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Special issue: Research report

Spatial working memory in Progressive Supranuclear Palsy

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ABSTRACT

The neural and cognitive mechanisms of spatial working memory are tightly coupled with the systems that control eye-movements but the precise nature of this coupling is not well understood. In particular, there are very few neuropsychological studies that explicitly examine how deficits of oculomotor control affect visuospatial working memory. Here, we examined the link between spatial working memory and the oculomotor system in a sample of patients with Progressive Supranuclear Palsy, a degenerative neurological disease characterised by defective vertical eye-movements but relatively preserved horizontal eye-movements. Consistent with the idea that the oculomotor system plays a critical role in spatial working memory performance, people with PSP had significantly shorter spatial spans when stimuli were presented along the vertical axis compared to the horizontal axis. This effect was not observed in age matched controls. We hypothesise that PSP disrupts a colliculo-parietal feedback loop that contributes to the maintenance of activation in a parietal priority map during the delay period. This result is the first direct neuropsychological evidence for an association between oculomotor function and spatial working memory and is broadly consistent with idea that rehearsal in visuospatial working memory is mediated by an 'oculomotor loop', as proposed by Baddeley (1986). We conclude that optimal spatial working memory performance depends on an intact oculomotor system.

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1. Introduction

Visuospatial short term memory (VSTM) is the ability to recall and manipulate information about the locations of objects in space. This function is essential for a range of everyday tasks, such as remembering or giving directions, or deciding if your car will fit into a small space. The cognitive processes involved

in visuospatial working memory have been extensively studied, and it is clear that VSWM is tightly coupled with the neural and cognitive processes involved in visuospatial attention and oculomotor control (Awh & Jonides, 2001; Awh, Vogel, & Oh, 2006). However, the exact nature of the link between oculomotor control and VSWM remains disputed, with some arguing that activity in oculomotor system is critical for

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optimal maintenance and recall (e.g., Belopolsky & Theeuwes, 2009; Johansson, Holsanova, Dewhurst, & Holmqvist, 2012; Lilienthal, Myerson, Abrams, & Hale, 2018; Pearson, Ball, & Smith, 2014) and others arguing it is an epiphenomenon of attentional rehearsal (e.g., Postle, Awh, Jonides, Smith, & D'Esposito, 2004; Scholz, Klichowicz, & Krems, 2018).

One influential idea is that offers a synthesis of these positions is that visuospatial memory, visuospatial attention and saccadic eye-movements are served by a common 'Priority map' that codes the spatial locations of greatest behavioural relevance (Ikkai & Curtis, 2011). The activation peaks in this Priority map corresponds to the likely locus of spatial attention (Bisley & Goldberg, 2010) and can be fed forward to oculomotor structures such as the Superior Colliculus to specify the co-ordinates of a saccadic eye-movement. With respect to VSWM, Ikkai & Curtis (2011) argue that the peaks in the priority map can be sustained after stimuli have disappeared, and therefore represent the short-term storage of the spatial locations of behaviourally relevant items. This proposal is consistent with neurophysiological evidence that spatial STM tasks activate brain areas known to be involved in the production of saccadic eye-movements and covert attention, such as Frontal Eye Fields (FEF) and Lateral Intraparietal Sulcus (LIP) (Cabeza & Nyberg, 2000; Ikkai & Curtis, 2011; Moore, Armstrong, & Fallah, 2003; Schafer & Moore, 2007; de Haan, Moryan, & Rorden, 2008) and neurostimulation studies demonstrating that transient disruption of these regions produce deficits of saccadic control (Zangemeister, Canavan, & Hoemberg, 1995), attentional orienting (Brighina et al., 2000; Ellison, Rushworth, & Walsh, 2003; Lane, Smith, Schenk, & Ellison, 2012b; Muggleton, Juan, Cowey, & Walsh, 2003; Smith, Jackson, & Rorden, 2005; 2009) and visual short-term memory (Campana, Cowey, Casco, Oudsen, & Walsh, 2007; Lane, Smith, Schenk, & Ellison, 2012a; Oliveri et al., 2001; Yang & Kapoula, 2011). These structures also signal the location of memorized stimulus even after the stimulus has been removed (Bruce & Goldberg, 1985; Sommer & Wurtz, 2001), and there are a handful of neuropsychological studies that show an association between frontal lesions, deficits of saccade control in anti-saccade tasks and impaired working memory (Walker, Husain, Hodgson, Harrison, & Kennard, 1998).

The overlap between oculomotor control, visuospatial attention and spatial working memory can also be observed behaviourally. Firstly, maintenance of a spatial location in working memory interacts with saccade execution, such that saccade trajectories to deviate away from the remembered location (Theeuwes, Olivers, & Chizk, 2005). Maintenance also affects the latency of saccadic eye movements, but the effects are inconsistent as some studies report inhibition of saccades to memorised locations, perhaps to protect the memory trace from interference (Belopolsky & Theeuwes, 2009) whereas others report facilitation of saccades to memorised locations (Wong & Peterson, 2013). Secondly, participants make spontaneous eye-movements to the location of absent stimuli during both rehearsal (Olsen, Chiew, Buchsbaum, & Ryan, 2014; Tremblay, Saint-Aubin, & Jalbert, 2006) and recall (Brandt & Stark, 1997; Johansson et al., 2012; Spivey & Geng, 2001). The accuracy of these movements is associated with enhanced memory performance (Lilienthal et al., 2018),

suggesting they play in functional role in mnemonic processing. However, similar gains can be seen when participants are instructed covertly attend to the location of the absent stimulus (Scholz et al., 2018), which is more consistent with the idea that the rehearsal-period eye-movements are an epiphenomenon of the activation of the priority map, rather than the cause of the enhanced retrieval per se. Thirdly, making saccadic eye-movements during the retention interval significantly impairs performance on the Corsi blocks task (Pearson & Sahraie, 2003; Postle, Idzikowski, Della Sala, Logie, & Baddeley, 2006), but not digit span or verbal memory. Notably, although eye-movements are known to precede by a mandatory shift of covert attention (Deubel & Schneider, 1996; Shepherd, Findlay, & Hockey, 1986), the disruptive effect of overt eye-movements on spatial memory is significantly greater than that of purely covert shifts of attention or that of eye-movements that are made with the eyes closed (Pearson & Sahraie, 2003) suggesting that the oculomotor system and covert attention make distinct contributions to spatial memory. Fourthly, disrupting the ability of healthy participants to plan and execute saccadic eye-movements during encoding and rehearsal significantly reduces memory span for spatial sequences (Ball, Pearson, & Smith, 2013; Pearson et al., 2014), but does not disrupt memory for visual patterns, or endogenous orienting of attention (Smith & Schenk, 2012; Smith, Ball, & Ellison, 2014) suggesting that the oculomotor system is particularly important when spatial sequence must be retained. Finally enforcing fixation at recall impairs memory performance (Johansson et al., 2012).

The neurophysiological and behavioural evidence therefore points towards a close coupling between visuospatial memory, visuospatial attention and oculomotor control. However, because eye-movements necessarily engage covert attention, and covert attention might engage the oculomotor system, the specific contribution of the oculomotor system to visuospatial working memory remains unclear. Neuropsychological studies of patients with oculomotor deficits have the potential to tease apart these relationships. Indeed, neuropsychology has played a critically important role in shaping the debates surrounding the role of the oculomotor system in spatial attention (see Smith & Schenk, 2012). Despite this rich potential, there are many fewer patient studies of the role of the oculomotor system in spatial working memory, and none that explicitly test the functional role of the oculomotor system in spatial STM.

We addressed this issue by examining spatial STM in Progressive Supranuclear Palsy (PSP). PSP, also known as Steele-Richardson-Olszewski syndrome (Steele, Richardson, & Olszewski, 1964), is a degenerative neurological disease that is associated with a number of motoric and cognitive symptoms, including postural instability leading to falls, akinesia and rigidity in the neck, problems with executive functions, apathy, impulsivity and impaired social cognition (Burrell, Hodges, & Rowe, 2014). Critically for the current study, a defining feature of PSP is paralysis of gaze ('supranuclear ophthalmoplegia') which initially affects vertical eye-movements, but can progress to affecting all eye-movements (Litvan et al., 2003). This vertical ophthalmoplegia is caused by degeneration of the medial longitudinal fasciculus (riMLF), a structure in the rostral midbrain

that drives vertical eye-movements. The vertical saccades are lost before horizontal saccades because the riMLF is more rostral than the parapontine reticular formation (which controls horizontal saccades) and therefore succumbs earlier in disease progression. Importantly, people with PSP typically do not have lesions in cortical areas involved in spatial processing and eye-movement control (e.g., LIP, FEF), so tend not to suffer from non-specific problems with spatial cognition. Indeed endogenous attentional orienting along the vertical axis is largely preserved in PSP (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988).

People with PSP have a unique combination of vertical ophthalmoplegia with relatively preserved vertical endogenous attentional orienting (Rafal et al., 1988). They therefore offer an ideal model to examine the specific role of the oculomotor system in visuospatial working memory. More specifically, we hypothesised that if the oculomotor system makes a unique contribution to visuospatial memory, we should observe an impairment of visuospatial memory when memoranda appear at locations that cannot become the goal of a saccadic eye-movement. We should therefore observe reduced Corsi-block spans for stimuli presented along the vertical compared to horizontal axis in patients with PSP.

2. Methods

2.1. Participants

Fourteen patients were approached via the Movement Disorder Service at The James Cook University Hospital, Middlesbrough following a clinical diagnosis of PSP made by Dr Archibald. Ten (6 female, aged 57–80, $M = 70$, $SD = 7$) agreed to participate, two of whom (1M, 1F) subsequently withdrew before completing the study. All participants met the National Institute of Neurological Disorders and Stroke and Society for PSP, Inc (NINDS-SPSP) (Litvan et al., 2003) criteria for clinically probable or definite PSP. We also recruited 8 age-matched controls from the local community (4 female; aged 57–80, $M = 68$, $SD = 6.4$). The study was approved by the North East - Newcastle & North Tyneside 1 Research Ethics Committee (15/NE/0254) and Durham University Department of Psychology REC.

2.2. Stimuli & apparatus

The experimental stimuli were generated using Eprime2 software and displayed on a 17-inch Sony Trinitron CRT monitor with a refresh rate of 100 Hz. Responses were collected on a KeyTech MagicTouch touchscreen attached to the monitor. Participants sat 40 cm from the display with the head supported by a chinrest. The height of the monitor was adjusted such that the centre of the screen was at eye level for each participant. The stimuli used for the modified Corsi task can be seen in Fig. 1. The stimulus array consisted of 12 grey discs (diameter of 2.2°) and a black fixation point presented on a white background. The array subtended $20^\circ \times 6^\circ$. Memoranda were indicated by the

appearance of black disc (diameter of 2.2°) in one of the placeholders.

2.3. Procedure

Participants with PSP completed a saccadometric test to establish their ocular motility. Participants were presented with a black spot at fixation. After 2000 msec the spot jumped into the periphery. Participants were instructed to follow the spot with their eyes and press a button when they were fixating it. Following the button press the spot returned to the centre and the next trial began. Each run consisted of 10 jumps that increased in magnitude in 1° steps, starting with a 2° jump. Participants completed 4 runs (Up, Left, Down, Right).

All participants then performed the modified Corsi blocks task. Trials began with the appearance of twelve placeholder discs arranged in a 6×2 array flanking a fixation point. The array was oriented along either the horizontal or vertical axis. After 1000 msec a sequence of memoranda were presented (starting with one up to a maximum of nine locations. Each placeholder could only flash once per sequence). Memoranda appeared for 250 msec and there was a 250 msec delay between consecutive items in a sequence. After presentation of the final item, the placeholder array disappeared and participants maintained fixation for 5 sec. The array then reappeared and participants were required to touch the placeholders in the order in which the items had been presented, using a stylus. On some trials participants accidentally pressed the screen or made an inaccurate pointing movement (i.e., they aimed at the correct location but landed outside the target area). In these cases the trial was repeated with the same number of items, but in a different configuration. The experimenter initiated each trial with a button press. The procedure is illustrated in Fig. 1. There were 3 trials at each level of difficulty. If at least 2 of the three sequences were correctly recalled an additional item was added to the sequence and the participant did 3 more trials. The task ended when participants made a mistake on two or more trials. Span was measured 3 times for each array orientation. Participants were instructed to maintain fixation on the central fixation point during each trial. We calculated the patients span by taking the average of the 3 memory spans at each orientation. Horizontal and vertical spans were assessed in blocks. The order of presentation was counterbalanced across participants.

3. Results

3.1. Saccadometry

All patients presented with supranuclear ophthalmoplegia that was more severe for vertical than horizontal saccadic eye-movements (this is a key diagnostic criteria for PSP and was established by Dr Archibald during clinical examination). The extent of the ophthalmoplegia was more formally assessed with saccadometry in 7/8 patients. Vertical eye-movements were absent in all participants with PSP. Horizontal eye-movements were present in all patients, but the

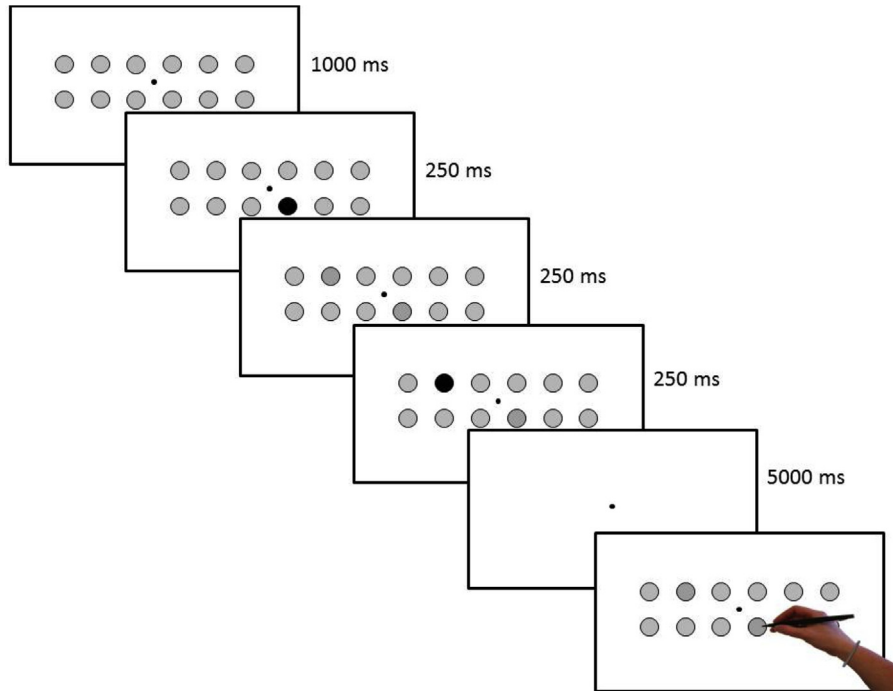


Fig. 1 – Illustration of the procedure for a 2-item trial in the horizontal condition.

main sequence was abnormal for left and/or rightwards saccades in 6/7 patients. The horizontal oculomotor range as was also restricted in 6/7 patients. Table 1 shows the oculomotor ranges of the 7 participants in the PSP group for whom saccadometric data were available. A paired t-test indicated that the restriction was more severe for leftwards than rightwards saccades [$t(6) = 3.1, p < .05$]. Patients 4 and 10 withdrew after completing the saccadometry and their data were excluded from the analysis.

3.2. Corsi blocks task

Fig. 2 shows the scores for the 8 participants in the PSP group and their healthy age-matched, controls. A 2 (Group: PSP, Age Matched Control) x 2 (Orientation: Horizontal, Vertical presentation) a mixed design ANOVA revealed a significant Group x Orientation interaction ($F_{(1,14)} = 8.34$;

$p = .012, \eta^2 = .37$). Paired t-tests showed that memory spans were statistically different for the vertical ($M = 2.58, SD = .83$) and horizontal ($M = 3.21, SD = .92$) in the PSP group; $t_{(7)} = 3.2, p = .014, dz = 1.13$. Horizontal and vertical memory spans were not statistically different in the Age Matched Controls; $t_{(7)} = .56, p = .6, dz = .18$. There was also a main effect of Orientation ($F_{(1,14)} = 4.86; p = .045, \eta^2 = .28$). The main effect of Group was nonsignificant ($F_{(1,14)} = 4.1; p = .061, \eta^2 = .23$).

To test the specific hypothesis that spatial memory span would be worse on the vertical than the horizontal in the PSP group (H_1) we calculated the Bayes factor for the horizontal versus vertical comparison in the PSP group. Priors were obtained from Ball et al. (2013), in which the effect of restricting ocular motility was a reduction of span by .6 items. In the current study the mean difference between horizontal and vertical span in the PSP group was .63 with a SE of .19. This

Table 1 – Saccadometry results. The oculomotor range was defined as the point at which participants ceased to scale their eye-movements with increasing target eccentricity. The main sequence describes the correlation coefficient between saccade amplitude and peak velocity. Meds: A = Amantadine, D = Donepezil, L = Levodopa.

Patient	Oculomotor Range (°)				Main Sequence (Pearsons r)		Medication
	Left	Right	Up	Down	Left	Right	
1	11	11	0	0	.16	.1	–
2	6.8	7.8	0	0	.73	.5	L
3	7	8	0	0	.70	.89	–
5	6.3	8.9	0	0	.38	.64	A
6	7.5	11	0	0	.8	.84	L
7	10.1	10.5	0	0	.3	.6	D, L
8	7.5	9	0	0	.5	.85	–
9	–	–	–	–	–	–	L
Mean	8.02	9.45			.51	.63	

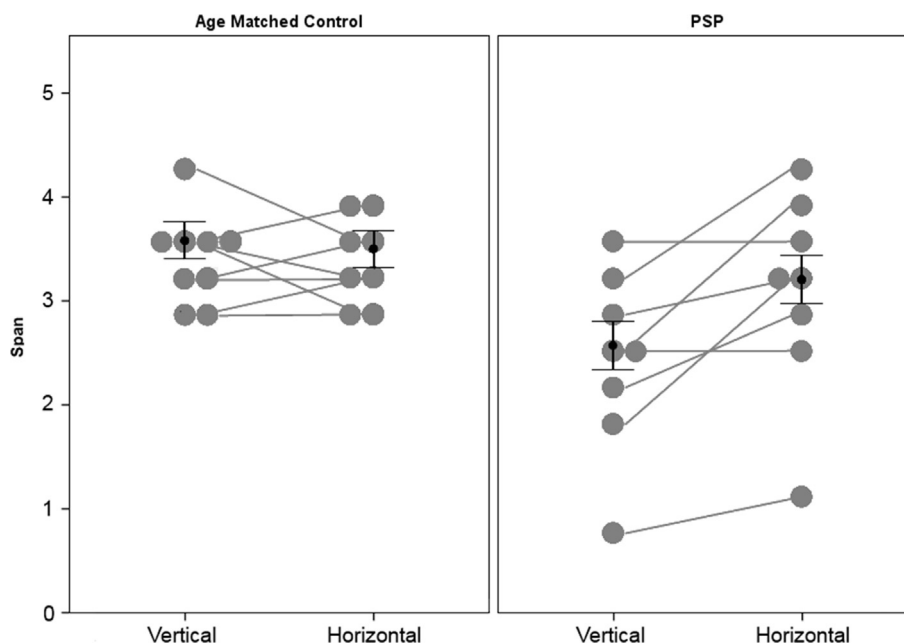


Fig. 2 – Performance on the Corsi blocks task in the Age-Matched Control and PSP group. Grey spots show individual participants, along with a numerical identifier for each participant to facilitate comparison across the horizontal and vertical conditions. Black spots show the group mean. Error bars show within-subject 95% Confidence Intervals (Cousineau 2005).

analysis produced a Bayes Factor of 76, which is strong evidence in favour of H_1 .

4. Discussion

We observed a significant impairment of spatial STM for stimuli presented along the vertically axis relative to the horizontal axis. In contrast, there was no horizontal/vertical asymmetry in a group of age-matched controls. These data suggest that the oculomotor system plays a pivotal role in the maintenance of spatial short-term memory, as the inability to make vertical eye-movements was associated with a significant reduction in span length for vertically aligned spatial sequences.

One straightforward interpretation of these data is that performance was impaired along the vertical but not horizontal axes because the patients with PSP were unable to implement an overt rehearsal strategy due to their ophthalmoplegia. However, the claim that overt rehearsal outperforms covert rehearsal of spatial sequences is contentious. While there is some evidence that overt rehearsal actively benefits recall when the maintenance phase lasts several seconds (Tremblay et al., 2006), this benefit is only observed when there is environmental support in the form of a constantly visible matrix of placeholders (Lilienthal et al., 2018). Furthermore, other studies argue that covert and overt rehearsal have a similar effect on memory when no placeholders are present (Godijn & Theeuwes, 2012; Scholz et al., 2018). Given that endogenous attention is relatively preserved in PSP (Rafal et al., 1988), that covert ‘attentional’ rehearsal is equivalent to overt oculomotor rehearsal when placeholders are removed during the maintenance interval (as

was the case in our study) and that healthy participants tend not to rely on overt rehearsal strategies when performing the Corsi blocks task (Patt et al., 2014) it seems unlikely that our patients’ memory impairment can be fully explained by an inability to engage in overt oculomotor rehearsal.

An alternative possibility is that the memory impairment in PSP has a neurological basis. It has been argued that VSWM is encoded and maintained in a parietal ‘Priority map’ that is also used to control visually guided action (Ikkai & Curtis, 2011; Zelinsky & Bisley, 2015). This map integrates bottom-up signal about the physical salience of different locations with top-down signal relating to the importance of the locations. Salient and/or important locations are represented at peaks of activation (Bisley & Goldberg, 2010; Fecteau & Munoz, 2006), and these peaks can be ‘read-out’ by the visual system to guide attention or by the oculomotor system to guide eye-movements. Activity in the map can be sustained one stimuli have disappeared (Ikkai & Curtis, 2011), and therefore represent the short-term storage of the spatial locations of behaviourally relevant items. Critically, there are feedback loops between this priority map and the oculomotor system, such that activity relating to saccade plans represented in the oculomotor system reinforces activity levels in the Priority map (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991). In this view, spatial short term memories are encoded as peaks in the priority map and their activation can be sustained by periodically covertly attending to these locations (Awh et al., 1999; Godijn & Theeuwes, 2012; Postle et al., 2004; Scholz et al., 2018), by planning eye-movements to those locations (Ball et al., 2013; Pearson et al., 2014) or by overtly fixating them (Silvana & Nicolas, 2018; Lilienthal et al., 2018; Tremblay et al., 2006). Damage to the oculomotor system would interfere with the feedback loop between signals in the oculomotor

system and the Priority map, thus reducing the potential for activity in the oculomotor system to contribute to the maintenance of activation peaks in the priority map during delay periods. This failure of maintenance would manifest as reduced spatial memory spans for locations that could not be represented in the oculomotor system, exactly as we have observed in our PSP group.

The oculomotor paralysis in PSP is caused by degeneration of the riMLF, a premotor structure in the brainstem that drives vertical eye-movements (Chen et al., 2010; Steele et al., 1964). riMLF is directly innervated by Frontal Eye Fields and Superior Colliculus. However, there are no feedback connections to these central oculomotor nodes (Munoz & Everling, 2004; Sparks & Mays, 1990) and riMLF is unlikely to be involved in the planning of a saccade. So, one might ask how a problem in this premotor structure could affect the activity levels in the central oculomotor structures. This apparent problem can be resolved if we consider the effect of loss of presynaptic neurons as a consequence of loss of trophic support from the post-synaptic cells, known as retrograde transneuronal degeneration (Pinching & Powell, 1971). Transneuronal degeneration has been observed in other parts of the visual system, such that lesions to striate cortex lead to degeneration of the optic tract and LGN (Cowey, Alexander, & Stoerig, 2011; Kisvarday, Cowey, Stoerig, & Somogyi, 1991). If a similar degeneration occurs following lesions in the oculomotor system, the loss of cells in riMLF would cause degeneration in the SC and/or FEF. This damage would be greater for the parts of the SC that code of eye-movements with a more vertical component and damage would have a profound impact on the ability of the patient to represent vertical eye-movements. In essence, we propose that memory impairment in PSP arises because degeneration in the brainstem oculomotor centres disrupts oculomotor activity in the SC and FEF, leading to a reduced ability to sustain delay-period activation in the priority map. This reduced activation level is expressed behaviourally as reduced spatial memory spans.

It is important to note that this view of rehearsal in spatial STM does not assume that activation of oculomotor system is the only mechanism involved in the maintenance of spatial memories. Other authors have convincingly argued that covert orienting of attention is also key rehearsal mechanism in spatial STM (Awh, Jonides, & Reuter-Lorenz, 1998; Godijn & Theeuwes, 2012; Postle et al., 2004). Rather, we propose that oculomotor activation interacts with other rehearsal mechanisms at the level of the priority map to maintain spatial sequences. This view of interacting oculomotor and attentional rehearsal mechanisms is consistent with the finding that teaching participants motor rehearsal strategies based on finger movements significantly extended digit spans when used in conjunction with phonological rehearsal (Reisberg, Rappaport, & Oshaughnessy, 1984), and is reminiscent of Baddeley's (Baddeley, 1986) proposal that rehearsal in visuo-spatial memory is mediated by an 'oculomotor loop'.

To summarize, we examined the role of the oculomotor system in spatial working memory using patients with a deficit of vertical eye-movements but relatively spared horizontal eye-movements. The PSP group had significantly reduced spatial memory spans, and this impairment primarily affected memoranda presented on the vertical but not the

horizontal axis. These data are clear evidence of a neuropsychological association between oculomotor control and spatial memory and are consistent with the idea that activation of oculomotor system plays a key role in the maintenance of spatial working memory by contributing to the maintenance of activation in the priority map.

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Supplementary data

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