feature (colour) information held in WM (Soto et al., 2012b).

Critically, the SFG connects to the VL, MD and pulvinar nuclei of the thalamus (Mesulam, 1990; Shipp, 2003, 2004; Sommer & Wurtz, 2006) and I showed that lesions to these areas can impair WM guidance of attention. Therefore, the SFG is in a good position to form part of a frontothalamic network in controlling orienting of covert and overt attention by information held in WM (Shipp, 2003, 2004; Sommer & Wurtz, 2006; Soto et al., 2007b; Soto et al., 2012b; Tanaka & Kunimatsu, 2011). For all of the above reasons, in Chapter 4 I investigated in more detail the contribution of the dorsal frontal cortex (e.g. SFG) on the interplay between WM contents and attention.

4.2. Experiment 7: Effects of frontal tDCS in WM-guidance of attention under high load (2 items) and low load (1 item) WM conditions

Effects of tDCS on behaviour seem to depend on the polarity of stimulation. Anodal tDCS causes a depolarization of the resting-membrane potential and increases the firing rates of cortical neurons in the brain region located under the stimulating electrode, whereas cathodal tDCS has the opposite effect, causing a hyperpolarisation of the resting-membrane potential and a decrease in the firing rates of the neurons (Nitsche, Cohen, Wassermann, Priori, Lang, Antal, Paulus, Hummel, Boggio, Fregni, & Pascual-Leone, 2008; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011) (see below Figure 22 for illustration of the tDCS). Furthermore, the effects of tDCS can outlast the period of stimulation by several minutes or even hours (Zaehle et al., 2011). It has previously been shown that anodal but not cathodal simulation to the DLPFC enhances WM performance (Fregni, Boggio, Nitsche, Bermpohl, Antal, Feredoes, Marcolin, Rigonatti, Silva, Paulus, & Pascual-Leone, 2005; Zaehle et al., 2011).

Figure 22. Illustration of tDCS stimulation. The blue electrode represents cathodal (negative) stimulation and the red electrode represents the anodal (positive) stimulation.

I delivered transcranial direct current stimulation (tDCS) to the dorsal frontal cortex (e.g. SFG) of a group of healthy volunteers and tested whether the effect of frontal-tDCS on WM guidance could be modulated by the level of WM load. As noted, previous evidence suggests that the SFG is involved in automatic WM guidance of attention (Soto et al., 2007b; Soto et al., 2012b). The hypothesis I tested is that tDCS may modulate WM guidance mainly under conditions were WM is stressed (holding 2 items in WM).

Prior investigations have shown that when WM load is stressed (when participants have to hold several items in memory) attentional guidance from the WM contents decreases, likely due to mutual suppression between memory items that compete for neural resources (Bays et al., 2008; Soto et al., 2012a; Soto & Humphreys, 2008b). I predicted that anodal frontal-tDCS may increase the pool of neuronal resources available for WM operations (Fregni et al., 2005; Soto et al., 2012a; Soto & Humphreys, 2008b; Zaehle et al., 2011) and hence reduce the competition between multiple items maintained in WM, leading to increased WM guidance of attention.

4.2.1. Methods

Participants

A total of eight healthy volunteers (5 Males, 3 Females; age range: 21- 29) were recruited to participate in the experiment. None of the participants had prior history of neurological or psychiatric disorders. All participants provided informed written consent and were economically rewarded for their participation. The study was approved by the West London Research Ethics committee.

Experimental Task and Procedure

Before starting the actual tDCS experiment participants received clear task instructions and performed some training trials until they felt comfortable with the task. At the beginning of each trial, participants received an instruction displayed in the computer screen (i.e. “Remember 1 item” or “Remember 2 items”) for 1000ms (Figure 23). This was followed by a fixation dot for 500 ms and by a cue display for 200 ms consisting of either one coloured shape (low load condition) or two coloured shapes (high load condition) presented on a grey background. Each of the presented stimuli was unique in colour and shape and was drawn from 1 of 5 possible shapes (square, triangle, diamond, circle, or hexagon) and 1 of 5 possible colours (red, blue, green, yellow, or pink). After the cue display, a fixation dot (500ms) was presented followed by the search display (500ms). The search

display was composed of 2 coloured shapes, each containing a black line, which could either be tilted to the left or to the right (i.e. the search target), or could be a vertical distracter line. There were two types of trials in which the validity of the memory cues for search varied: in valid trials, the target (tilted line) was surrounded by one of the 2 items held in WM (high load condition) or by the single item held in WM (low load condition). In invalid trials, the pre-cued object was re-represented in the search display but contained a distracter vertical line instead of the search target (Figure 23). The 2 trial types occurred randomly and with equal probability. The search display remained onscreen for 500ms. Participants indicated the orientation of the target (right tilted or left tilted) by means of button press during a time window of 1.5 seconds since the onset of the search display. A memory test followed the search response. A single colour shape was presented and participants were required to match it to the cue display. In responding to the memory item, participants had to indicate (via button pressing) whether or not the memory item matched both the colour and the shape of any of the 2 items held in memory (in the high-load case) or whether it matched the single item held in memory (in the low-load case). Participants had an unlimited time window to respond in the memory test and they were instructed to try to be as accurate as possible in the memory test. Each participant performed one block of the task containing 127 trials in which validity and load levels were selected randomly on each trial (Figure 23).

tDCS

I localized the site of stimulation based on the 20-30 EEG system. I first determined the location of the cortical area corresponding to F3 which is known to correspond well with the left dorsolateral prefrontal cortex (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003). I then placed the anterior end of the stimulating electrode in the F3 region so that the stimulating area of the electrode covered part of the left dorsolateral prefrontal cortex extending more posteriorly towards the left SFG. The reference electrode was located in the right arm contralateral to the site of stimulation. Participants were required to perform the task in two different sessions (anodal vs.

cathodal) each separated by at least 24 hours. During each session, participants were stimulated with either anodal or cathodal stimulation for 15 minutes with a current of 1.5 mA. The order of stimulation was counterbalanced across participants. After stimulation, participants conducted a block of 127 trials of the task (Figure 22) that lasted around 10 minutes.

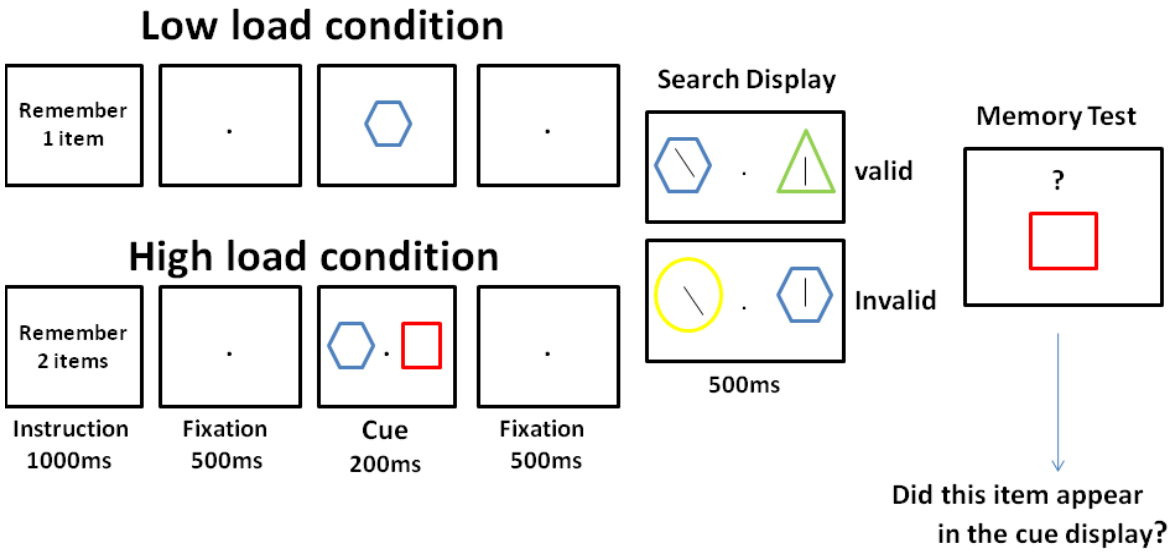

Figure 23. WM guidance of attention paradigm under varying levels of WM load: low load (1 item) and high load (2 items).

4.2.2. Results

Only trials with correct responses in the search task and memory test were included in the analyses of search RTs. I conducted a 2 (WM load: high load, low load) X 2 (validity: valid, invalid) x 2 (type of stimulation: anodal, cathodal) repeated measures ANOVA on the median search RTs. There was no effect of load ($F(1, 7) = 1.22$, $p=0.306$). There was an effect of validity ($F(1, 7) = 18.5$, $p=0.004$) such that RTs were faster in valid relative to invalid conditions (Figure 24A). There were no main effects of tDCS on the median search RTs ($F(1, 7) = 0.5$, $p=0.5$) such that overall RTs did not differ across anodal and cathodal conditions. There was no interaction between the load factor and tDCS ($F(1, 7) = 1.27$, $p=0.29$) and no interaction between validity and tDCS ($F(1, 7) = 0.17$, $p=0.68$). There was however an interaction between load and validity ($F(1, 7) = 17.2$, $p= 0.004$), reflecting that the size of the validity effect (Invalid RT – Valid RT) was bigger in the low than in the high load.

In other words, the validity effect reduced as load increased (Figures 24A and 24B). Critically, for the aims of the experiment, there was a significant interaction between load, validity and tDCS ($F(1, 7) = 6.24$, $p = 0.039$). This interaction effect showed that under high WM load conditions, the size of the validity effects increased after anodal relative to cathodal stimulation (Figures 24A and 24B). To assess this interaction effect I computed a score reflecting the reduction in validity effect (Invalid RT – Valid RT) from the low load to the high load condition (validity effect in low load – validity effect in high load) and assessed whether it was affected by tDCS. For that, I performed a paired t-test to assess differences in this score as a function of cathodal vs. anodal stimulation. There was a significant difference ($t(7) = 2.5$, $p=0.039$) showing that after cathodal stimulation the validity effects decreased in 69.4 ms from the low to the high load condition; however, after anodal stimulation the validity effects decreased only in 39.06 ms (Figure 24C). This shows that the cost produced in the strength of the validity effects as a result of increasing WM load was minimized after anodal stimulation relative to cathodal stimulation (Figures 24B and 24C).

In addition, I also performed a similar 2 x 2 x 2 repeated measures on search accuracy. Only the effect on validity was significant ($F(1, 7) = 12.4$, $p = 0.01$) such that search accuracy was higher in valid conditions (98%) compared to invalid conditions (94%). No effects of load ($F(1, 7) = 1.15$, $p = 0.32$) and tDCS ($F(1, 7) = 0.13$, $p = 0.73$) were present on search accuracy. Also no two-way interactions between load and validity ($F(1, 7) = 0.26$, $p=0.62$), validity and tDCS ($F(1, 7) = 0.085$, $p=0.78$), load and tDCS ($F(1, 7) = 2.32$, $p=0.17$) was apparent on mean search accuracy. There was also no interaction between load, validity and tDCS ($F(1, 7) = 0.14$, $p=0.72$).

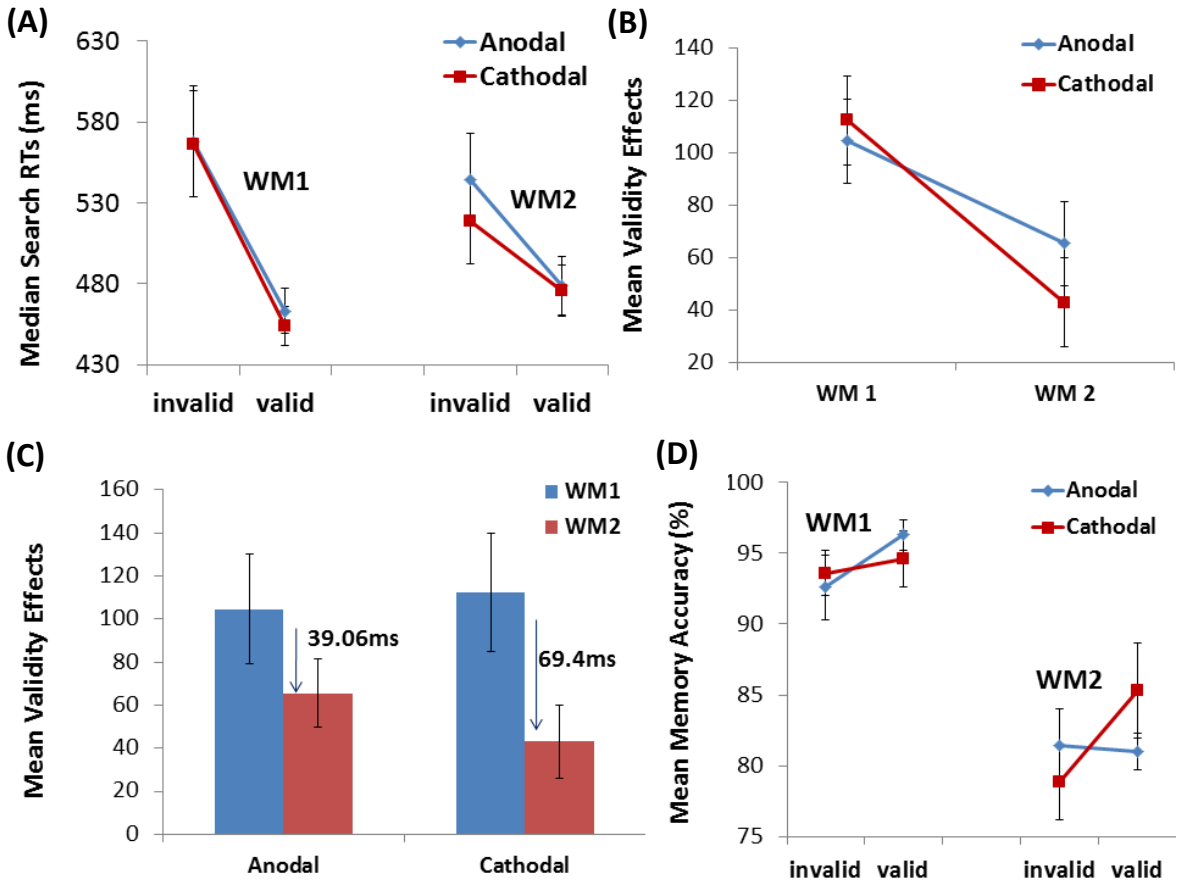

Figure 24. (A) Median search RTs as a function of load (WM1, WM2), validity (invalid, valid) and type of stimulation (anodal, cathodal) (B) Validity effects (Invalid Search RTs – Valid Search RTs) as a function of load and type of stimulation (C) High WM load produced a WM guidance cost by reducing the size of the validity effects but that cost was minimized in the anodal relative to cathodal stimulation condition (D) Mean Memory accuracy as a function of load, validity and type of stimulation (error bars depict SEM).

Next, I also assessed the influence of WM load (high, low), validity (valid, invalid) and tDCS (anodal, cathodal) on memory accuracy. An effect of load ($F(1, 7) = 25.7$, $p = 0.001$) on memory accuracy was observed such that participants were more accurate in the low compared to the high load condition (Figure 24D). No effect of validity ($F(1, 7) = 4.0$, $p = 0.084$) and tDCS ($F(1, 7) = 0.021$, $p = 0.88$) was present. Also there were no significant interactions between load and validity ($F(1, 7) = 0.04$, $p=0.851$), validity and tDCS ($F(1, 7) = 0.37$, $p=0.562$), load and tDCS ($F(1, 7) = 0.233$, $p=0.64$) on mean memory accuracy. The three-way interaction was also non-significant ($F(1, 7) = 1.75$, $p=0.23$).

4.2.3. Discussion

This study replicates previous work that the contents of WM guide the deployment of attention in the visual field. Search responses were faster in valid conditions (when the search target matched the memory content) compared to invalid conditions. The bias of attention towards the WM-matching item was higher in the low load condition compared to the high load condition, replicating prior findings that WM guidance reduces with higher WM loads (Soto et al., 2012a; Soto & Humphreys, 2008b). It is possible that reduced WM guidance under high WM load conditions may be due to increased competition for processing resources and the precision of memory representations may also be impaired (Soto et al., 2012a; Soto & Humphreys, 2008b). In line with this, the results showed that memory accuracy was higher in the low load compared to the high load WM condition.

The main aim of this experiment was to test whether anodal stimulation of the dorsal frontal cortex (including SFG) could facilitate WM guidance under high load conditions. The results showed that even though overall WM guidance was reduced in the high-load condition (relative to the low load), the application of anodal-tDCS reduced this cost, so that the size of the validity effect was less affected by WM load compared to cathodal stimulation. In the high WM load condition, cathodal and anodal stimulation conditions were associated with similar search RTs in the valid condition. I take this to suggest that the effect of tDCS operated mainly on invalid trials. Here, search RTs were slower after anodal relative to cathodal stimulation. This suggests that anodal tDCS to the dorsal frontal cortex modulated the bias of attention towards irrelevant memory matching information, hence leading to increased distraction and slower search RTs. However, I note that with the current experimental design it is difficult to determine whether it was anodal stimulation that leads to enhanced capture from irrelevant information or whether it was cathodal stimulation that leaded to inhibition of capture by irrelevant (invalid) WM-matching items.

Either way, the results are in accordance with a role of the dorsal frontal cortex in WM guidance of attention mainly under high WM load conditions, since anodal tDCS modulated guidance under stressing WM conditions relative to the cathodal stimulation. As indicated earlier in the introduction of this chapter, regions of the dorsal frontal cortex (i.e. SFG) connect to the VL, MD and pulvinar nuclei of the thalamus (Mesulam, 1990; Shipp, 2003, 2004; Sommer & Wurtz, 2006). Therefore, I propose that the dorsal frontal cortex is in a good position to form part of a frontothalamic network that controls the orienting of attention (Sommer & Wurtz, 2006; Soto et al., 2007b; Tanaka & Kunimatsu, 2011). One mechanism by which frontal-tDCS might have facilitated guidance was by enhancing the functional connectivity in this frontothalamic network and perhaps also through modulation of top-down frontoparietal signals for attentional control (Corbetta & Shulman, 2002; Egner et al., 2008).

4.3. Experiment 8: Effects of frontal tDCS in WM-guidance of attention under even higher load (3 items) WM conditions

One aim of Experiment 8 was to assess whether tDCS could influence WM guidance at even higher levels of WM loads. Accordingly, I increased the WM load from 2 items (Experiment 7) to 3 items. Note that Experiment 7 failed to detect any differences in memory performance across cathodal or anodal tDCS and this may be because a WM load of 2 items was not sensitive enough to detect tDCS effects in memory accuracy. A second aim was to test the hypothesis that dorsal frontal tDCS effects on memory accuracy may be detected more easily at higher (i.e. 3) WM loads.

4.3.1. Methods

Participants

A total of twelve healthy volunteers (8 Males, 4 Females, age range: 22- 29) were recruited to participate in the new experiment. None of the participants had prior history of neurological or psychiatric disorders. All participants provided written informed consent and were economically rewarded for their participation.

Experimental Task and Procedure

Before starting the actual experiment participants received clear instructions and performed some training trials until they felt comfortable with the task. Figure 25 illustrates an example of the sequence of events. At the beginning of each trial, participants were presented with the instructions “Remember 3 items” for 1000ms. This was followed by a fixation dot for 500ms and by a cue display of three items for 200ms that participants had to keep in memory. Each of the stimuli were unique in colour and shape and appeared in 1 of 5 possible shapes (square, triangle, diamond, circle, or hexagon) and 1 of 5 possible colours (red, blue, green, yellow, or pink). After the cue display, a fixation dot was presented for 500 ms, followed by a search display presented for

another 500ms. Critically, on some trials the search display was not presented and instead a memory test appeared. Because participants could not predict whether a search display or a memory test would follow fixation, they were always required to keep the three items in memory (Figure 25). Also, by including a surprise memory test I could assess memory accuracy without interference from the presentation of the search display. Like in the previous experiment, the search display was composed of 2 coloured shapes, each containing a black line which could either be tilted (target) or vertical (distracter). There were two types of trials in which the validity of the memory cues for search varied: in valid trials, the target (tilted line) was surrounded by one of the 3 items previous held in memory; in invalid trials, one of the three pre-cued objects was re-represented in the search display but contained a distracter vertical line instead of the search target. The 2 trial types occurred randomly and with equal probability. The search display remained onscreen for 500ms and was followed by a further 1.5 seconds response period during which a blank screen was presented. Participants indicated the orientation of the target (right tilted or left tilted) by means of button pressing (Figure 25). During the memory test condition, a single coloured shape was presented and participants were required to match it to the memory cue display. In responding to the memory item, participants had to indicate (via button pressing) whether or not it matched both the colour and the shape of any of the 3 items previously held in memory.

tDCS

Stimulation was applied as in Experiment 7. Following the stimulation, participants performed 96 trials of the task (64 trials were search trials only and 32 trials were WM trials only; see Figure 25) which lasted about 10 minutes.

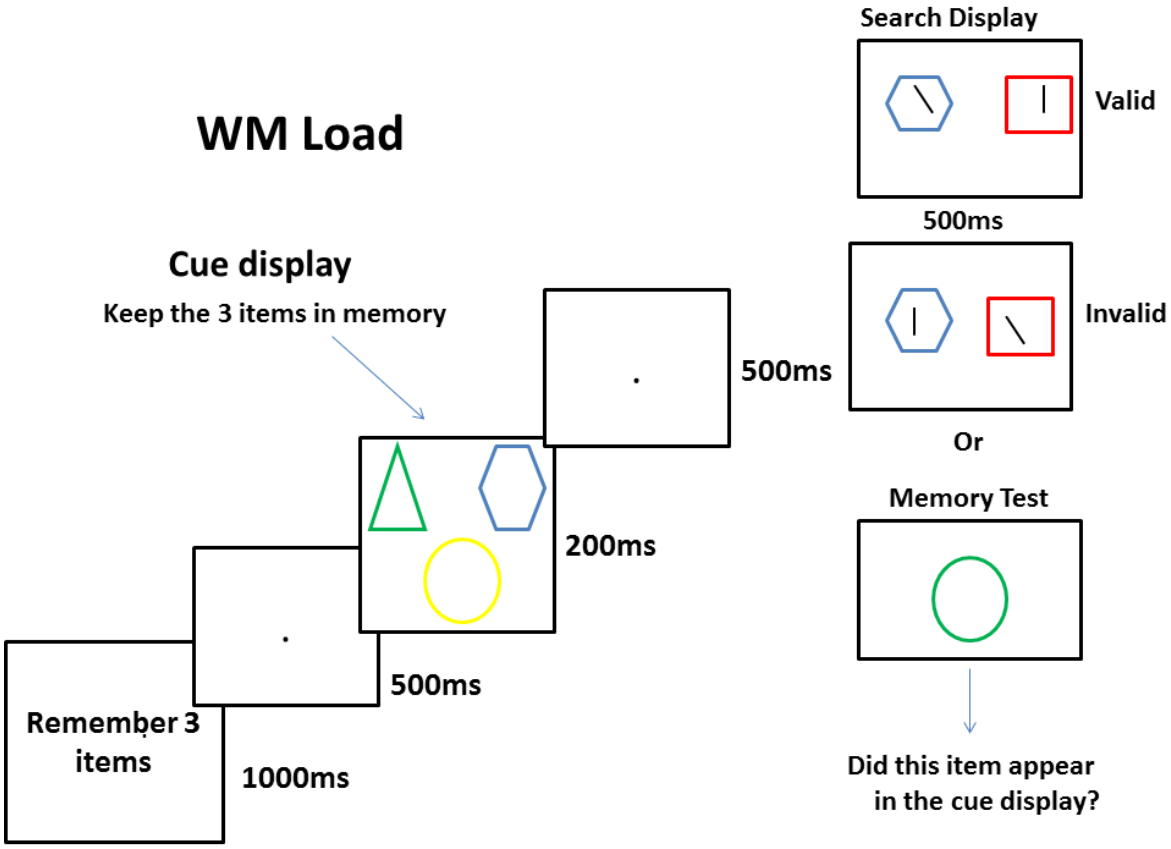

Figure 25. High WM-load (3 items) is followed by one of two possible conditions: search display or memory test.

4.3.2. Results

Only trials with correct responses in the search task were included in the analyses. I conducted 2 x 2 repeated measures ANOVA to assess the effect of validity and tDCS type on the median search RTs. There was an effect of validity ($F(1, 11) = 14.46$, $p = 0.003$) such that median search RTs were faster in valid relative to invalid conditions (Figure 26A). No effect of tDCS ($F(1, 11) = 1.7$, $p=0.21$) and no interaction between validity and tDCS ($F(1, 11) = 0.22$, $p=0.65$) were present on the median search RTs.

Analyses for the mean search accuracy showed an effect of validity ($F(1, 11) = 13.57$, $p=0.004$). Search accuracy was higher in valid relative to invalid conditions (Figure 26B). An effect of tDCS was also present ($F(1, 11) = 4.82$, $p=0.05$) such that search accuracy was higher after cathodal relative to anodal stimulation (Figure 26B). Most importantly, there was a trend towards an

interaction between validity and tDCS (F (1, 11) = 4.77, p=0.052) which shows that during invalid conditions search accuracy was lower in the anodal relative to cathodal stimulation (Figure 26B).

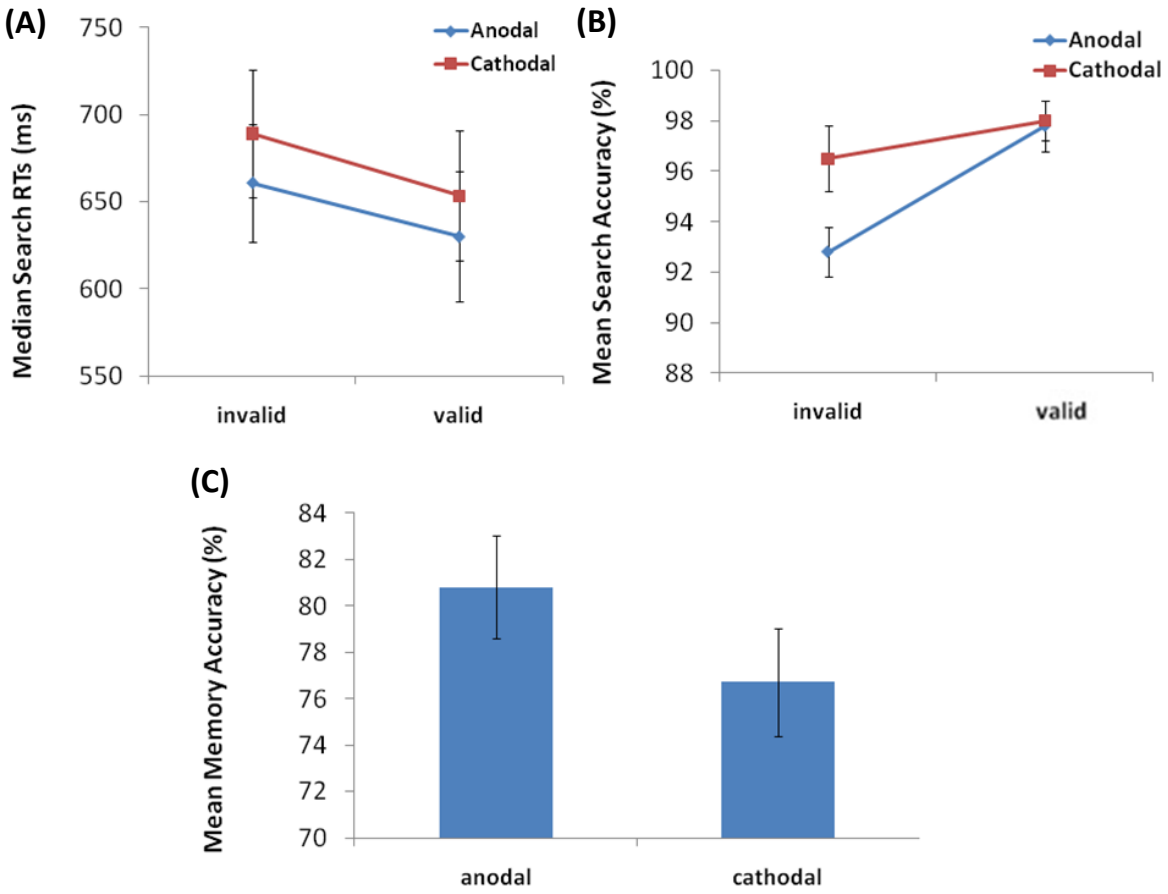

Figure 26. (A) Median search RTs as a function of validity (invalid, valid) and tDCS (anodal, cathodal) (B) Mean search accuracy as a function of validity and tDCS (C) Mean memory accuracy as a function of tDCS (error bars depict SEM).

In terms of the analysis for memory accuracy there was no effect of tDCS (F (1, 11) =1.31, p=0.276) although mean memory accuracy was slightly higher after anodal (80.8%) relative to cathodal (76.7%) stimulation (Figure 26C).

4.3.3. Discussion

This experiment replicates our previous study in that search RTs where faster in valid conditions compared to invalid conditions, suggesting that attention was guided by the WM contents. A trend for the interaction effect between validity and tDCS was present here on search accuracy and indicated that during invalid conditions, search accuracy decreased after anodal stimulation in comparison to cathodal stimulation. I interpret this as showing that tDCS promoted the automatic capture of attention towards the irrelevant (invalid) WM-information, leading to decreased search accuracy and impaired discrimination of the target that was presented elsewhere. Search accuracy in the valid condition was similar across stimulation conditions. These patterns of results resemble the pattern of results found in Experiment 7 in search RTs. In Experiment 7, anodal tDCS was associated with slower RTs in the invalid trials relative to the cathodal condition, while no differences were apparent in the valid trials. The tDCS-effects on search occurred in RTs in Experiment 7 but on accuracy in Experiment 8. It is possible that the higher WM load in Experiment 8 may have prompted participants to try to prioritise response speed in the search display (i.e. to avoid forgetting the cues). Like in Experiment 7, dorsal frontal tDCS may have enhanced the automatic capture of attention towards the irrelevant WM-matching information but then here participants tried to quickly re-orient their attention to give a fast response to the search target presented elsewhere. Note that overall search RTs tended to be slower in Experiment 8 relative to Experiment 7, likely showing the increased WM load of 3 items. Under this stressing WM conditions, participants may have attempted to react faster in the search leading to more errors. Thus, this should explain why tDCS effects were on error rates rather than RTs.

Overall memory accuracy was high but it did not differ significantly as a function of either anodal or cathodal stimulation. The results do not support the hypothesis that dorsal frontal-tDCS influences the maintenance of information in WM. Nonetheless, this does not necessarily mean that there were no effects of tDCS on WM processing as it could have been the case that our

experiment might have not been sensitive enough to detect such differences on memory accuracy. For example, previous studies that found tDCS effects on WM performance placed the centre of the electrode in F3 (Boggio, Ferrucci, Rigonatti, Covre, Nitsche, Pascual-Leone, & Fregni, 2006; Fregni et al., 2005; Zaehle et al., 2011), which is supposed to be more in the vicinity of the DLPFC, while in my studies I placed the anterior margin of the active electrode in F3 so that the centre of the electrode was more posterior and closer to the SFG. The difference in the sites of electrode placement might explain the apparent divergence on the absence of tDCS effects on WM processing, that is, maybe is just that the DLPFC is an area more sensitive to detect effects of tDCS on WM processing of multiple items in comparison to the SFG. Additionally, it was previously shown that the application of 1mA anodal frontal tDCS (relative to sham) was not sufficient to detect differences in WM as indexed by task accuracy whereas application of 2mA of anodal tDCS produced a significant improvement in WM accuracy (Boggio et al., 2006). I only used an intermediate 1.5mA and maybe by increasing the current to 2 mA I could have detected an effect on memory accuracy. Also in some experiments the stimulation period is 20 minutes (Boggio et al., 2006), whereas here I only applied tDCS current for 15 minutes. Methodological differences between studies may explain the lack of the tDCS effects on memory accuracy.

In any case, the results reported here and also in experiment 7 indicate that the influence of frontal–tDCS on attention guidance by WM information may not necessarily be mediated by an effect of tDCS on WM processes only. Instead, the effects of frontal-tDCS appear directly related to the modulation of the process of WM guidance of attention itself. As I have already suggested this could be achieved by frontal tDCS enhancing top-down frontothalamic modulation of early visual sensory cortex.

Chapter 5: Role of the thalamus and frontoparietal network in WM-guidance of attention based on learning of abstract cue-target feature associations: an fMRI study

5.1. Chapter Introduction

Human beings constantly face novel situations and must acquire new rules to guide behaviour and maximize survival. Rules-based processing may be an overall principle that governs higher-level thoughts and guide one's behaviour (Miller & Buschman, 2007; Schank & Abelson, 1977). For example, I know that when I enter a restaurant I must wait until a table is available. With experience and familiarity, behavioural responses to these principles become automatic without requiring any cognitive demand, allowing us to respond quickly to environmental demands. However, this must be preceded by learning the critical rules in difference contexts: for example, waiting for a table in a busy restaurant. Novel and unfamiliar situations require more controlled behaviour and hence rely on more explicit top-down processing modulation. Because abstract rules are acquired through long-term experience they also provide the basis for predicting future events (Miller & Buschman, 2007). Here, I am interested in understanding what sort of brain mechanisms lead to the learning of complex abstract rules that are necessary to guide attention from WM.

So far, the evidence reported in this thesis from focal-thalamic patients suggests that the thalamus may be key in promoting WM guidance of visual attention but this guidance involved a relatively direct correspondence between the WM cue and the stimulus (i.e. "Red" label in mind to red physical objects). The main aim of the fMRI study presented here is to assess the potential role of the thalamus in WM–guidance when cue-target associations need to be learned. I hypothesized that given the importance of the thalamus in more direct forms of WM guidance then its role might also extend to learning of abstract cue-target feature associations to guide goal-directed behaviour in search. Also, I aimed to establish the role of the VL thalamus in the interplay between memory and attention as part of a broader cortical (i.e. frontoparietal) and subcortical network. This important question could not be addressed by the lesion studies reported in Chapter 2 and 3.

5.2. Experiment 9: Neural correlates for learning complex abstract cue-target feature associations to guide search attention

5.2.1. Methods

Participants

Sixteen right-handed healthy participants (seven females, nine males; age range: 18-31 years) who provided written informed consent participated in the study in return for £20. They were native-English speakers and naive with regards to the experimental aims and hypothesis. Due to a technical problem behavioural data from one participant could not be recorded. No participant had a prior history of neurological or neuropsychiatric disorders, and all had normal or corrected-to-normal vision. The study was approved by the West London Research Ethics Committee.

Experimental Task and Procedure

The behavioural task was programmed and controlled using E-Prime v2.0 (Psychology Software Tools Inc., Pittsburgh, USA; www.pstnet.com/eprime.cfm). The sequence of events follows.

Learning phase: Each trial of the learning phase (Figure 27A) began with a fixation point from 500ms in a black background. After, participants were presented with one of eight possible Japanese Hiragana symbols (the cues) for 500ms. Then, a blank screen was presented for 1500ms, which was followed by a search display containing 4 coloured circles (red, green, yellow and blue). Three of the circles contained a vertical distracter line and one circle contained the target line, which could be tilted either to the left (\) or to the right (/). Participants task was to search for the tilted line and to respond to its orientation via button press (Figure 27A). The search display remained onscreen for 100ms (to minimise eye movements). Four of the Hiragana cues were predictive symbols (i.e. valid condition) and each was associated with particular coloured circles surrounding the search target (see Figure 27A for an illustration of trials with predictive cues). Note that the

colour circle that each Hiragana cue predicted was maintained throughout the experiment. Four other Hiragana cues were non-predictive (i.e. neutral condition) and were not associated with the colour of the circle that contained the search target (see same Figure 27A for an illustration of trials with non-predictive cues).

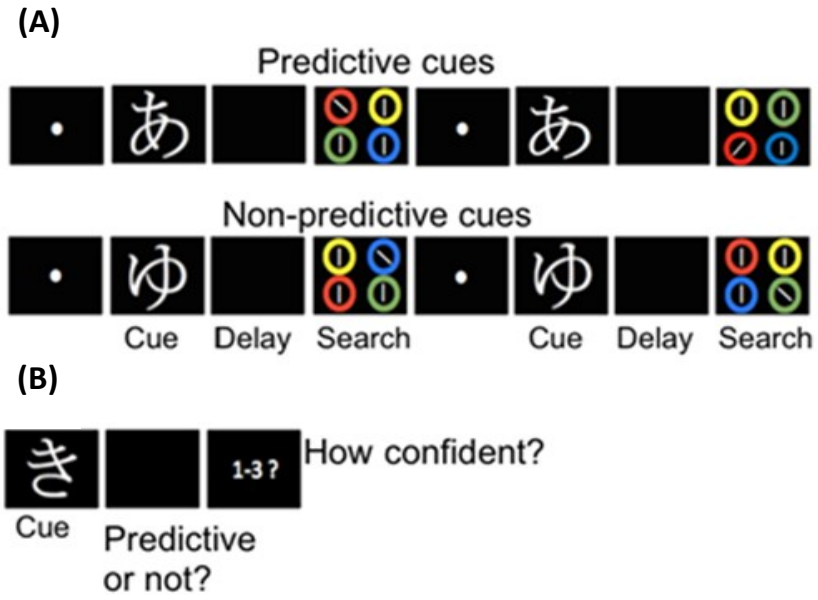

Figure 27. Illustration of display sequences during the learning phase and subsequent recognition test (A) Predictive cues. Here, あ is predictive of a red circle; Non-predictive cues. ゆ is not predictive of any coloured circle because this Japanese symbol follows a display with a blue circle that surrounds the search target and in a subsequent trial a display with a green circle that surrounds the search target (B) Example of display sequence in the recognition test. Participants were required to report whether a cue was predictive or non-predictive, and rate how confident (on a scale of 1-3) they were on their decision about the predictability of the cue.

The learning-search task was composed of 5 blocks of trials and each block was composed of 16 trials (8 predictive and 8 non-predictive). The inter-trial time interval (ITI) was jittered between 2.5 and 4 s, with a pseudo-exponential distribution (50% of ITIs were 2.5 s, 25% of ITIs were 3 s, 12.5% were 3.5 s, and 12.5% were 4 s), to facilitate the independent estimation of BOLD responses across trials (Ollinger, Corbetta, & Shulman, 2001). A central fixation point was presented during the ITI.

Recognition test: Each 'search' block was followed by a recognition test (Figure 27B) to ensure that participants were indeed attempting to learn the predictive value associated with the different hiragana cues. The recognition test was also included to encourage participants to learn the associations. On each trial, participants were presented with one of the hiragana cues for 500 ms, followed by a blank screen for 2500 ms during which participants had to indicate via button press whether the symbol was predictive or non-predictive. Following this, participants were asked to rate how confident they were of their decision during a time window of 1500 ms. A 1-3 rating scale was used (1: low; 2: medium; 3: high confidence). Each recognition block comprised 8 trials, one for each of the hiragana cues used (4 predictive and 4 non-predictive).

Prior to scanning, participants received instructions and training on the task. Note that the hiragana cues used in the training phase were different from the ones used in the scanner. During this training phase participants were explicitly trained to maintain central fixation throughout the trials and to avoid eye movements. The duration of the search display was initially set at 500 ms increasingly reduced during the training phase down to 100 ms to minimise the occurrence of saccades.

Functional MRI data Acquisition and Scanning Parameters

A Siemens Magnetom Avanto 1.5T MRI scanner and a 32-channel head coil was used. An out-bore screen was mounted at the end of the scanner bore and visual stimuli was displayed by a projector in the adjacent room to the scanner. A mirror was placed above the head rest at 45˚ enabling participants to see the screen looking straight upwards. Following a brief localiser scan to determine the orientation of the participants head within the field, T2-weighted volumes in an anatomical sagittal image were acquired (342 volumes for the learning task and 95 volumes for the verbal cueing task) with a field of view (FOV) of 205 × 205 mm, repetition time (TR) of 2500 ms, echo time (TE) of 44 ms, and slice thickness of 3.2 mm. A six minutes T1-weighted structural scan was also collected.

Imaging Data Analysis

fMRI data processing was performed using FEAT (fMRI Expert Analysis Tool) Version 6.0, as part of FSL (www.fmrib.ox.ac.uk/fsl). The first four volumes of the echo-planar imaging (EPI) scans were removed to account for T1 equilibrium effects.

First level analysis: For the within subject analysis the following pre-statistics were applied: Non-brain removal was performed using Brain Extraction Tool (Smith, 2002). Motion correction of functional scans was carried out using FMRIB's Linear Image Registration Tool (Jenkinson, Bannister, Brady, & Smith, 2002). I also applied a 100 s high-pass temporal filtering to remove low frequency noise, and spatial smoothing using a FWHM Gaussian kernel of 6.0 mm. Time-series statistical analysis were conducted using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001).

The learning-search task was modelled from the onset of each of the hiragana symbols with duration of 2.1s (including 0.5 s exposure of the cue, 1.5 blank screen delay and 0.1s search display). I followed the same principle for the recognition test periods. For each of the five learning blocks separately, I modelled the onset of search periods with predictive and non-predictive cues separately. For each of the five recognition blocks separately, I modelled the onset of predictive and non-predictive cues and also included regressors for the onset of the confidence rating periods. Finally, I modelled the search error trials and onsets for the instructions in the search and recognition test and the motion parameters. I used a double gamma function convolved with the hemodynamic response. I then set up our contrasts for predictive > unpredictive cue trials (and also for predictive < non-predictive) creating the correspondent contrasts of parameter estimates (COPES) separately for each search/learning block.

Second level, within-subject analysis: The above COPEs were submitted to a within-subject (fixed-effects) analysis testing for linear, quadratic and exponential trends across the learning blocks.

Linear model - Learning effects were first modelled using a linear model for the COPES across the blocks [-2, -1, 0, 1, 2]. The second-level analysis derives the parameter estimates representing this linear trend. Note that reversing the model to a linear decrease 2, 1, 0, -1, -2 on those COPES is the same as showing linear increases in learning for unpredictive > predictive differences. I followed the same principle for the two remaining models (exponential and quadratic).

Exponential and Quadratic Model - I tested an exponential model of learning with the corresponding values in the contrast design matrix [-5, -4, -2, 2, 9]. I also introduced quadratic models of learning with contrast specification [-1, 0, 2, 0, -1] and [1, 0, -2, 0, 1]. These models were tested because the behavioural data (search RTs) indicated that learning had an abrupt onset in block 4. Thus, I assessed the neural regions that show little evidence of learning early on but then later on switch to modulate their activity during training.

Third level analysis: Finally, I performed higher level group analyses using FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects) as implemented in FEAT. This was done in the form of a one-sample t test to assess whether the average BOLD responses for the three models of learning (linear, exponential, and quadratic) is consistent across the 16 participants.

Individual functional data were registered to individual high-resolution structural images using FLIRT Boundary-Based Registration (Greve & Fischl, 2009), and then co-registered into standard MNI space. For the whole brain analyses, I report maps of BOLD responses thresholded using clusters determined by a voxelwise Z threshold of 2.3 and a cluster significance threshold of P=0.05, corrected for multiple comparisons across the whole brain (Worsley, 2001). I also performed ROI-based analyses based on the thalamic lesions and the statistical maps were corrected for multiple comparisons using a false discovery rate with a FDR threshold of 0.05. The location of the activations was determined based on the Harvard-Oxford Structural Atlas in FSL.

5.2.2. Results

Behavioural Performance

I conducted a 5 (block) × 2 (cue types: predictive and non-predictive) repeated measures ANOVA over the median search RTs, search accuracy (ACC), memory ACC and confidence ratings. Analyses for search RTs were made for correct responses only.

There was a main effect of block ($F(4, 56) = 5$, $p = 0.006$) such that search performance became faster with block (Figure 28A). There was also a reliable effect of cue type ($F(1, 14) = 8.7$, $p = 0.01$) with faster performance on predictive trials relative to non-predictive trials (Figure 28A).

Most importantly, block and cue type interacted ($F(4, 56) = 4.3$, $p=0.007$); as training developed, search performance became increasingly faster in predictive relative to non-predictive trials (Figure 28A).

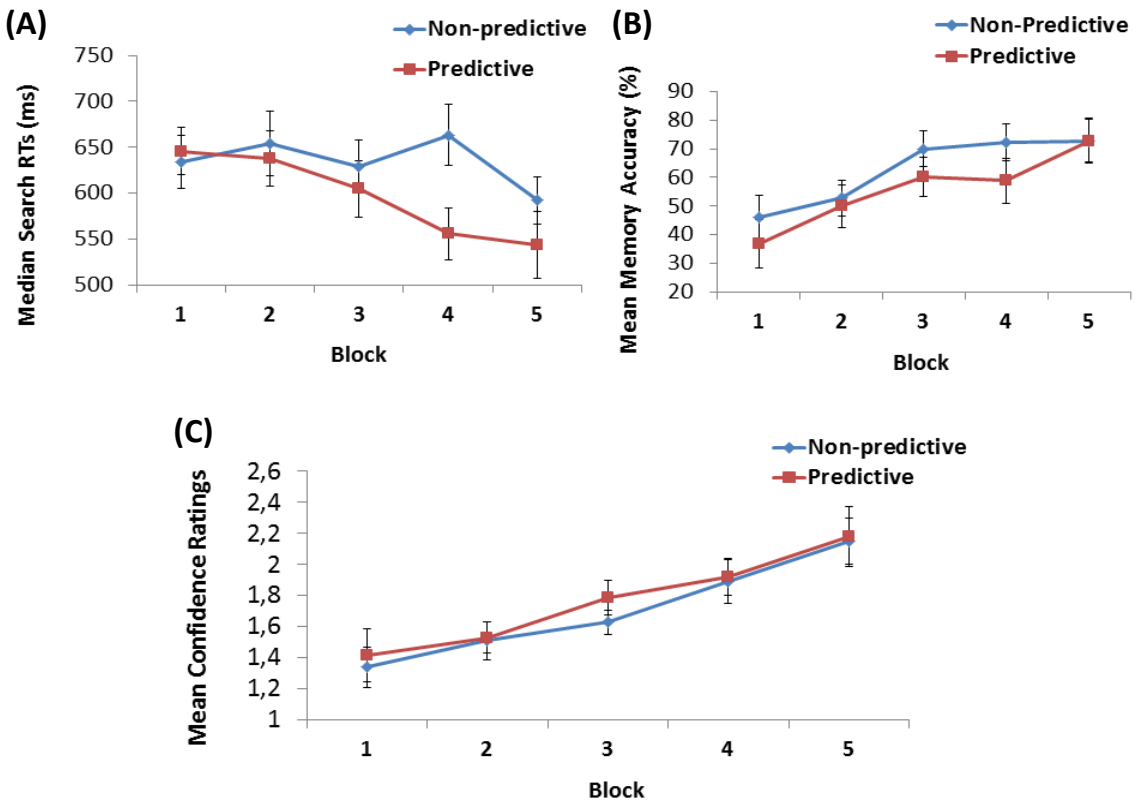

Figure 28. (A) Median search RTs as a function of block and cue type (predictive, non-predictive) (B) Memory accuracy for cue predictability (C) Mean confidence ratings in the recognition test increased with training block (error bars depict SEM).

Search accuracy in the training phase was very high (predictive trials = 92%; non-predictive trials = 93%) and did not differ across blocks ($F(4, 56) = 0.3$, $p = 0.69$). There was no effect of cue type ($F(1, 14) = 0.076$, $p = 0.78$) and no interaction between block and cue type ($F(4, 56) = 0.85$, $p = 0.45$) on search accuracy.

Performance during the recognition tests demonstrates that participants learned the association between the Japanese symbols and the coloured circles. There was a noticeable effect of block ($F(4, 56) = 6.5$, $p = 0.001$), which shows that the recognition of the predictive value of the Japanese symbols increased with block (Figure 28B). There was no significant effect of cue type ($F(1, 14) = 0.9$, $p = 0.3$) and no interaction between block and cue type factors ($F(4, 56) = 0.6$, $p=0.5$) on mean memory (recognition) accuracy.

In the confidence ratings, there was a significant effect of block ($F(4, 56) = 9.4$, $p = 0.001$) showing that confidence in the response to the predictiveness of the Japanese symbols increased with block (Figure 28C). There was no reliable effect of cue type ($F(1, 14) = 1.83$, $p = 0.19$) and no interaction between block and cue type ($F(4, 56) = 0.3$, $p=0.74$) on the confidence ratings.

fMRI results

I first conducted ROI-based analyses using a mask around the left anterior VL thalamus (i.e. 6 mm spherical ROI centred at MNI -10 -10 10) which overlapped the lesion sites of the left anterior VL thalamic patients (VL1, VL2, VL3) studied in Chapters 2 and 3.

I found that responses in left VL thalamus tracked the predictiveness of the hiragana cues across the learning phase, consistent with both linear and exponential learning trends ($Z>2$; $p<0.011$, FDR corrected; Figure 29, left panel).

To further examine whether other thalamic regions may be critical, I used anatomical ROIs comprising the entire left or right thalamus. I found a cluster in the right thalamus ($p<0.05$, corrected for multiple comparisons across the ROI; Figure 29, right panel) involving the same VL

region found in left thalamus which responded to the predictability of the cue in a way that was consistent with both linear and exponential learning models.

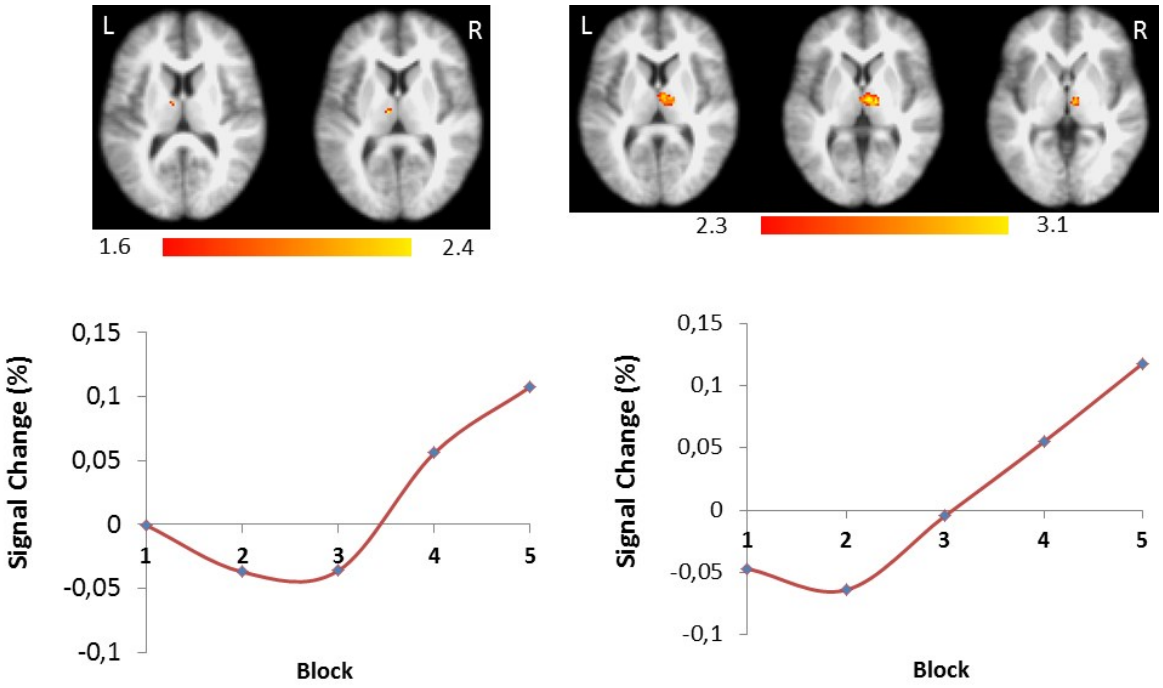

Figure 29. Thalamus responses are associated with exponential trend of learning. Anatomical ROI analysis in the left anterior VL thalamus showed increased responses to the predictability of the cues across the learning blocks. A similar pattern was found in the ROI analysis of the whole right thalamus.

Overall, the results show that responses in bilateral right and left VL thalamus tracked the predictiveness of the hiragana cues across the learning phase.

Finally, I performed whole-brain analyses (Z>2.3, whole-brain corrected) to assess whether other regions in addition to the thalamus that may be relevant for learning-related guidance of attention. These whole-brain analyses showed that responses to cue predictability in bilateral parietofrontal regions (e.g. bilateral posterior parietal, middle and superior frontal and ventrolateral and anterior PFC), and subcortical substrates in the basal ganglia and, critically, bilateral anterior VL thalamus (Figure 30) were consistent with a quadratic model of training.

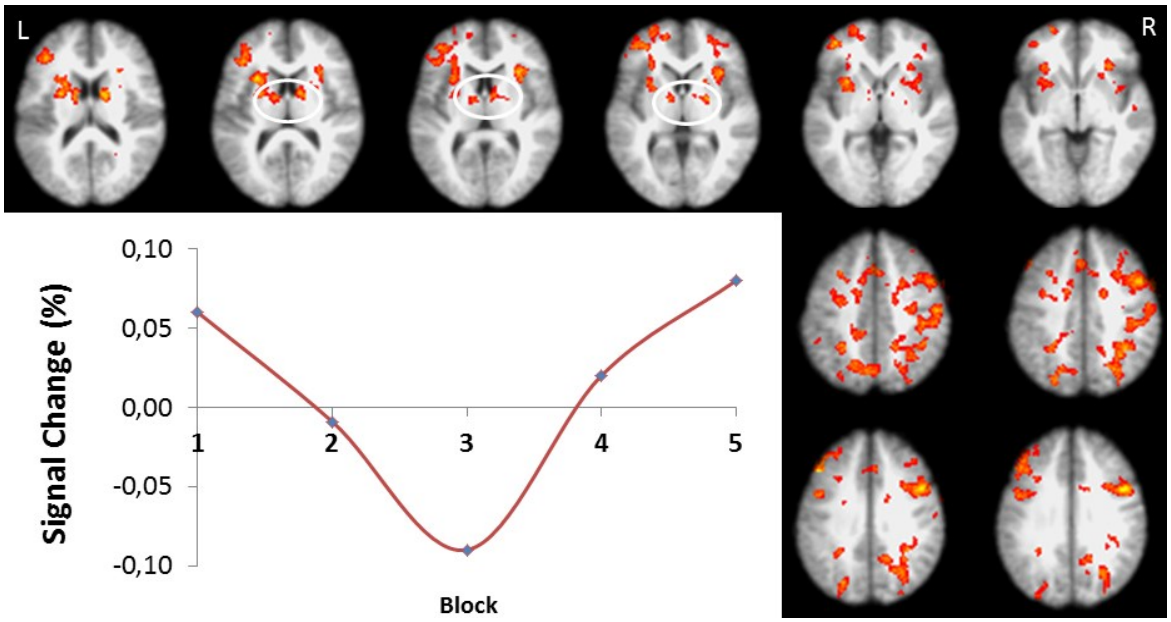

Figure 30. Whole-brain responses to the predictiveness of the hiragana cues across the learning blocks. Bilateral anterior thalamus (Left: MNI -10 -4 10; Right: 6 -4 8), showed a response profile consistent with a quadratic model of learning as part of a network involving the basal ganglia (Right/left caudate, +-14 -2 16) and bilateral frontoparietal regions (posterior parietal cortex, BA7 +-34 -60 54; superior frontal gyrus, BA6 +-30, -2 60; middle frontal gyrus, BA8 +- 26 2 54; ventrolateral PFC, BA45, +- 44 32 18, BA47 +- 28 26 -4; rostral PFC BA11, +-26 52 6); insula, BA48 +- 30 16 10; paracingulate gyrus, BA32 6 14 48; precuneus BA7, 0 -68 50.

5.2.3. Discussion

Behavioural data shows that search performance was increasingly faster on predictive trials relative to non-predictive trials throughout the learning phase. This learning effect seemed to have an abrupt onset in block 4 onwards. These findings are further supported by increased recognition accuracy on the predictability of the Japanese symbols as training increased, which also had associated higher confidence in the recognition responses. Overall, the behaviour results show that participants were able to learn and use the target feature predictability associated with the symbols to direct attention in the search display and enhance performance.

The imaging data analysis identified BOLD responses in our thalamus ROIs based on the lesion data from Chapters 2 and 3. Specifically, neural responses to the predictability information of the hiragana cues in the right and left anterior VL thalamus increased throughout the learning blocks.

Whole brain-level analysis identified activation in the anterior VL thalamus as part of a cortical network involving bilateral middle frontal gyrus, posterior parietal lobe network and subcortical substrates in the basal ganglia which was in accord with a quadratic model of learning (Figure 29). The response profile of this network reflected response attenuation (i.e. neural repetition suppression) for predictive relative to non-predictive cues during an initial phase of training. This could be attributed to an implicit mechanism of learning, that is, while there is some familiarity on abstract cue-target feature associations, the associations are not yet consciously integrated (Henson, 2003). This phase was followed by the opposite pattern of increased responses to predictive relative non-predictive cues from block 4 onwards. This latter pattern might reflect repetition enhancement which has been previously associated with the re-appearance of information that matches the contents of WM (Dudukovic, Preston, Archie, Glover, & Wagner, 2011; Greene & Soto, 2012). In this case, repetition enhancement would follow learning of cue-target associations as participants begin to consciously represent in WM the cue-target association to intentionally guide search, and this processes may also be accompanied by increased responses in the frontoparietal regions associated with top-down control of attention (Corbetta & Shulman, 2002; Egner et al., 2008).

In addition to thalamus and frontoparietal regions, the basal ganglia also displayed sensitivity to the predictiveness of cues as learning emerged which is in keeping with previous evidence suggesting it is associated with the learning and maintenance of task rules (e.g. cue-response associations) (Pasupathy & Miller, 2005; Xue, Ghahremani, & Poldrack, 2008).

The lesion study in Chapters 2 and 3 established that the thalamus and in particular its VL parts are important for direct forms of WM guidance of attention where there is a clear and well established correspondence between the feature memory cues and the search items. The present fMRI results suggests that bilateral anterior VL thalamus in conjunction with cortical (i.e. frontoparietal network) and subcortical (i.e. basal ganglia) regions can track the learning of abstract

cue-target feature associations to promote the guidance of attention. The results appear to indicate an earlier increase in activity in the right anterior VL thalamus (from block 3 onwards) relative to other activated regions and therefore I speculate that this area might have been the primary source for learning of cue-target associations.

5.3. Experiment 10: Neural correlates of verbal WM guidance of visual attention

In the second fMRI experiment with healthy volunteers, I used a verbal guidance of attention paradigm very similar to the one used with stroke patients. This experiment can be seen as a complement of our lesion study with thalamic patients (Chapters 2 and 3). The main purpose was to further explore for the role of the thalamus in verbal WM guidance of visual attention. Previously, I showed that focal-brain lesions of the thalamus, in particular to the VL nucleus, can lead to deficits in verbal WM guidance of attention. Following these observations, I hypothesized that fMRI-correlated activity should be present in the left VL thalamus when healthy participants use verbal information to guide attention in the visual search task. I also expected that frontoparietal regions may also be activated given previous evidence that these regions activate in goal-directed attention tasks guided by either spatial or feature cues (Corbetta & Shulman, 2002; Egner et al., 2008).

5.3.1. Methods

Participants

The same 16 healthy participants from the previous Experiment took part.

Experimental Task and Procedure

There were two trial types depending on the validity of the cue: valid and neutral (Figure 31). Each trial began with a blank screen (3000 ms) followed by the presentation of a verbal cue for 500 ms either in form of a colour word (i.e. RED, GREEN, BLUE or YELLOW) or as a non-word (WOTL,

YRE, RNWEO or LBERUG), randomly selected on each trial. Next, a blank screen was presented for a 1500ms delay period before the onset of the search display identical to the prior Experiment 9. Participants were instructed that the word cues were always valid and that they predicted the colour of the circle surrounding the tilted target. They were encouraged to use the cue to boost search performance. They were also instructed to try to respond as fast and as accurate as possible without errors. There was one block of 32 trials (16 valid and 16 neutral).

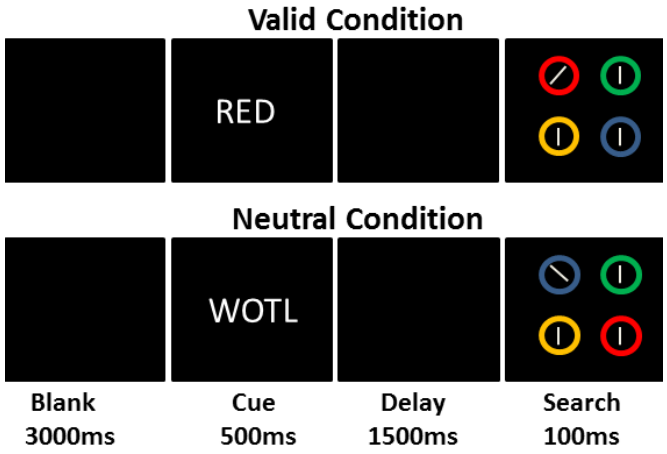

Figure 31. Example of display sequence in the verbal cueing paradigm used in the fMRI.

Imaging Data Analysis

The same image pre-processing steps from Experiment 9 were applied here. For each participant, I modelled separately the onsets of the valid and neutral cues with duration of 2.1s (similar to Experiment 9). I then set up two contrasts (i) valid > neutral (1, -1) and (ii) valid < neutral (-1, 1). As in Experiment 9, I ran higher-level analyses across participants using mixed effects in the form of a one-sample t-test to assess regions that were consistently activated at a group level as a function of cue validity. Individual functional data were registered to individual high-resolution structural images as described in Experiment 9.

5.3.2. Results

Behavioural performance

Analyses of search RTs were made for the correct search responses only. One-way ANOVA with validity (neutral, valid) as factor revealed an effect of validity ($F(1, 14) = 29.9$, $p < 0.0001$) such that search responses were faster in valid relative to neutral conditions (Figure 32A).

There was also an effect of validity on search accuracy ($F(1, 14) = 28.2$, $p < 0.0001$) such that search responses were more accurate on valid (93.8%) relative to neutral conditions (82.2%) (Figure 32B).

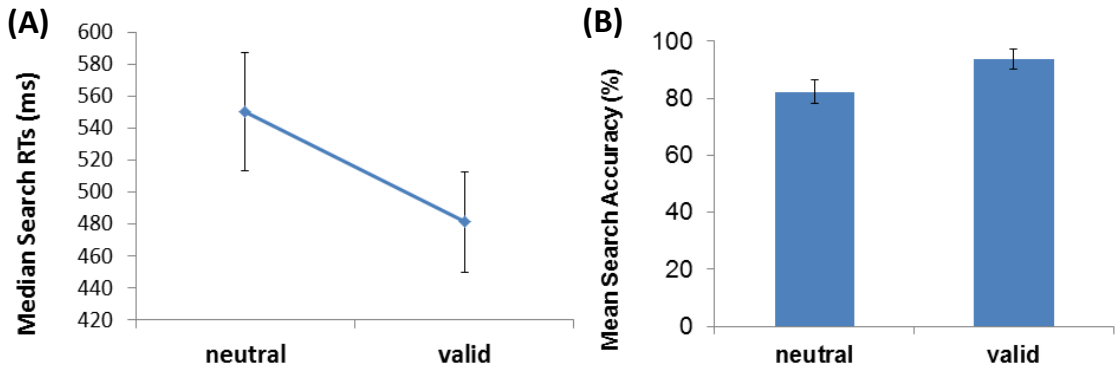

Figure 32. (A) Median search RTs were faster in valid relative to neutral conditions (B) Mean search accuracy was higher in valid relative to neutral conditions (error bars depict SEM).

fMRI Results

Neural substrates of verbal memory cueing: I conducted anatomical ROI analysis using the previously created thalamic mask based on the lesion site of the VL patients. I conducted this analysis in order to demonstrate that the same thalamic region co-activates in the healthy brain as function of the validity of the cues for search. As predicted, responses in left VL thalamus were enhanced in valid relative to neutral trials ($Z>2$; $p=0.019$, FDR corrected, Figure 33A).

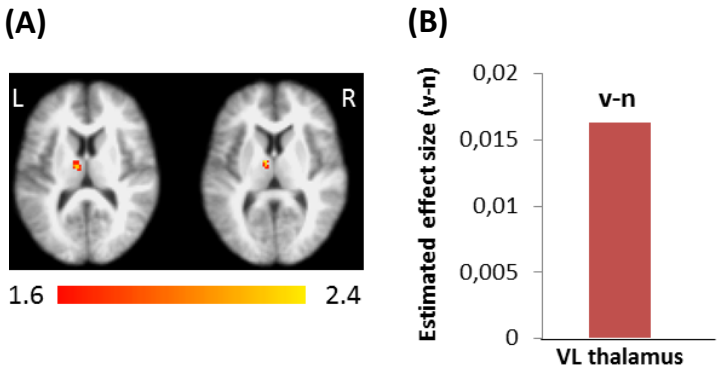

Figure 33. (A) VL thalamus displayed higher responses to valid relative to neutral cues (B) BOLD signal change in valid relative to the neutral conditions.

Whole brain analyses showed that verbal cueing of attention was associated with increased bilateral posterior parietal (MNI -50, -56, 38; 54, -40, 38) responses to valid relative to neutral cues and also in the left anterior PFC (MNI -36, 62, 2) ($p<0.05$, corrected for multiple comparisons; Figure 34A).

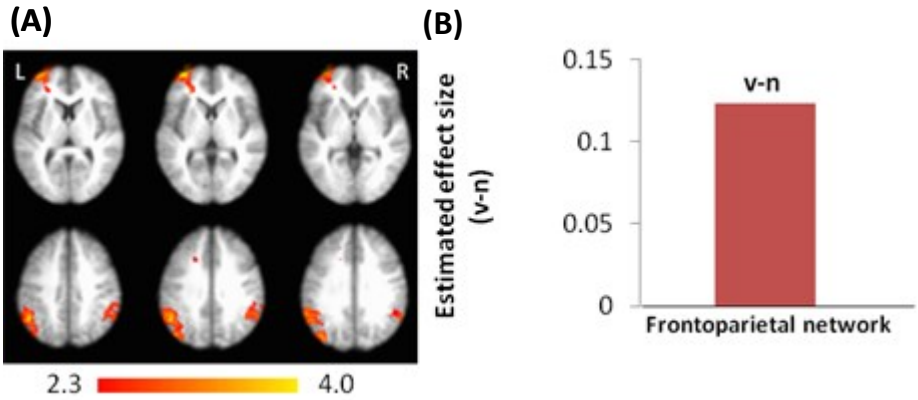

Figure 34. Frontoparietal network displayed sensitivity to valid relative to neutral cues (A) Clusters of fMRI activations in the left frontal pole and bilateral parietal cortex (B) Estimated effect size in percentage of signal change in valid relative to neutral cues.

I also found a cluster in the left occipito-temporal cortex (MNI -34, -94, 0) which responded more in the neutral relative to the valid condition (Figure 35A).

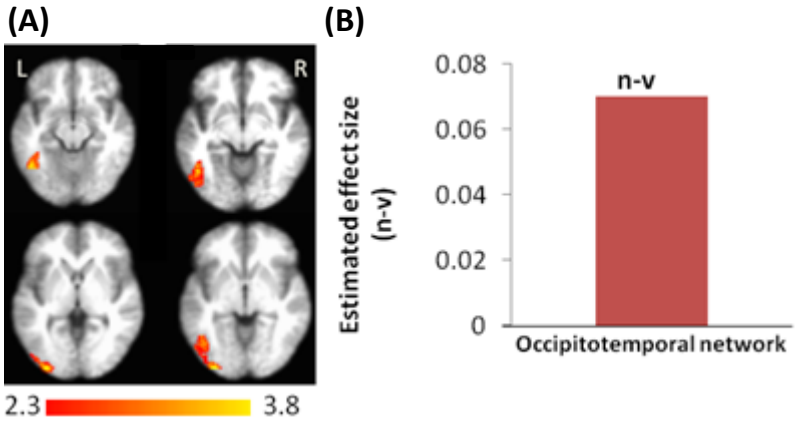

Figure 35. The occipitotemporal network displayed sensitivity to neutral cues (A) Clusters of activity in the left occipital cortex and left inferior temporal gyrus (B) BOLD signal change in neutral relative to valid conditions.

5.3.3. Discussion

In the behavioural analysis, I verified that search responses were faster in valid relative to neutral trials showing that participants were able to use the verbal cue to guide attention in visual search. Results from the fMRI analyses identified responses in the left anterior VL thalamus and also in frontoparietal cortex including the left frontal pole and bilateral parietal cortex associated with verbal guidance of visual attention (valid > neutral contrast).

The critical finding according to the hypothesis was the presence of a cluster in the left anterior part of the VL thalamus which provides confirmatory evidence in the healthy functioning brain of the findings demonstrated previously in the thalamic patients (Chapters 2 and 3). Hence, the left VL thalamus appears to mediate verbal guidance of visual attention. I also found responses in frontoparietal regions previously associated with attentional control (Corbetta & Shulman, 2002; Egner et al., 2008). Together, the findings support for a role of the VL thalamus in promoting verbal-WM guidance of visual attention which may be understood as operating as part of a cortical (frontoparietal), subcortical network.

Chapter 6: Final Discussion

6.1. General Findings and Implications

The findings reported in this thesis established the functional contribution of the thalamus in WM guidance of visual attention.

The results of the lesion studies reported in Chapter 2 and 3 showed that focal-thalamic lesions lead to impaired guidance of visual attention by verbal information held in memory. Thalamic patients with pulvinar and MD lesions display reduced validity effects (in terms of benefit and cost) in comparison to the control groups of age-match controls and patients with lesions outside the thalamus. Critically, patients with VL thalamic damage displayed the highest impairments of WM cueing. In valid conditions, when the contents of WM matched the sought after target, VL thalamic patients displayed impaired memory guidance, with search RTs faster in neutral relative to valid trials. The same pattern of performance held in an experiment where the delay between the cue and search was manipulated (2 vs. 6 sec) to allow patients more time to use the cue. In invalid conditions, when the contents of WM matched a search distracter, search RTs in invalid trials were faster relative to neutral trials. The pattern of performance in VL patients is consistent with attention being driven away (inhibited) from the contents of WM that are re-represented during search. As opposed to the VL patients, the controls groups of age-matched controls and patients with lesions outside the thalamus displayed the normal effect of capture of attention from the contents of WM, with faster RTs on valid trials relative to the neutral condition and with slower RTs on invalid trials relative to the neutral condition.

The ´reversed´ memory-validity effect in VL patients cannot be attributed to memory impairments. Overall, thalamic patients and in particular VL patients displayed high scores in the memory tests and analysis of search performance were made for correct responses only in the memory test in experiments 4 and 6. Moreover, that VL patients display improved search performance when the WM contents specify distracter information (and hence needed to be suppressed) may prompt us to believe that the VL patients exerted a great cognitive control over

the irrelevant WM contents in order to favour behavioural goals. However, when the contents of WM are consistently valid for attentional goals, VL patients actually showed impaired search performance, which suggests that patients failed to integrate the WM content with the search target.

The data from both memory scores and memory-validity effects suggest that VL thalamic lesions impair how ´online´ memory information is used to bias attention and are in accordance to our previously established hypothesis that thalamic lesions disrupt biases of attention from information that is held in WM.

As just stated, the deficit is not due to poor commitment of the cues to memory. According to this view, information may be retained in working memory in the thalamic patients but in a state that precludes top-down enhancement of attention (Downing & Dodds, 2004; Olivers et al., 2011). For example, patients may store the memory input in a more "passive" state so it fails to access the sensory system. Rather, the 'reversed' pattern of memory effect on search indicates that VL lesions can trigger inhibition of matching signals between the contents held in memory and the incoming perceptual input; hence attention is directed away of memory-matching stimuli (see below).

Role of the VL thalamus in memory-based control of attention

In the introduction section of this thesis, I hypothesized that ablation of WM biases of attention in thalamic patients could be the result of disruption of important thalamo-cortical circuits that are critical for promoting top-down orienting of attention by the contents of WM.

Therefore, to understand the nature of the 'reversed' memory validity effect, and, more broadly, to understand the role of the VL thalamic nucleus in the interplay between memory and attentional selection, it is fundamental consider once more in the final discussion of this thesis the current evidence on the functions of anterior VL thalamic nuclei as part of a broader cortico-subcortical network.

In addition to the mediodorsal thalamus, the anterior thalamus around the VL nucleus is an integral part of a cortico-subcortical circuit alongside superior frontal regions in controlling eye movements (Kronenbuerger et al., 2010; Sommer & Wurtz, 2006; Tanaka & Kunimatsu, 2011). This is one pathway through which VL thalamus may be critical to generate attention biasing signals. Furthermore, the anterior thalamus also forms part of a network comprising the hippocampus, fornix, mammillary bodies, retrosplenial and posterior cingulate cortex that is relevant for recollective aspects of memory (Aggleton et al., 2010; Vann et al., 2009). This is another pathway through which anterior VL thalamus may be involved in triggering attention biasing signals from the contents held in memory.

I also found that pulvinar lesions reduced the influence of memory contents on attention. As noted earlier, the pulvinar is dynamically linked to parietal regions (Shipp, 2003, 2004) involved in WM and attention (Corbetta & Shulamn, 2002; Todd & Marois, 2004) and also feeds-back to visual regions. Hence, the pulvinar is in a good position to promote the interplay between WM and attention. Damage of related thalamo-cortical networks should explain why pulvinar patients display deficits of WM guidance of visual attention.

A frontothalamic pathway for memory-based control of attention

In Chapter 4, I delivered tDCS to the dorsal frontal areas (i.e. including SFG) which are known to be structurally connected to distinct thalamic nuclei (VL, MD and Pulv) (Mesulam et al., 1990; Shipp, 2003, 2004; Sommer & Wurtz, 2006); and investigated whether the effects of frontal-tDCS (anodal vs. cathodal) on WM guidance of attention could be modulated by the level of WM load (remembering 1 vs. 2 vs. 3 cues) and whether frontal-tDCS would facilitate WM guidance even when WM capacity is more stressed. I found that despite the effect of WM guidance of attention decreased from the low load to the high load condition, anodal relative to cathodal stimulation to the dorsal frontal cortex (e.g. SFG) of healthy individuals could still facilitate WM guidance in these conditions. These observations suggest that the dorsal frontal areas (e.g. SFG) may be important for

automatic WM guidance of attention and are in accordance with previous findings from Soto and colleagues (2007b). Critically, given that the dorsal frontal cortex is structurally connected to the VL thalamus, which plays a causal role in WM guidance as demonstrated by the lesion studies, here I conclude that the dorsal frontal cortex (e.g. SFG) is in a good position to form part of a frontothalamic network promoting the interplay between WM and attention.

Role of VL thalamus in experience-dependent learning for attention control

In Chapter 5, I reported neuroimaging evidence from healthy participants which corroborated that VL thalamus mediates the biasing of attention by abstract (verbal) cues but more critically it further illustrated that the response profile of the VL thalamus tracks the learning of stimulus associations that are used to optimize attentional selection in visual search.

Studies in rodents point to a role of the anterior thalamus and the tract connecting it with the mammillary bodies in learning (Aggleton, Neave, Nagle, & Hunt, 1995; Vann & Aggleton, 2003), and studies in macaques also indicate that the fornix, mammillary bodies and anterior thalamic nuclei form a network for the learning of visual discriminations ('object-in-place') that are aided by contextual information (Parker & Gaffan, 1997). Human studies have also implicated VL thalamus in memory and language (Johnson & Ojemann, 2000). These findings, together with the present neuroimaging data, indicate that the VL thalamus can mediate attention control driven by memory cues that are already consolidated in the cognitive repertoire (e.g. colour labels) as well as mediating the role of experience and the learning of new regularities that help to guide attention.

The role of anterior VL thalamus in experience-dependent attentional control may be understood as part of a broader cortico-subcortical network. Accordingly, I found that as learning of cue predictiveness developed during training to boost search, anterior VL thalamus co-activated as part of a distributed network comprising frontoparietal regions, such as middle and superior frontal and posterior parietal areas classically implicated in attentional control (Corbetta & Shulman, 2002) as well as regions previously associated with the acquisition and maintenance of

task rules such as the basal ganglia (Pasupathy & Miller, 2005; Xue et al., 2008).

"Filtering" vs. "Biasing" role of the thalamus

The main aim of this thesis was to test whether thalamic lesions would lead to deficits in "filtering" vs "biasing" mechanisms of memory-based control of attention.

Recent investigations suggest that the thalamus is important for controlling the orienting of attention while separating/filtering irrelevant distracter information from relevant target information (Snow et al., 2009; Ward et al., 2002). For example, Snow and colleagues (2009) found that, relative to controls, patients with pulvinar lesions were impaired in filtering irrelevant distracter information when target information was presented in the context of salient distracters (i.e. of high luminance). As noted earlier, even though our study was not specifically devised to test this idea, the results are consistent with a pulvinar role in the deployment of attention, namely, from the contents held in memory rather than distracter filtering, such an account would have predicted here that pulvinar patients ought to show exacerbated distraction by memory-matching irrelevant stimulus.

Moreover, fMRI research from Soto and colleagues (2007b) proposed that a frontothalamic pathway may be involved in monitoring the relevance of the contents held in memory for current selection goals (i.e. whether the current memory content overlaps with a target or a distracter) (Soto et al., 2007b; Soto et al., 2012b). Nonetheless, this suggestion was based on correlative fMRI findings, which as such preclude the formulation of causal inferences between brain activity and behaviour. Our lesion evidence enhances understanding of the nature of the functional role of the thalamus for memory/attention interactions beyond what could be anticipated from fMRI findings alone. If the functional role of the thalamus were to regulate the activation state of memory representations based on their current relevance for task goals (e.g. down-weighting representations associated with memory distracters for search), then I would have expected thalamic lesions to produce magnified attention biases by irrelevant contents held in memory. This

was clearly not the case. That our thalamic patients showed attenuation of the memory bias indicates that the thalamus is involved in the generation of a biasing signal that drives attention to matching information in the perceptual input, regardless of the behavioural relevance of the contents being maintained.

6.2. Future Research and Conclusion

Further neuroimaging research is needed to understand how the different nuclei of the thalamus interact with cortical networks (i.e. frontoparietal, visual networks, default-mode network) as function of WM and attention task demands and their interplay. For example, imaging studies such as resting state fMRI or diffusion tensor imaging with thalamic patients could help identify damage in functional connectivity between specific cortico-thalamic systems (i.e. relative to healthy controls) that can characterise deficits of WM guidance of visual attention. This important issue was not addressed in our lesion study with thalamic patients. Moreover, this is an important consideration since the functional role of the thalamus in cognition is determined by its functional connection to other structures.

Additional lesion approaches in conjunction with functional connectivity analyses may also probe useful to assess how subcortical damage outside the thalamus, for example in memory substrates (i.e. hippocampus) may directly impair WM guidance at the behavioural level and identify impairments in cortico-subcortical connectivity which may account for behavioural deficits of WM guidance. In order to do this, the focus should be on recruiting patient populations with damage in subcortical structures such hippocampus, middle temporal lobe regions associated with memory, and even basal ganglia regions that are involved in learning (Pasupathy & Miller, 2005; Xue et al., 2008) to directly assess how damage to such subcortical structures impair functional connectivity in cortical networks (e.g. frontoparietal).

Future studies could also assess how WM guidance is influenced by cognitive training. It is possible that WM training per se or even training in WM-guided search paradigm can lead to facilitation in WM guidance and it would be relevant to assess whether the behavioural benefit correlates with some form of brain plasticity, namely, with reconfiguration of the already mentioned brain circuits. Likewise, it would be interesting to assess this issue in patient populations and assess whether WM training, for example, in cortical lesion patients, can help to restore or reconfigure cortico-subcortical networks that can lead to recovery of attention function.

Conclusion

The findings reported in this thesis provide novel evidence for thalamic implication in "biasing" rather than "filtering" mechanisms of memory-based control of attention, hence stressing the importance of understanding the role of subcortical nuclei beyond cortico-cortical (e.g. parietofrontal) mechanisms of attentional control.

To date, understanding of the functional role of the thalamus in higher-level cognition remains limited. The recent review paper in Neuron by Saalmaan and Kastner (2011) illustrates very clearly these limitations. The current thesis demonstrates the role of the thalamus in higher-level cognition and highlights, for the first time, the thalamus as a key substrate for guidance of visual attention through working memory and experience-dependent learning.

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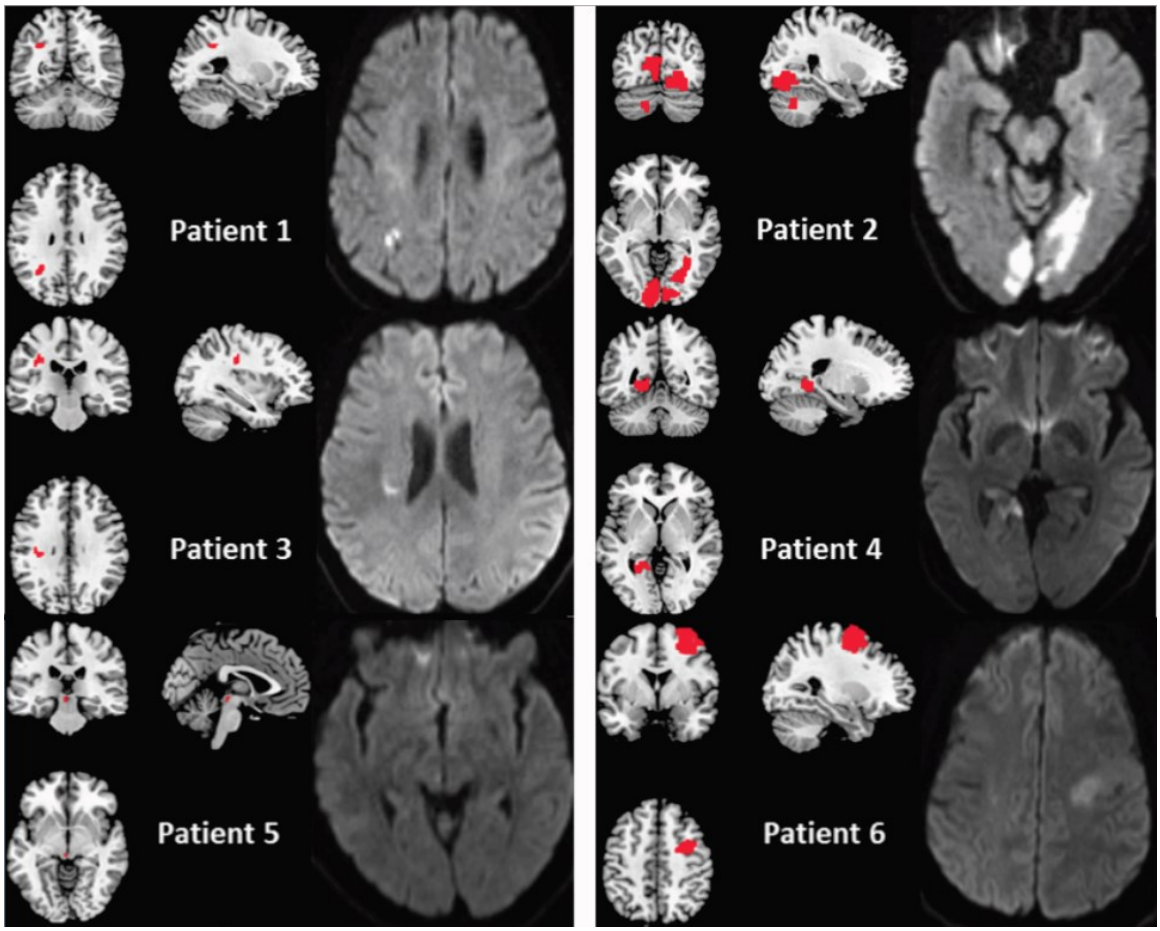
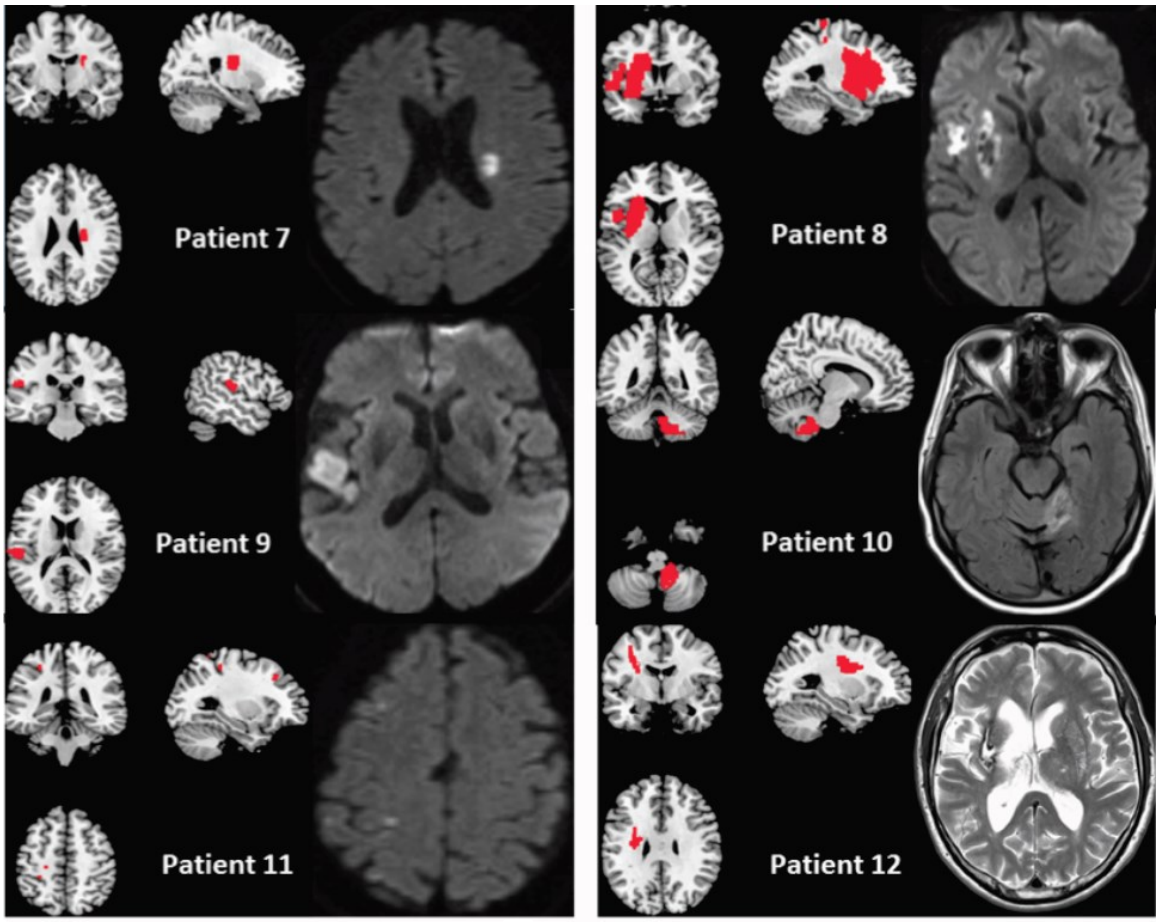
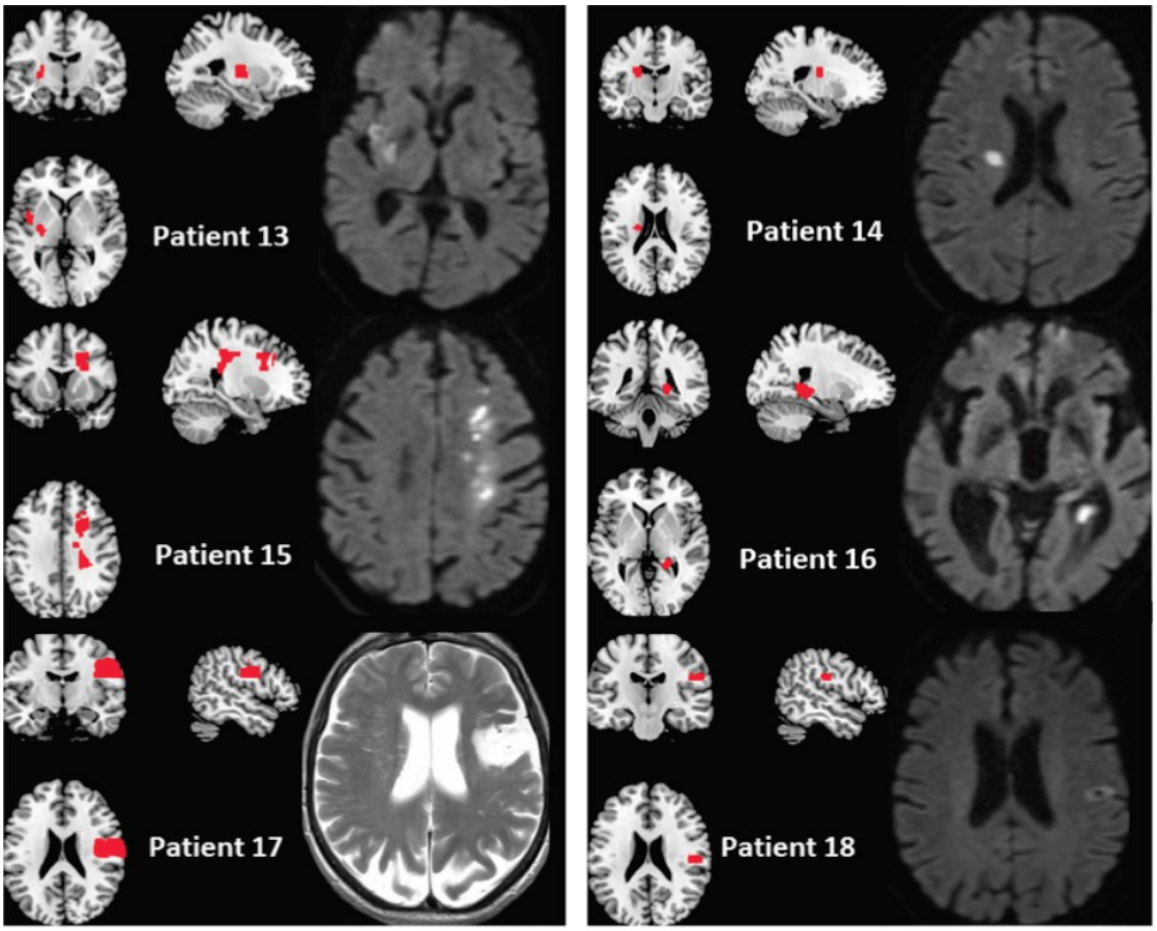
Appendices

Appendix I: Illustration of the lesion anatomy of the stroke patients with damage outside the thalamus.




Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12


Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18