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Spatial attention and spatial short term memory in PSP and Parkinson's disease

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ABSTRACT

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder characterised by deterioration in motor, oculomotor and cognitive function. A key clinical feature of PSP is the progressive paralysis of eye movements, most notably for vertical saccades. These oculomotor signs can be subtle, however, and PSP is often misdiagnosed as Parkinson's disease (PD), in its early stages. Although some of the clinical features of PD and PSP overlap, they are distinct disorders with differing underlying pathological processes, responses to treatment and prognoses. One key difference lies in the effects the diseases have on cognition. The oculomotor system is tightly linked to cognitive processes such as spatial attention and spatial short-term memory (sSTM), and previous studies have suggested that PSP and PD experience different deficits in these domains. We therefore hypothesised that people with PSP (N = 15) would experience problems with attention (assessed with feature and conjunction visual search tasks) and sSTM (assessed with the Corsi blocks task) compared to people with PD (N = 16) and Age Matched Controls (N = 15). As predicted, feature and conjunction search were sgnificantly slower in the PSP group compared to the other groups, and this deficit was significantly worse for feature compared to conjunction search. The PD group did not differ from AMC on feature search but were significantly impaired on the conjunction search. The PSP group also had a pronounced vertical sSTM impairment that was not present in PD or AMC groups. It is argued that PSP is associated with specific impairment of visuospatial cognition which is caused by degeneration of the oculomotor structures that support exogenous spatial attention, consistent with oculomotor theories of spatial attention and memory.

1. Introduction

Progressive Supranuclear Palsy (PSP) is a rare (Nath et al., 2001) and devastating neurodegenerative disease. It is typically considered as a movement disorder because the most salient symptoms include progressive gait disturbance associated with frequent backwards falls, oculomotor dysfunction, bradykinesia, rigidity of the limbs and problems with speech and

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swallowing (Golbe, 2014; Höglinger et al., 2017). However, PSP has also been associated with changes to behaviour such as dysexecutive syndrome (Gerstenecker, Mast, Duff, Ferman, & Litvan, 2013; Ghosh, Carpenter, & Rowe, 2013; Robbins et al., 1994), apathy (Brown et al., 2010), impulsivity (Zhang et al., 2016), and problems with social and visuospatial cognition (Burrell, Hodges, & Rowe, 2014; Ghosh et al., 2012; Kimura, Barnett, & Burkhart, 1981; Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988; Smith & Archibald, 2019, 2020). Diagnosis of PSP is challenging because there is considerable heterogeneity in presentation and no definitive blood or genetic test. Post-mortem studies demonstrate that many patients either receive the wrong diagnosis during life or succumb to the disease before ever receiving a correct diagnosis (Boxer et al., 2017; Williams et al., 2005; Yoshida et al., 2017). In these cases, patients are often given a diagnosis of Parkinson's disease, and PSP has been described as an atypical Parkinsonian disorder, despite being quite distinct from PD.

On first inspection many of the symptoms of PSP appear similar to those associated with Parkinson's disease, but one key area of difference is the effect on eye movements. PSP is typically characterised by progressive paralysis of gaze (the 'vertical supranuclear palsy') that affects vertical eye-movements in the early stages of the disease, then progresses to affect horizontal and vertical components of eye-movements (Chen et al., 2010; Steele, Richardson, & Olszewski, 1964). The progressive ophthalmoplegia affects stimulus-driven and volitional eye-movements, although the Optokinetic Nystagmus (OKN response) is typically preserved (Chen et al., 2010). This deficit is most likely the result of degeneration of the medial longitudinal fasciculus (riMLF), which contains the premotor neurons that drive vertical eye movements, the interstitial nucleus of Cajal (INC), which controls the maintenance of stable fixation and, later in the disease, the paramedian pontine reticular formation (PPRF) which controls horizontal saccades. Vertical saccades are lost before horizontal saccades because the riMLF is more rostral than the PPRF and succumbs earlier in disease progression (Chen et al., 2010; Steele et al., 1964). In contrast, oculomotor deficits in Parkinson's disease are more subtle and heterogenous (Anderson & MacAskill, 2013). Stimulus driven saccades may be faster, slower or no different to controls, depending on the eccentricity of the saccade goal (Chambers & Prescott, 2010) and display small hypometria, whereas volitional eye-movements and memory guided saccades are reliably slowed and hypometric (Anderson & MacAskill, 2013; Lueck et al., 1992). Volitional eye-movements are also disrupted during visual search, such that amplitudes are lower and fixation durations prolonged (Archibald, Hutton, Clarke, Mosimann, & Burn, 2013; Matsumoto et al., 2011) and patients with PD can present with problems inhibiting reflexive eye-movements (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005).

The fact that PSP and PD have very different effects on oculomotor control has potentially important implications for understanding cognitive function in the two diseases, because the eye-movement system is thought to be tightly coupled with mental processes such as attention (Awh, Armstrong, & Moore, 2006; Casteau & Smith, 2019; Hunt, Reuther, Hilchey, & Klein, 2019; Rizzolatti, Riggio, Dascola, & Umilta, 1987; Smith & Schenk, 2012), and spatial short term memory (STM) (Belopolsky & Theeuwes, 2009; Noton & Stark, 1971; Postle, Idzikowski, Della Sala, Logie, & Baddeley, 2006; Van der Stigchel & Hollingworth, 2018; Wynn, Shen, & Ryan, 2019). For example, it is well established that tasks that engage covert attention and spatial STM activate brain areas that are important for oculomotor control (Campana, Cowey, Casco, Oudsen, & Walsh, 2007; Corbetta et al., 1998; de Haan, Morgan, & Rorden, 2008; Gaymard, Ploner, Rivaud-Pechoux, & Pierrot-Deseilligny, 1999; Hamidi, Tononi, & Postle, 2008; Ikkai & Curtis, 2011; Nobre, Gitelman, Dias, & Mesulam, 2000; Smith, Jackson, & Rorden, 2005, 2009) and that planning and executing a saccadic eye-movement is associated with a mandatory shift of presaccadic shift of attention to the saccade goal (Deubel & Schneider, 1996; Shepherd, Findlay, & Hockey, 1986) and enhanced short-term memory for items at the saccade goal (Bays & Husain, 2008). Consistent with the idea of a functional coupling between spatial attention, spatial memory and the oculomotor system, deficits to oculomotor control are associated with disrupted visuospatial attention in patients with 6th nerve palsy (Craighero, Carta, & Fadiga, 2001), Duanes Syndrome (Gabay, Henik, & Gradstein, 2010) and ophthalmoplegia (Jackson et al., 2005; Smith, Rorden, & Jackson, 2004). Healthy participants can also show disrupted spatial attention when eye-movements are experimentally constrained (Casteau & Smith, 2020a; Craighero, Nascimben, & Fadiga, 2004; Michalczyk, Paszulewicz, Bielas, & Wolski, 2018; Morgan, Ball, & Smith, 2014; Smith, Ball, & Ellison, 2014; Smith, Ball, Ellison, & Schenk, 2010; Smith, Rorden, & Schenk, 2012). However, Hanning, Szinte, and Deubel (2019) found this effect did not generalise to highly trained participants performing discrimination task, suggesting that the tight coupling between exogenous attention and oculomotor control might be broken, given sufficient practice (Reeves & McLellan, 2020).

Spatial STM is also impaired when the motility of the eye is experimentally constrained (Ball, Pearson, & Smith, 2013; Pearson, Ball, & Smith, 2014) or when saccades are made during the retention interval of a spatial STM task (Pearson & Sahraie, 2003; Postle et al., 2006). Furthermore, deviations in the trajectory of saccadic eye-movements can be observed when participants either attend a distractor location (Sheliga, Riggio, & Rizzolatti, 1994) or hold a distractor location in spatial STM (Belopolsky & Theeuwes, 2009; Theeuwes, Olivers, & Chizk, 2005). Together, these studies are consistent with the claim that spatial attention and spatial STM are tightly coupled to oculomotor control.

Given the evidence that severe oculomotor dysfunction is associated with deficits of spatial attention and spatial STM, and the fact that people with PSP experience much more severe oculomotor impairments than people with Parkinson's disease, it seems reasonable to predict that people with PSP will experience more severe problems with spatial attention and memory than people with Parkinson's disease. Consistent with this proposal, Rafal and colleagues (Posner, Cohen, & Rafal, 1982; Rafal et al., 1988) conducted a series of studies exploring covert attention in PSP and PD using cueing tasks. The key manipulation was that cues could appear on either the horizontal or vertical axis, with delays of 10, 150, 350 or 550 msec between cue and target (cue-target onset asynchrony: CTOA). Patients with PD showed the typical biphasic exogenous cueing effect

(Posner, 1980), such that RTs were faster at the cued than uncued locations at short CTOAs (attentional facilitation) but slower at cued locations at longer CTOAs (Inhibition of Return: IOR). Facilitation and IOR were similar in magnitude in both the horizontal and vertical alignment conditions. In contrast, patients with PSP had significantly reduced facilitatory cueing effects when stimuli were aligned along the vertical axis and these effects were delayed until 350 msec. Similarly, IOR was disrupted along the vertical axis but not the horizontal. Rafal et al., concluded that a deficit of exogenous orienting was probably part of the PSP syndrome and likely to be caused by the degeneration of the oculomotor system.

Patients with PSP have also been reported to have impaired visual search compared to patients with PD. For example, Kimura et al. (1981) asked patients to locate a target picture among distractors and found the PSP group to be significantly slower and less accurate than patients with PD, patients with frontal lesions and patients with occipital lesions. The finding that people with PSP are more impaired on visual search than patients with occipital lobe lesions is striking, given that occipital lesions typically produce hemianopia, which is associated with highly disorganised visual search (Lane, Smith, Ellison, & Schenk, 2010; Zihl, 1995). Monza and colleagues (Monza et al., 1998; Soliveri et al., 2000) also reported that people with PSP perform worse than PD patients on the Visual Search Test, but the test used in their studies actually measured the ability to name pictures of objects rather than the ability to locate a target stimulus among distractors per se, so some caution is required when interpreting this result in terms of attention. Furthermore, both the Visual Search Test and Kimura's task require patients to identify complex drawings of objects, which is likely to engage endogenous attentional processes. It is also important to note that none of the studies of visual search explicitly examined the stimulus-driven mode of attention required when searching for salient feature singletons, so do not offer a very thorough characterisation of the nature visual search problems in PSP. We (Smith & Archibald, 2019) recently attempted to address this issue by examining feature and conjunction search in a group of patients with PSP. Following Rafal et al., (1989) we compared performance for targets displayed on the horizontal axis with targets on the vertical axis. Consistent with their observations using a cueing task, we observed that search was significantly slower when targets appeared on the vertical, but only for the feature search task. The PSP group were also significantly slower than the controls. These data seem consistent with the idea that PSP is associated with a deficit of spatial attention which is more severe for exogenous orienting and related to their oculomotor dysfunction. However, in Smith and Archibald (2019) the comparison group were healthy, age-matched older people rather than people with PD. It therefore remains unclear to what extent the search impairment was specific to PSP and therefore potentially useful as a diagnostic tool, or whether it reflects a more general problem associated with neurodegenerative diseases affecting the motor system.

Studies of spatial STM in PSP have produced more mixed results. Robbins et al. (1994) reported that PSP and PD were associated with impaired spatial STM as measured with the Corsi blocks task, which requires the participant to recall a sequence of locations. In this case the there was no difference between the degree of impairment in the two groups. In a related study Grafman, Litvan, and Stark (1995) reported no STM impairment in people with PSP when assessed using for the Sternberg memory task, which required patients to hold between 2 and 6 digits in memory and report which digit coincided with a dot-probe. However, in a recent study (Smith & Archibald, 2020) we tested spatial STM in patients with PSP using the Corsi task, hypothesising that their vertical gaze palsy would be associated with a selective deficit of memory for location along the vertical midline. This prediction was confirmed, such that the PSP group had significantly lower spans compared to a control group of age-matched controls for vertically aligned stimuli, although a limitation of this study was that the PSP group were not compared to a PD control group, so it is not clear to what extent the vertical deficit in spatial STM is specific to PSP.

To briefly summarize, PSP is a movement disorder that is characterised by a vertical paralysis of gaze. In other disorders paralysis of gaze is associated with problems with visuospatial attention, and similar associations between disrupted eye-movements and impaired attention and spatial STM have been observed using experimental disruptions of eye-movements in healthy participants. This disruption appears to be more severe for the exogenous mode of attention. Parkinson's disease is also a movement disorder, but patients do not experience such severe ophthalmoplegia. It therefore seems reasonable to predict that people with PSP will also experience more severe problems with attention and spatial memory than people with Parkinson's disease. Previous studies have offered partial support for this prediction but are limited because the tasks used did not differentiate between different modes of attention and in some cases did not directly compare groups with PSP and PD. Here, we address these issues by presenting previously unreported data from a sample of people with PD and PSP alongside a re-analysis and extension of data reported by (Smith & Archibald, 2019, 2020) which allows a direct comparison of PSP, PD and age matched controls. It was predicted that people with PSP would show impaired visual search and spatial short-term memory compared to PD and age matched controls, that this impairment will be more severe for feature search than conjunction search, and that PSP patient's deficits of spatial STM will be more severe when stimuli appear along the vertical axis compared to horizontal axis.

2. Methods

2.1. *TOPS compliance statement*

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.2. *Participants*

Fifteen people with PSP (8 female, M_{age} 69.5, age range: 53–80 years, $M_{disease\ duration}$ 35 months), 16 with Parkinson's Disease (M_{age} 68.2, age range 58–78, $M_{disease\ duration}$ 62 months) and 15 Age Matched Controls (M_{age} 69.7, age range 58–80) volunteered

to take part. All participants in the PSP group 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. All participants in the Parkinson's Disease group fulfilled the UK Brain Bank Criteria for a diagnosis of PD (Hughes, Daniel, Kilford, & Lees, 1992). These inclusion criteria were established prior to data analysis. Participants had the choice of participating in their own homes during a home visit by DS or in the Psychology Laboratories at Durham University. Fifteen people decided to participate at home (7 PSP, 7 PD, 1 AMC) and 31 came to the laboratory (8 PSP, 9 PD and 14 AMC). Participants took part having taken their usual medication. The study was approved by the North East Newcastle and North Tyneside 1 Research Ethics Committee (15/NE/0254) and Durham University Department of Psychology Research Ethics Committee. All participants gave informed consent and the study was conducted in accordance with the BPS code of ethics. The sample size was based on exceeding the sample of 8 participants per group collected by Rafal et al. (1988) and was not established with an apriori power analysis.

2.3. Stimuli and apparatus

2.3.1. Saccadometry

Eye-movements were recorded using a BioPac Systems MP150 with EOG100C amplifier modules recording horizontal and vertical EOG at 500 Hz. Stimuli were generated using a Cambridge Research Systems ViSaGe graphics card and displayed on a 17-inch monitor. The saccade target was a black spot (1°) presented on a grey background.

2.3.2. Visual search task

In the lab the experimental stimuli were generated using a Cambridge Research Systems ViSaGe graphics card and displayed on a 17-inch monitor. In the home experimental stimuli were generated using Eprime-2 software and presented on a 17-inch monitor. Responses were collected using a two-button box. The visual search target was a blue 'c' shape oriented at 45°. In the Feature search task the all distractor items were also blue 'c's, oriented at 215°. The Conjunction search task distractors could also be ether blue 'c's, oriented at 215° or yellow 'c's, oriented at 45°. Array items were presented at 10° from the centre of the screen on a black background. In 4-item arrays the stimuli appeared on the cardinal compass directions (N, E, S, W). In 8-item arrays stimuli appeared at cardinal directions and intermediate points (N, NE, E, SE, S, SW, W, NW). Some participants (7 PSP, 8 PD and 7 AMC) were presented with 16 item arrays in addition to the 4 and 8 item arrays. In order to allow comparison with the remaining participants the trials using 16 item arrays were excluded from the analysis. Participants sat about 50 cm from the display.

2.3.3. Corsi Blocks task

The experimental stimuli were generated using Eprime-2 software and displayed on a 17-inch monitor. Responses were collected on a KeyTech MagicTouch touchscreen attached to the monitor. Participants used a stylus. The same equipment was used for lab and home testing. Participants sat about 40 cm from the display. The height of the monitor was adjusted such that the centre of the screen was at eye level for each participant. 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° x 6°. Memoranda were indicated by the appearance of a black disc (diameter of 2.2°) in one of the placeholders.

2.4. Procedure

2.4.1. Saccadometry

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 1.5° jump. Participants completed 4 runs (Up, Left, Down, Right).

2.4.2. Visual search

The tasks began with the appearance of a fixation point for 1000 msec, followed by the appearance of a search array comprising 4 or 8 items. This array remained present until a response was made. Participants were instructed to press one button when a target was present, and the other if the target was absent. They were also instructed to fixate the centre of the array and try not to make eye-movements. There was a 2:1 ratio of 8 item arrays to 4-item arrays and a 2:1 ratio of target present to target absent trials. On target present trials the target appeared at each location in the array with equal probability.

Participants were given the opportunity to complete practice trials until they felt comfortable with the task (Conjunction $M = 27$ trials, range 7–40; Feature $M = 26$, range 8–64). There was also some variation in the number of experimental trials each participant completed due participants differing tolerance for the search tasks (Conjunction Search: $M_{PSP} = 196$, range 40–288; $M_{PD} = 185$, range 96–216; $M_{AMC} = 192$, range 108–216. Feature Search $M_{PSP} = 165$, range 40–288; $M_{PD} = 170$, range 96–216; $M_{AMC} = 164$, range 108–216).

2.4.3. Corsi Blocks task

The experimenter initiated each trial with a button press. Trials began with the appearance of twelve placeholder discs arranged in a 6 x 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 there was a 5 s rehearsal interval. The array then reappeared and participants responded by touching 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 in a different configuration. 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. Memory span was calculated as the mean 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

Data were analysed with JASP .9.1 (JASP Team 2020). Inferential statistics used an alpha of .05 and where appropriate Holm-Bonferroni corrections were applied to post-hoc *t*-tests to control for multiple comparisons. No part of the study procedures or analyses was preregistered prior to the research being conducted.

3.1. *Saccadometry*

Saccade data were collected from all participants in the PSP and PD groups who elected to do lab-based testing (8 PSP, 9 PD) and 11 of the age matched controls. Amplitudes were analysed using a 4 (Direction: Left, Right, Up, Down) x 3 (Group: PSP, PD, AMC) ANOVA. Analysis revealed a main effect of direction ($F_{(4,28)} = 100$, $p < .001$, $\eta_p^2 = .80$).and a Group × Direction interaction ($F_{(1,9)} = 74$, $p < .001$, $\eta_p^2 = .86$). Post-hoc *t*-tests effects indicated that leftwards saccades in PSP group were hypometric compared to AMC (8.19° v 10.8°; $t_{(18)} = 4.69$, $p < .01$, $d = 1.93$) and PD (8.19° v 10.79°, $t_{(16)} = 4.47$, $p < .01$, $d = 1.91$). Rightwards saccades were also hypometric for the PSP group compared to the AMC (9.58° v 11.76°; $t_{(18)} = 4.23$, $p < .01$, $d = 1.78$), but not compared to the PD group (9.58° v 10.68°; $t_{(18)} = 2.3$, $p = .15$, $d = .99$). Up and down saccades were absent in the PSP group. There were no differences between PD and AMC on up ($F_{(1,18)} = 1.9$, $p = .19$) or down ($F_{(1,18)} = 1.58$, $p = .22$) saccade amplitudes Fig. 1.

3.2. *Visual search: target present trials*

Two participants from the PSP group completed the Feature search task but not the Conjunction search task (participants 4 and 6) and two others completed the Conjunction Search task but not the Feature Search (participants 9 and 10). One participant in the PSP group (participant 2) had median reaction times that was more than 3 SD longer than the group mean during Conjunction search and was excluded from the analysis. One participant in the AMC group had a false positive rate of 98% in the conjunction search task. We therefore excluded their data from the analyses. These exclusion criteria were not explicitly established prior to analysis. Thus, 13 people with PSP completed the Feature search task and 12 completed the Conjunction search task. As not all participants completed both search tasks, Task was treated as a between-subjects factor. The data were filtered to remove anticipations (RT < 100 msec, <1% in all groups) and misses (6% PSP group, 4% PD group, <1% AMC group).

Median reaction times on target present trials were analysed with a 2 (Set Size) x 2 (Task) x 3 (Group) mixed ANOVA. Analysis revealed main effects of Set Size ($F_{(1,78)} = 16.02$, $p < .01$, $\eta_p^2 = .16$), Task ($F_{(1,\ 78)} = 8.4$, $p < .01$, $\eta_p^2 = .06$), Group ($F_{(2,78)} = 19.5$, $p < .01$, $\eta_p^2 = .28$) and a Group × Task interaction ($F_{(1,72)} = 5.2$, $p < .01$, $\eta_p^2 = .08$). Post hoc *t*-tests showed that during Feature search the PSP group was significantly slower than the AMC group (3525 msec v 910 msec, $t = 4.74$, $p < .01$, $d = 1.48$) and the PD group (3525 msec v 1375 msec, $t = 4.07$, $p < .01$, $d = 1.24$), but the PD and AMC group were not significantly different (910 msec v 1375 msec, $t = .89$, $p = .38$, $d = 1.28$). During Conjunction search the PSP group was significantly slower than the AMC group (1744 msec v 834 msec, $t = 5.2$, $p < .01$, $d = 1.91$) and the PD group (1744 msec v 1191 msec, $t = 3.16$ $p < .01$, $d = .10$). The PD group was also significantly slower than the AMC group (1191 msec v 834 msec, $t = 2.22$, $p < .05$, $d = 1.32$). Fig. 2 illustrates these effects.

To test the hypothesis that Feature search would be more impaired than Conjunction search in the PSP group we examined the simple main effects of Task at each level of Group. Consistent with this hypothesis there was a significant effect of Task in the PSP group such that Feature search was significantly slower than Conjunction search (3526 msec *vs* 1744 msec; $F = 5.04$, $p < .01$), but not the PD group ($F = 1.35$, $p = .26$) or AMC group ($F = 3.79$, $p = .06$).

We examined the accuracy of participants responses by subjecting the hit rates to a 2 (Set Size) x 2 (Task) x 3 (Group) mixed ANOVA. There were no statistically significant main effects or interactions ($M_{PSP} = 92.5\%$, $M_{PD} = 93.4\%$, $M_{AMC} = 98\%$).

Median reaction times on target absent trials were also analysed with a 2 (Set Size) x 2 (Task) x 3 (Group) repeated measures ANOVA. Analysis revealed main effects of Set Size ($F_{(1,78)} = 27.49$, $p < .01$, $\eta_p^2 = .24$), Task ($F_{(1,78)} = 9.5$, $p < .01$, $\eta_p^2 = .075$) and Group ($F_{(2,78)} = 15.73$, $p < .01$, $\eta_p^2 = .25$). There was also a Set Size × Task interaction ($F_{(1,78)} = 7.53$, $p < .01$, $\eta_p^2 = .065$)

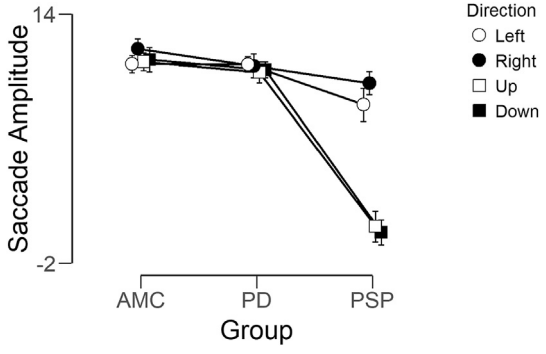

Fig. 1 – Saccade amplitudes in degrees. Error bars show 95% confidence intervals.

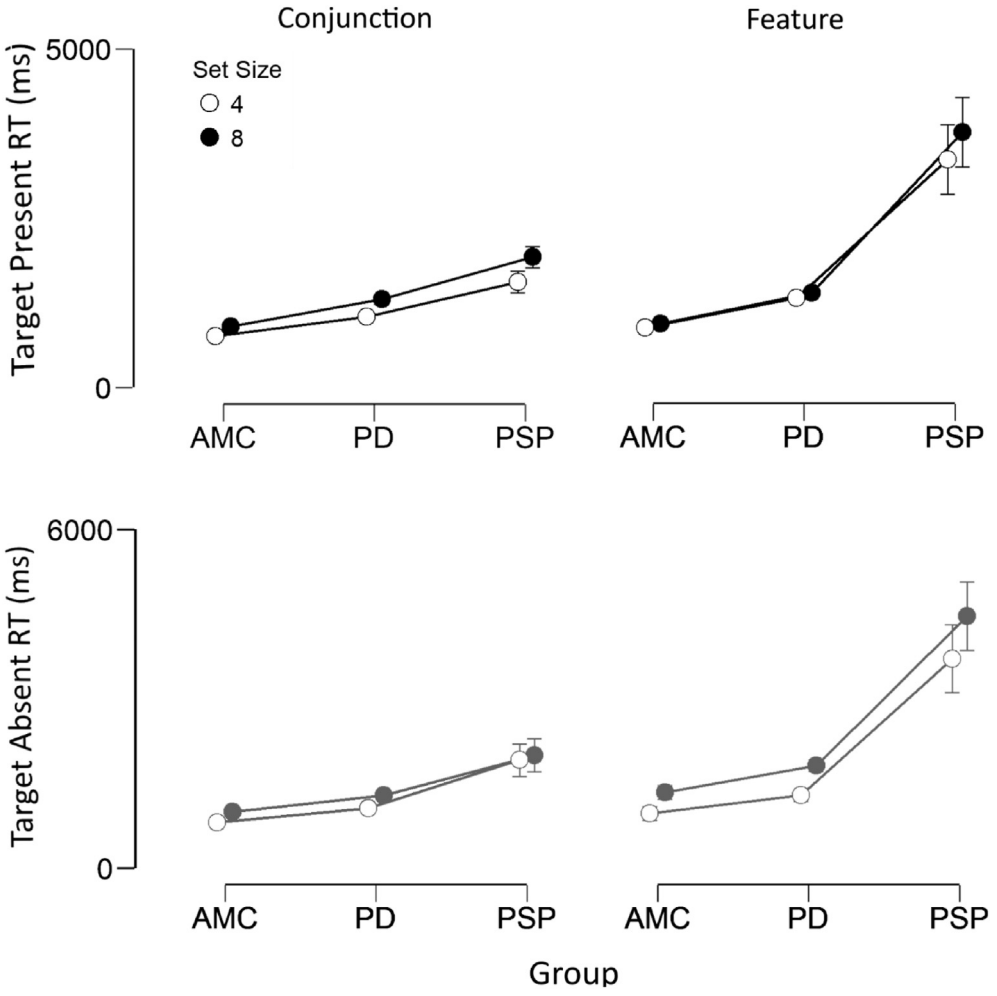

Fig. 2 – Upper panels show median reaction times for target present trials on conjunction and feature search tasks at each set size. Lower panels show RTs for correct rejections on target absent trials. Error bars show 95% CI's.

and a Group × Task interaction ($F_{(1,78)} = 3.79$, $p < .05$, $\eta_p^2 = .06$). Post hoc *t*-tests showed that during Conjunction search the PSP group was significantly slower than the AMC group ($t = 3.42$, $p < .01$, $d = 1.13$) and the PD group ($t = 2.53$, $p < .01$, $d = .8$), but the PD and AMC group were not significantly different ($t = .97$, $p = .34$, $d = 1.03$). During Feature search the PSP group was significantly slower than the AMC group ($t = 4.36$, $p < .01$, $d = 1.35$) and the PD group ($t = 3.9$ $p < .01$, $d = .12$). The PD group was not ignificantly different to the AMC group ($t = .61$, $p = .55$, $d = .95$). Analysis of the Set Size × Task interaction indicated there were a significant set-size effect on target absent RT for both Conjunction ($F = 22.99$, $p < .01$) and Feature search ($F = 24.55$, $p < .01$).

We examined the accuracy of participants responses by subjecting their correct rejection rates to a 2 (Set Size) x 2 (Task) x 3 (Group) mixed ANOVA. There was a small but statistically significant effect of Set Size, such that the correct rejection rate was higher for the 4 item sets (95%) than the 8 item sets (94.5%) ($F_{(1,78)} = 4.17$, $p = .045$, $\eta_p^2 = .047$). There were no other main effects or interactions (M_{PSP} = 92.5%, M_{PD} = 95.2%, M_{AMC} = 97%).

3.3. *Corsi Blocks task*

Four participants from the PSP group and 1 from the PD group did not complete the Corsi Blocks task. A 3 (Group: PSP, PD, AMC) x 2 (Orientation: Horizontal, Vertical) mixed design ANOVA revealed significant effects of Orientation ($F_{(1,38)} = 13.92$; $p < .01$, $\eta_p^2 = .21$) and Group ($F_{(2,38)} = 6.53$; $p < .01$, $\eta_p^2 = .26$) and a Group × Orientation interaction ($F_{(2,38)} = 6.53$, $p < .01$, $\eta_p^2 = .20$). Post-hoc *t*-tests were used to compare the groups at each level of orientation. When stimuli were oriented along the Horizontal axis the PSP group had significantly shorter spans compared to the AMC group ($M_{PSP} = 3.15$, SD = .89, $M_{AMC} = 4.07$, SD = .87; $t = 2.7$, $p < .05$, $d = 1.04$), but not the PD group ($M_{PSP} = 3.15$, SD = .90, $M_{PD} = 3.46$, SD = .81; $t = .89$, $p = .38$, $d = .36$). The AMC and PD group were not significantly different ($t = 1.96$, $p = .12$, $d = .73$). For the Vertical orientation the PSP group had significantly shorter spans compared to both the AMC group (M_{PSP} = 2.43, SD = .87, M_{AMC} = 3.84, SD = .81; t = 4.21, $p < .01$, d = 1.69) and the PD group ($M_{PSP} = 2.42$, SD = .87, $M_{PD} = 3.48$, SD = .87; $t = 3.12$, $p < .01$, d = 1.21). The PD and AMC group were not significantly

different ($t = 1.18$, $p = .73$, $d = .44$). Fig. 3 illustrates these effects.

4. Discussion

This study examined visual spatial attention and spatial STM in PSP and PD. The key findings were that (a) the PSP group were significantly slower at feature and conjunction search compared to PD and AMC, but the PSP and PD groups did not differ on accuracy, (b) within the PSP group feature search was significantly slower than conjunction search, (c) the PD group were slower and less accurate than AMC on both search tasks, but the difference in search time was only statistically significant for conjunction search, and (d) the PSP group had significantly reduced spatial memory spans compared to AMC, and a significantly reduced span along the vertical axis compared to the PD group.

The finding that PSP is associated with significantly more severe impairment of feature and conjunction search than PD is an important extension of prior work by Kimura et al. (1981), who reported impaired search performance in complex displays that required effortful search, but did not test visual search for single features and did not report data from target absent trials. The finding that impaired visual search generalises from complex scenes to conjunction search and simple feature search tasks is important because feature search tasks typically engage low-level, automatic attentional processes and do not require serial search through the array (Treisman, 1986). The observation that feature search is significantly more disrupted than conjunction search indicates that the search impairment in PSP cannot be attributed solely to a problem with effectively searching the stimulus array with overt eye-movements, as this would manifest as slowest performance during conjunction search, which requires serial selection of prospective target items. Instead, it seems that a problem orienting attention to salient locations forms a key part of the search deficit in PSP. Given that feature search probably relies on the same stimulus-driven attentional mechanisms as peripheral cueing (Briand & Klein, 1987), the conclusion that PSP is associated with a problem orienting to salient locations is in agreement with previous work arguing that people with PSP were significantly more impaired on covert, exogenous orienting compared to covert, endogenous orienting when tested using a cueing task (Posner et al., 1982; Rafal et al., 1988). They concluded that the subcortical oculomotor system plays an important role in exogenous orienting, and subsequent studies have identified the oculomotor system as a neural substrate for the salience maps hypothesised to underpin visual search. It therefore seems likely that search impairment in PSP reflects a problem with computing stimulus salience the level of the salience map.

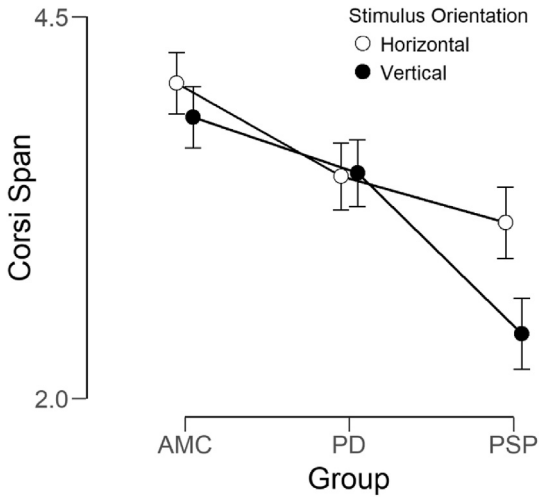

Fig. 3 – Corsi block spans for each group. Error bars show 95% confidence intervals.

A similar disruption to feature search can be observed in healthy participants whose eye-movements have been experimentally constrained, such that experimental disruption to the oculomotor system elicits a deficit in feature search but not in conjunction search (Smith et al., 2010, 2014). One issue with the studies is that they utilise the 'eye abduction' manipulation, which requires healthy participants to maintain an uncomfortable and unusual position with the eye abducted 40°from the canonical position (see Craighero et al., 2004). In two recent studies we kept the eye in the centre of the orbit and explored the effect of placing stimuli beyond the range of eye-movements, such that they could be seen but not foveated with a saccadic eye-movement, on visual search (Casteau & Smith, 2020b). Consistent with previous experiments, feature search was delayed and exogenous orienting abolished. A notable finding in Smith et al., 2014, Smith et al., 2010 and Casteau & Smith, 2020b was that although feature search was delayed, participants did not switch to a serial search strategy, suggesting that disruption to the oculomotor system reduces the efficacy of stimulus driven orienting, but may not necessarily abolish it completely (Smith & Archibald, 2019). This pattern of delayed stimulus-driven orienting when the oculomotor system is disrupted is similar to that observed in the PSP patients in the current study, and by Rafal et al., (1989) and broadly consistent with oculomotor theories of attention such as Oculomotor Readiness theory of Exogenous Orienting (Casteau & Smith, 2019) which we recently proposed as an revised version of the Oculomotor Readiness Hypothesis (Klein 1980) and Premotor Theory (Rizzolatti et al., 1987).

Patients with PSP also took almost twice as long to correctly reject no-target trials as patients with PD, although in contrast to the target-present trials, performance was equally impaired in the feature and conjunction search tasks and was modulated by set-size. This latter finding suggests that participants in the PSP group set a high criterion for target absent trials, such that failing to detect a feature singleton led to a serial search through the array to confirm that no target was present, rather than an immediate target absent response.

The PD group were slower than AMC on both search tasks, but this difference was only statistically significant for the conjunction search. Previous studies examining visual search in PD have produced somewhat contradictory findings. Some authors have argued that PD is associated with defective feature search (Mannan, Hodgson, Husain, & Kennard, 2008; Troscianko & Calvert, 1993; Weinstein, Troscianko, & Calvert, 1997), whereas others report no deficit (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Cormack, Gray, Ballard, & Tovee,

2004), or a mixed pattern such that feature search was disrupted but only for low salience targets (Horowitz, Choi, Horvitz, Cote, & Mangels, 2006; Lieb et al., 1999). Horowitz et al. (2006) argue that search deficits in PD arise because dopamine plays a key role in enhancing the signal-to-noise ratio of salient signals. When dopamine is depleted salient signals are weakly represented and competing signals are not efficiently suppressed. This leads to problems with search specifically when the target is low salience, (e.g., if the target shares some properties with distractors and/or the distractors are heterogenous). They further argue that this problem can be attenuated if the observer knows the identity of the target, and is thus able to enhance signal to noise using top-down processes, noting that feature search is typically normal when target identity is known and the distractors are homogenous. In our study the target was always the same and the distractors homogenous, so the finding that feature search was spared in PD is in accordance with this line of argument. In contrast, previous studies generally find that conjunction search is preserved in PD (Horowitz et al., 2006; Weinstein et al., 1997) and it not clear why the PD group were impaired in the current study. It is likely that participants made eye-movements during the conjunction search task, and as PD is associated with subtle deficits of visual search (Archibald et al., 2013), it is possible that the slowed search reflects less efficient overt search movements, rather than disordered attention per se.

Patients with PSP performed significantly worse than patients with PD and age matched controls on the spatial short-term memory task. In the most directly comparable prior study (Robbins et al., 1994), reported a significant short-term spatial memory impairment in both PD and PSP when measured with the Corsi task, but the impairment was of a similar magnitude in the two groups. Grafman et al. (1995) reported no memory impairment for the Sternberg memory task. One key difference between the previous studies was the location of the stimuli. Robbins et al. (1994) presented their blocks in a pseudo-randomised pattern but did not control the vertical and horizontal aspects of the arrays, Grafman et al. (1995) presented stimuli along the horizontal midline whereas our stimuli were either vertically aligned or horizontally aligned. In the current study, the data from the horizontal condition are quite similar to that of Robbins et al. (1994) in that the PSP group showed a significant impairment in spatial STM relative to AMC, but not the PD group, although in our case the difference between the PD and AMC groups did not reach statistical significance. However, the data from the vertical condition diverge somewhat from those of Robbins et al., and Grafman et al., in that the PSP group were markedly impaired relative to both PD and AMC. Given the evidence that spatial STM is related to oculomotor control, that the oculomotor control in the PSP group is particularly impaired along the vertical axis, previous studies may have underestimated the extent of the spatial STM deficit because they did not differentiate between memory spans for horizontally and vertically presented stimuli. There are also differences in timing, such that Robbins et al., displayed memory item for 3 s with no inter-item delay, whereas our stimuli were presented for 300 msec with a 300 msec inter-item delay. Average memory spans were shorter by ~1 item in our study than in Robbins et al., suggesting that participants found our task more difficult, and it this many also have contributed to the discrepant results.

From a theoretical perspective there are two possible reasons why problems with oculomotor control might lead to an impairment in spatial STM. Firstly, as oculomotor problems disrupt attention and attention is needed to encode stimuli into memory, it may be that the memory deficit reflects a problem with encoding the spatial locations, rather than a problem with maintaining the memory representation per se (Awh & Jonides, 2001). However, as we have argued elsewhere (Casteau & Smith, 2019), the endogenous attentional mechanisms implicated in STM encoding are largely independent of oculomotor control so it is unlikely that the memory deficit could be fully explained by encoding problems. Alternatively, it may be that the oculomotor problems interfered with the maintenance of the representations by disrupting the 'oculomotor loop', which acts as a rehearsal mechanism in spatial STM (Baddeley, 1986; Ball et al., 2013; Pearson & Sahraie, 2003). Consistent with this explanation, disruption of eye-movement in healthy participants produces the greatest STM impairment when applied during the maintenance phase, rather than during encoding or recall (Pearson et al., 2014).

The observation that people with PSP have significant impairments of visual search and spatial STM compared to patients with PD may have important practical implications. As was noted in the Introduction, misdiagnosis of PSP as PD is a relatively common problem. This is an important issue, because the pathology of PSP is very different to that of PD. Misdiagnosis is upsetting for patients, and patients often have poor response to the standard treatments for Parkinson's disease. Furthermore PSP is much more aggressive than PD, with a mean life expectancy of only 6 years post diagnosis, so correct diagnosis is essential in order to give patients and carers the best opportunity to make appropriate care plans and access the resources needed to maintain as good a quality of life as possible as the disease progresses. If cognitive tasks such as visual search can reliably differentiate PSP and PD, there seems to be a promising avenue for developing relatively cheap and effective tools that might enable earlier and more accurate diagnosis.

There are some limitations to the study that should be noted before drawing our conclusions. Firstly, due to the mobility issues associated with motor disorders such as PSP and PD, not all of the participants were able to be tested under the same laboratory conditions. It was therefore not possible to precisely control some aspects of testing, such as the ambient lighting or the distance from the monitor for some participants. However, as our tasks were not psychophysical and did not demand fine-grained perceptual discriminations we feel these differences are unlikely to explain the large differences between the groups. Secondly, we were only able to record eye-movements for subset of the patients, so were unable to objectively evaluate the extent of any problems with horizontal gaze in all the PSP patients. It is therefore possible that there was some heterogeneity in the extent of oculomotor disfunction in the PSP group. However, this alone is unlikely to be the cause of any between group differences as all patients had their vertical gaze paralysis confirmed during a

clinical exam prior to enrolment in the study. A further important issue is that the majority of PD patients were taking medication that effectively alleviated their movement problems, whereas the medications available to the PSP patients were less effective at controlling motor problems. This is potentially problematic, given that a key outcome measure of the visual search task was the reaction time for target detection. It is therefore possible that the visual search impairment we attributed to problems with attention can be at least partially explained in terms of delayed motor execution. However, a global motor impairment could not explain the why feature search should be more disrupted than conjunction search, and cannot account for performance on the Corsi task, which was untimed. A final limitation was that although participants were screened for cognitive function as part of the recruitment process to exclude participants with severe cognitive impairment we did not assess general cognition as part of the experimental protocol. As a consequence, we could not directly compare the PD and PSP for global cognitive impairments. However, the PSP and PD groups performed at an equally high level of accuracy on both visual search tasks, suggesting that both groups understood the tasks and were able to implement the instructions. We are therefore confident that these effects reflect a specific differences in visuospatial cognition between the groups and are not an artefact of their differing treatment regimens or a global cognitive impairment that was present in the PSP group but not the PD group.

To summarize, this study examined visuospatial attention and short-term memory in patients with PSP, PD and age matched controls. All patients with PSP presented with severe vertical gaze paralysis. Horizontal eye-movements in the PSP group were also slow and hypometric compared to those of patients with PD and controls. The PSP group were significantly slower than the PD group and controls at feature search and conjunction search, whereas people with PD differed from controls on only conjunction search. Furthermore, the search impairment in PSP was observed for target present and target absent trials and was more pronounced for feature search than conjunction search, but was not modulated by set-size. The PSP group also had shorter spatial memory spans than people with PD and controls. This deficit was more severe when memoranda appeared along the vertical midline than the horizontal midline. It is argued that these cognitive impairments arise as a consequence of the dysfunction in the oculomotor system, consistent with oculomotor theories of attention and STM. These data indicate that patients with PSP may have specific impairments in visuo-spatial cognitive functions that differentiate them from patients with PD. Measures of visuospatial cognition have the potential to be a promising avenue of enquiry for the development of new tools to assist with the early and accurate diagnosis of PSP.

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