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Role of the left hemisphere in visuospatial working memory

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Abstract

Visuospatial processing deficits are typically associated with damage to the right hemisphere. However, deficits on spatial working memory have been reported among some individuals with focal left hemisphere damage (LHD). It has been suggested that the left hemisphere may play a role in such non-verbal working memory tasks due to the use of subvocal, verbally-mediated strategies. The current study investigated the role of the left hemisphere in spatial working memory by testing spatial span performance, both forward and backward, in a large group of individuals with a history of left hemisphere stroke. Our first aim was to establish whether individuals with LHD are indeed impaired on spatial span tasks using standardized span tasks with published normative data. Our second aim was to identify the role that language plays in supporting spatial working memory by comparing LHD individuals with and without aphasia, and by relating spatial span performance to performance on a series of language measures. Our third aim was to identify left hemisphere brain regions that contribute to spatial working memory using voxel-based lesion symptom mapping (VLSM), a whole-brain statistical approach that identifies regions critical to a particular behavior on a voxel-by-voxel basis. We found that 28% of individuals with LHD performed in the clinically-impaired range on forward spatial span and 16% performed in the clinically-impaired range on backward spatial span. There were no significant differences in performance between individuals with and without aphasia, and there were no correlations between spatial span performance and language functions such as repetition and comprehension. The VLSM analysis showed that backward spatial span was associated with a left fronto-parietal network consisting of somatosensory cortex, the supramarginal gyrus, lateral prefrontal cortex, and the frontal eye fields. Regions identified in the VLSM analysis of forward spatial span did not reach the conservative statistical threshold for significance. Overall, these results suggest that spatial working memory, as measured by spatial span, can be significantly disrupted in a subset of individuals with LHD whose lesions infringe on a network of regions in the left hemisphere that have been implicated in domain-general working memory and attentional control mechanisms.

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Keywords

Aphasia; Working memory; Spatial span; Voxel-based lesion symptom mapping; Left hemisphere; Fronto-parietal network

1. Introduction and background

Working memory is typically described as a higher-order process that provides cognitive space for the temporary storage and manipulation of both verbal and spatial information (Baddeley, 1992; 2003). In research and clinical neuropsychology, working memory is often tested with span tasks that require examinees to reproduce a series of either verbal or visuospatial sequences (Baldo, Katseff, & Dronkers, 2012; De Renzi, Faglioni, & Previdi, 1977; Kessels, Kappelle, de Haan, & Postma, 2002; Kessels, van Zandvoort, Postma, Kappelle, & De Haan, 2000; Luciana, Burgund, Berman, & Hanson, 2001; Nys, van Zandvoort, van der Worp, Kappelle, & de Haan, 2006; Wilde, Strauss, & Tulsky, 2004). In visuospatial span tasks, the examiner points to a series of spatial locations on a board and the examinee is instructed to point to the locations in the same order (forward spatial span) or reverse order (backward spatial span; Corsi, 1972; Milner, 1971). Performance on spatial span is typically measured as accuracy in reproducing/reversing the sequences.

Early models of spatial working memory posited a visuospatial sketchpad that is activated in forward spatial span tasks to temporarily hold the locations and order in mind (Baddeley & Hitch, 1974), with additional engagement of the central executive for the manipulation of information required for backward spatial span (Baddeley, 1986; Hester, Kinsella, & Ong, 2004). More recent findings, however, have suggested that both forward and backward spatial span rely on common working memory mechanisms that engage central executive systems, with backward span requiring additional attentional control (Vandierendonck, Kemps, Fastame, & Szmalec, 2004; Wilde et al., 2004). In addition, domain-general theories suggest that attentional control processes are critical for working memory regardless of modality (Barrouillet, Bernardin, & Camos, 2004; Cowan, 1995).

Visuospatial functioning in general has been associated primarily with the right hemisphere and this holds true for visuospatial working memory as well (De Renzi et al., 1977; Jonides et al., 1993; Kessels et al., 2002, 2000a,b; Smith, Jonides, & Koeppe, 1996). Consistent with this notion, a few studies have shown that individuals with left hemisphere damage (LHD) perform well on spatial span tasks relative to individuals with right-hemisphere lesions or neurologically-intact individuals (Beeson, Bayles, Rubens, & Kaszniak, 1993; Corsi, 1972). However, other studies have reported that individuals with LHD do exhibit deficits on spatial span tasks (Burgio & Basso, 1997; De Renzi & Nichelli, 1975; Kasselimis et al., 2013).

There are a number of factors that might account for the discrepancy in spatial span findings in the literature. One of these factors is the presence/degree of aphasia in the samples, as verbal mediation has been suggested to play a role in spatial span performance (Postma & de Haan, 1996; Rausch & Ary, 1990). A few studies have looked at the potential role of aphasia/language abilities on spatial span and found that the presence or severity of aphasia or other phonological abilities have an impact on spatial span performance (Kasselimis et

al., 2013; Lang & Quitz, 2012; Martin & Ayala, 2004; Potagas, Kasselimis, & Evdokimidis, 2011). Conversely, negative findings with respect to the impact of aphasia on spatial span performance have also been reported for both the presence and type of aphasia (Burgio & Basso, 1997; De Renzi & Nichelli, 1975; Kasselimis et al., in press). It is possible that this mix of positive and negative findings with respect to the role of language in spatial span is due to some studies relying solely on a general aphasia or subtype classification rather than assessing distinct language processes.

Another possible confounding factor in previous studies of spatial span in individuals with LHD is the specific location of lesions. Lesion site is typically not included as a factor in analyses and when included, has often been arbitrarily-defined or has included large regions of interest (e.g., anterior vs. posterior; Beeson et al., 1993; Burgio & Basso, 1997; De Renzi & Nichelli, 1975; Lang & Quitz, 2012). There is some evidence that posterior left hemisphere regions play a role in forward spatial span performance (De Renzi & Nichelli, 1975). However, other studies have not replicated this effect for forward spatial span (Beeson et al., 1993; Burgio & Basso, 1997) or backward spatial span (Kasselimis et al., 2013). In the neuroimaging literature, there is evidence for a domain-general dorsal attention network comprised of superior frontal cortex and the intraparietal sulcus that supports working memory, so that lesions in both anterior and posterior regions could affect spatial span (Majerus et al., 2016, 2012; Todd & Marois, 2004).

Yet another possible explanation for the mixed findings on spatial span in individuals with LHD is that the majority of studies have focused on forward spatial span alone (Beeson et al., 1993; Burgio & Basso, 1997; De Renzi & Nichelli, 1975; Martin & Ayala, 2004). As mentioned above, backward spatial span has been posited to engage additional rehearsal and/or manipulative mechanisms in some models. It may be that forward and backward spatial span are thus differentially affected in LHD individuals (Baddeley, 1986; Harnish & Lundine, 2015; Hester et al., 2004).

Last, spatial span performance is sometimes discussed as *relatively* preserved in individuals with LHD, without establishing whether spatial span performance is in fact in the “normal” range. Most studies have relied on previously published cut-off scores from a sample of patients hospitalized for non-neurological illnesses (De Renzi & Nichelli, 1975; Martin & Ayala, 2004; Potagas et al., 2011).

In summary, the literature on spatial working memory in LHD individuals has been mixed due to a number of factors: 1) presence/degree of aphasia and related language functions, 2) lesion site, 3) test conditions (forward vs. backward span), and 4) lack of normative data (i.e., establishing what is “impaired” performance). The first aim of this study was to identify whether the left hemisphere contributes to spatial working memory by evaluating spatial span performance in individuals with LHD using standardized span tasks with published normative data. The second aim was to determine whether language plays a role in supporting spatial working memory by comparing LHD individuals with and without aphasia and by assessing the relationship between performance on spatial span and specific language measures. The third aim was to identify which left hemisphere brain regions are critically related to spatial span performance using a whole-brain voxel-based lesion

symptom mapping approach (VLSM), which allowed for the identification of brain regions that play a critical role in supporting spatial span performance.

2. Methods

2.1. Participants

Spatial span, language, and brain imaging data were retrospectively analyzed from 50 individuals (12 female) who met the following criteria: History of a single, left hemisphere stroke, pre-morbidly right-handed, English as a first language, minimum 10th grade education, chronic phase of stroke (> 5 months), no other neurologic history, no neglect and/or visual field deficits, no severe psychiatric history (e.g., bipolar disorder, schizophrenia) or substance abuse history, reconstructed computerized tomography (CT)/ magnetic resonance imaging (MRI) scan, ability to comply with task instructions, and completion of visuospatial and language testing. The mean age of the sample was 64.3 years (*SD* = 11.5, range 31–84), mean educational attainment was 15.5 years (*SD* = 2.8, range 10–22), and mean duration post-stroke was 70.0 months (*SD* = 78.7, range 5–328).

2.2. Materials and procedures

Testing took place at the VA Northern California Health Care System. The study was carried out in accordance with the Helsinki Declaration and approved by the VA Northern California Healthcare System Institutional Review Board. Participants signed informed consent forms prior to participation and the privacy rights of participants were observed.

Participants were administered a test battery that included neuropsychological measures as part of an existing research protocol. A subset of these measures was analyzed in the current study.

2.2.1. Spatial span task—All participants were administered the forward and backward conditions of the Spatial Span subtest from the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). This task involves the examiner touching a series of blocks in different locations that are mounted on a board in a randomized order. The examiner touches the tops of the blocks at a rate of approximately one block per second. In the forward spatial span condition, examinees are asked to touch the blocks in the same order as the examiner. In the backward spatial span condition, examinees are asked to touch the blocks in the reverse order. The number of blocks in each series increases as long as the examinee can accurately reproduce/reverse the sequence on at least one of the two trials at each span length. The task is discontinued when two consecutive trials of the same length are failed.

All participants in this study were able to comply with task demands, despite comprehension deficits in some participants. Gestures were used as necessary to convey instructions (e.g., pointing), in addition to the standard verbal instructions. If a participant could not comply with the task demands, the test was not completed or scored and thus was not included in the analyses for this study. That is, any spatial span performance deficits in the current sample cannot be attributed to a failure to understand task instructions. Although all individuals were pre-morbidly right-handed, some participants used their left hand for the spatial span task due to weakness/paralysis.

Age-corrected, standardized spatial span scores from the WMS-III manual were used to establish the number of individuals with LHD in the “clinically-impaired” range. A standardized score was considered “clinically-impaired” when it fell at or below the 9th percentile (≥ −1.33 SDs). Since standard scores compress raw scores into smaller ranges of possible values, in some analyses we utilized raw scores (with corrections for age) in order to maintain data variability.

2.2.2. Language testing—All participants were administered the Western Aphasia Battery (WAB; Kertesz, 1982) to evaluate speech and language abilities. Based on the WAB classification system, the current sample included 15 individuals with anomic aphasia, 8 with Broca’s aphasia, 6 with Wernicke’s aphasia, 2 with conduction aphasia, 1 with global aphasia, 1 with transcortical sensory aphasia, and 17 who scored within normal limits. This latter group includes individuals with very mild or no aphasic symptoms who scored above the WAB cut-off score for normal language on the overall WAB score, ≥ 93.8 out of 100 points, and are referred to as LHD individuals “without aphasia” for purposes of comparison in the analyses below. There were no significant differences between individuals with and without aphasia with respect to age ($t = -0.74$, $p = .46$), education ($t = -1.44$, $p = .16$), or months post stroke onset ($t = 0.11$, $p = .91$). However, participants with aphasia had significantly larger lesion volumes ($t = 5.96$, $p = < .001$). For this reason, analyses comparing individuals with and without aphasia additionally included lesion volume as a covariate.

The WAB provides scores for overall aphasia severity (overall WAB score) as well as subtest scores for auditory comprehension, fluency, repetition, and other related functions (see Table 1). In the current study, we assessed the relationship between spatial span performance and 1) overall aphasia severity (overall WAB score), which is a composite score that includes spontaneous speech, comprehension, repetition, and naming; 2) auditory comprehension, which is based on accuracy in answering yes/no questions, auditory word recognition, and following sequential commands; 3) verbal repetition, which is based on accuracy repeating single words, short phrases, and sentences; and 4) fluency, which refers to the fluency level of an individual’s spontaneous speech.

2.2.3. Lesion reconstructions—High-resolution brain imaging was acquired for all participants in the chronic phase of stroke around the same time as behavioral testing (at least 5 months post-stroke), so that lesion site and behaviors were relatively stable. In 45 individuals, MRI scans were obtained on a 3T Siemens Verio scanner (Syngo MR B17) or a 1.5T Phillips Eclipse scanner; five individuals with MRI contraindications were scanned on a Siemens Somatom Emotion 16 CT scanner with 3 × 3×3mm imaging. For those individuals with digital MRI scans, lesion sites were visualized and reconstructed using MRIcro/MRIcron software (Rorden & Brett, 2000). Lesions were manually traced on the native scans based primarily on the T1-weighted images, with yoked T2-weighted and FLAIR images to verify lesion boundaries. Lesions were then registered with the Montreal Neurological Institute (MNI) template using the standard nonlinear spatial normalization procedure from statistical parametric mapping (SPM8). Cost function masking was used for the normalization process to minimize distortions in the image (Brett, Leff, Rorden, &

Ashburner, 2001). When digital brain images were not available, lesions were manually drawn from hard-copy onto an 11-slice atlas template (DeArmond, Fusco, & Dewey, 1976) by a board-certified neurologist who was blind to the study goals and the individuals' clinical presentations and test performance. These reconstructions were then digitized and non-linearly transformed into MNI space in SPM5 using 50 control point pairs that matched anatomical features on the templates (Collins, Neelin, Peters, & Evans, 1994). The slices were aligned using a local weighted mean transformation implemented by Matlab *cpselect*, *cp2tform* and *imtransform* image processing toolbox functions.

An overlay of participants' lesion reconstructions is shown in Fig. 1. Only those voxels with a minimum of five individuals in each voxel are highlighted to be consistent with the 5-individual minimum in the VLSM analyses. The lesions encompassed a large portion of the left hemisphere, primarily the middle cerebral artery territory. The average lesion volume was 93.5 cc (*SD* = 85.6, range = 1–380 cc).

2.2.4. VLSM analyses—Voxel-based lesion symptom mapping (VLSM) was used to relate participants' brain lesions to their performance on behavioral testing (Bates et al., 2003; available at https://langneurosci.mc.vanderbilt.edu/resources.html). In VLSM, linear regression functions are estimated at every voxel, comparing behavioral scores (i.e., spatial span data) in individuals with and without a lesion in each voxel of the whole brain. This method allows for the analysis of all brain regions at once on a single map, rather than arbitrarily dividing participants into groups (e.g., anterior lesion vs. posterior lesion). Analyses were limited to those voxels with at least 5 individuals (10%) with a lesion in each voxel in order to minimize biased regression parameter estimates. Significant regions associated with span performance were based on permutation testing (1000 iterations) with voxelwise significance thresholding set at 0.05, a relatively conservative method for addressing the problem of multiple comparisons (Kimberg, Coslett, & Schwartz, 2007). A colorized map was then generated based on the resultant significant *t*-values at each voxel. VLSM results displayed below show only those voxels surpassing this significance threshold. The identity of the brain regions associated with the significant voxels was determined by yoking the VLSM maps to the Brodmann, Anatomical Automatic Labeling (AAL), and Johns Hopkins white matter atlas templates in MRIcron.

3. Results

3.1. Behavioral findings

Based on age-corrected normative scores from the WMS-III, a subset of 28% of individuals with LHD (14 out of 50) were in the clinically-impaired range (≤9th percentile) on forward spatial span, and 16% (8 out of 50) were in the clinically-impaired range on backward spatial span. Also, 12% of individuals (6 out of 50) performed in the clinically-impaired range on both forward and backward spatial span.

Spatial span performance was not significantly affected by the presence of aphasia: 27% of individuals with aphasia versus 29% of LHD individuals without aphasia were in the clinically-impaired range on forward spatial span; and 18% of individuals with aphasia versus 12% of LHD individuals without aphasia were in the clinically-impaired range on

backward spatial span (forward, $\chi^2 = 0.03$, $p = .87$; backward, $\chi^2 = 0.34$, $p = .56$). Consistent with this finding, the subset of 14 individuals in the clinically-impaired range on forward spatial span varied widely in terms of their language impairment: 5 individuals had no aphasia, 3 had anomic aphasia, 3 had Broca's aphasia, 1 had conduction aphasia, 1 had global aphasia, and 1 had transcortical sensory aphasia. Similarly, the subset of 8 individuals who scored in the clinically-impaired range for backward spatial span included two individuals with no aphasia, 3 with anomic aphasia, 1 with Broca's aphasia, 1 with global aphasia, and 1 with transcortical sensory aphasia.

A one-way analysis of variance with age and lesion volume as covariates was computed to evaluate differences on spatial span raw scores between LHD individuals with and without aphasia. The ANOVA revealed no significant differences between LHD individuals with and without aphasia on forward spatial span ($F = 2.17$, $p = .15$) or backward spatial span ($F = 0.19$, $p = .66$), consistent with our findings above.

Pearson correlation coefficients were computed to assess the relationship between forward and backward spatial span, and between spatial span performance and the WAB language measures. There was a significant correlation between forward spatial span and backward spatial span ($r = .49$, $p < .001$). There were no statistically significant correlations between spatial span and the language variables: The overall WAB score was not significantly correlated with forward spatial span ($r = 0.21$, $p = .15$) or backward spatial span ($r = 0.19$, $p = .18$). Likewise, neither comprehension, fluency, nor repetition scores from the WAB were significantly correlated with either forward or backward spatial span (see Table 2).

3.2. Lesion findings

The VLSM analysis of forward spatial span performance did not yield any voxels exceeding the conservative statistical threshold established with permutation testing. The VLSM analysis of backward spatial span revealed a number of significant regions in a left frontal-parietal network that included portions of the left precentral gyrus, lateral prefrontal cortex, Broca's area, post-central gyrus, the frontal eye fields, and the supramarginal gyrus (see Fig. 2). The cluster also extended into Heschl's gyrus, insular cortex, and the superior temporal pole. The highest *t*-value (4.14) was in the white matter medial to the left precentral gyrus, between the corona radiata and superior longitudinal fasciculus (−32, −4, 30).

The VLSM findings are consistent with lesion-behavior patterns that we observed in the individual participants. Of the 8 individuals whose performance was in the clinically-impaired range on backward spatial span (9th percentile and below), four had relatively small lesions (< 50 cc) that overlapped with the nodes identified in the VLSM analysis: One individual had a lesion exclusively involving the left superior corona radiata; another individual had a subcortical lesion in the posterior limb of the internal capsule; another individual had a focal precentral gyrus lesion; and the other individual had a focal inferior parietal lesion. The other four individuals whose performance fell in the clinically-impaired range on backward spatial span had large left fronto-parietal or fronto-temporo-parietal lesions that overlapped to the greatest extent in the lateral prefrontal cortex. Fig. 3 shows an overlay of these individuals' lesions, along with a lesion overlay of the 8 individuals who scored in the superior range (91st percentile and above) on backward spatial span. The

contrast is notable for the more anterior-focused lesions in the impaired individuals (left side of Fig. 3) and the relative sparing of frontal-parietal cortex in the high-performing individuals (right side of Fig. 3).

4. Discussion

Typically, visuospatial processing is associated with right hemisphere functioning (Colonna & Faglioni, 1966; Heilman, Watson, & Valenstein, 1993; Ratcliff, 1979; Warrington & Rabin, 1970); however, some visuospatial functions such as spatial working memory have produced mixed findings with respect to lateralization (Cowan et al., 2011; Todd & Marois, 2004; Xu & Chun, 2006). The first aim of the present study was to identify whether spatial working memory is dependent on the left hemisphere by testing forward and backward spatial span in individuals with left hemisphere damage (LHD) due to stroke. We found that a subset of 28% of LHD individuals performed in the clinically-impaired range (≤9th percentile) on forward spatial span, and 16% performed in the clinically-impaired range on backward spatial span. These results suggest that spatial working memory is significantly impaired in a subset of individuals with LHD, consistent with some previous studies (Burgio & Basso, 1997; De Renzi & Nichelli, 1975; Kasselimis et al., 2013), but inconsistent with others (Kasselimis et al., in press).

One possible explanation that has been proposed to account for a deficit in spatial working memory in LHD individuals is that such tasks rely in part on a verbally-mediated strategy and thus could be sensitive to the presence of language disturbance (Postma & de Haan, 1996; Rausch & Ary, 1990). Thus, our second aim was to evaluate whether the left hemisphere plays a role in spatial working memory via its role in language functions. In the current study, we found no evidence of this, as individuals with and without aphasia did not differ on spatial span performance, and spatial span performance did not correlate with any of the language measures (e.g., overall WAB score, comprehension, repetition, fluency). Moreover, of the individuals whose performance was in the clinically-impaired range on spatial span, language abilities ranged widely from no aphasia to global aphasia. These findings are in keeping with two previous studies that also found no difference between individuals with and without aphasia on spatial span (Burgio & Basso, 1997; De Renzi & Nichelli, 1975). It is always possible that the language measures employed here were not reflective of subvocal mechanisms normally recruited to mediate spatial working memory. However, this is unlikely as we have successfully used these same language measures to show that the degree of language impairment correlates with the degree of impairment on non-verbal tasks that require subvocal mediation, such as the Wisconsin Card Sorting Test and Raven’s Matrices (Baldo et al., 2005, 2010, 2015).

The third aim of this study was to identify left hemisphere regions associated with spatial span performance. Backward spatial span was associated with a left fronto-parietal network consisting of left somatosensory cortex, lateral prefrontal cortex, frontal eye fields, and the supramarginal gyrus. In keeping with these findings, half of the individuals who scored in the clinically-impaired range on backward spatial span had relatively small lesions that overlapped with these different nodes, suggesting that focal disruptions along network pathways may have the potential to impact functioning in a clinically meaningful way. The

other half of individuals in the clinically-impaired range on backward spatial span had large peri-Sylvian lesions that encompassed two or more of these nodes and overlapped in the left lateral prefrontal cortex. Previous lesion studies of spatial span divided individuals into large lesion groups (e.g., anterior vs. posterior) and produced mixed results (e.g., Kasselimis et al., 2013). The network of brain regions implicated in the present findings may partially explain this discrepancy in the literature, as the regions do not fit neatly into an anterior-posterior dichotomy.

The brain network identified in the current VLSM analysis is consistent with findings from functional imaging studies of spatial working memory in healthy individuals that have reported activation in fronto-parietal regions, predominantly in the right hemisphere, but also bilaterally (Majerus et al., 2016). Specific findings include the bilateral posterior parietal lobes, bilateral sensorimotor cortex, bilateral anterior cingulate cortex, and bilateral frontal lobes (Ricciardi et al., 2006); bilateral (right > left) lateral prefrontal cortex (Bor & Owen, 2006; Smith et al., 1996); left intraparietal sulcus (Cowan et al., 2011); bilateral intraparietal sulcus (Todd & Marois, 2004; Xu & Chun, 2006); bilateral (right > left) inferior parietal and somatosensory cortex (Smith et al., 1996); and right prefrontal cortex, right posterior parietal lobe, right occipital lobe, and right premotor cortex (Jonides et al., 1993). This rightward bias in spatial working memory is consistent with previous lesion studies of spatial span that have directly compared spatial span in individuals with right hemisphere damage (RHD) versus LHD and have shown that RHD individuals are relatively more impaired (e.g., De Renzi & Nichelli, 1975; Kessels et al., 2000a,b). At the same time, the significant activation of left hemisphere fronto-parietal regions (albeit less than right hemisphere activation) is consistent with our findings of impaired spatial working memory in a subset of LHD individuals with damage to this network. Also consistent with our findings, functional imaging findings by Majerus et al. (2016) has suggested that there are domain-general networks comprised of superior frontal cortex and the intraparietal sulcus that support both verbal and spatial working memory in the left and right hemisphere.

A number of studies have argued that the left lateral prefrontal cortex and the inferior parietal cortex are critical for executive control aspects of working memory rather than simply temporary storage of visuospatial information (Baldo & Shimamura, 2000; Bor, Duncan, Wiseman, & Owen, 2003; Chao & Knight, 1996; D'Esposito et al., 1995; Kessels, Postma, et al., 2000; Shimamura, 1995; Tsujimoto & Postle, 2012). With respect to spatial working memory, this would include functions such as inhibiting responses to spatial locations that were relevant on a previous trial and increasing attention/reducing distractibility to irrelevant information. This interpretation is the most parsimonious explanation of the pattern of impairment observed in the current findings, as we did not find evidence linking span performance to a verbally-mediated strategy, nor did participants exhibit any frank spatial impairments (e.g., field cuts, neglect) that could account for the findings.

In the current study, the peak voxel in the VLSM analysis was centered in the white matter underlying the left pre-central gyrus, a somatosensory region. Since spatial span tasks require a simple pointing response and individuals could use either hand, we were not expecting to see any association with somatosensory regions. However, a recent study by

Mackey, Devinsky, Doyle, Meager, and Curtis (2016) showed that spatial working memory was only impaired in individuals whose prefrontal cortex lesions encroached on the precentral sulcus. They concluded that this precentral region is critical for the "transformation" of a spatial memory into an action plan. The VLSM analysis in the present study also identified the left frontal eye fields as a significant region involved in spatial working memory. The frontal eye fields have been previously associated with spatial working memory performance in monkeys (Bruce & Goldberg, 1985) and have been implicated in shifting visual attention (Schall, 2009), such as likely occurs during spatial span tasks.

In the current study, we found evidence of clinical impairment in a subset of LHD individuals on both forward and backward spatial span tasks, and forward and backward span were significantly correlated with each other. Early models of working memory posited that forward and backward span relied on distinct mechanisms as described above (Baddeley & Hitch, 1974; Baddeley, 1986). Some studies continue to find intraindividual discrepancies in forward and backward spatial span among LHD individuals (Kasselimis et al., in press). However, other papers have suggested that both forward and backward spatial span tasks rely on similar working memory and executive control mechanisms (Vandierendonck et al., 2004; Wilde et al., 2004). The present findings in LHD individuals are more consistent with the latter argument since forward and backward spatial span were correlated.

The retrospective nature of the current study allowed for the analysis of a relatively large group of well-characterized individuals with a single left hemisphere stroke who met strict inclusion and exclusion criteria. One drawback is that participants were only tested on a single measure of spatial working memory. Spatial Span was initially chosen for inclusion in our research battery because it was developed as a non-verbal analogue to digit span, a common way of assessing auditory-verbal working memory. Other types of spatial working memory tasks involve somewhat overlapping cognitive processes but may also recruit additional mnemonic and executive processes (e.g., n-back tasks, maze-learning).

Another limitation of the current study is that it focused on the role of the left hemisphere in spatial working memory and thus did not directly compare performance between individuals with RHD and LHD. We are currently recruiting individuals with RHD and plan to use VLSM to investigate the relative contributions of the two hemispheres to spatial working memory. Based on the current findings as well as findings in the literature, we would predict that a parallel fronto-parietal network in the right hemisphere would be associated with spatial working memory in RHD individuals. With respect to behavioral performance, we would expect both forward and backward spatial span to be disrupted in individuals with damage to this right hemisphere network, but that language/verbal span would be in the normal range.

Another limitation of the current study is that there was not sufficient power to detect significant neural correlates of forward spatial span using VLSM. This does not mean that the left hemisphere does not play a role in forward spatial span, but that the statistical variability and effect sizes for forward spatial span were simply not large enough to exceed the conservative statistical threshold set for the VLSM analyses. Using a simple lesion

overlay, however, the greatest degree of lesion overlap in the individuals in the clinically-impaired range for forward spatial span was in the left precentral gyrus and supramarginal gyrus, consistent with the lesion findings for backward spatial span. Additional recruitment of individuals with LHD is also ongoing to address this limitation, along with recruitment of individuals with RHD.

Last, we were not able to contrast spatial span performance with a verbal span task like digit span, because verbal span data were not available on all study patients in this retrospective analysis. However, digit span data were available for a subset of 31 out of 50 of the patients. In those 31 patients, there was a significant correlation between backward digit span and backward spatial span (r = 0.47, $p < .01$). No other correlations between digit span and spatial span were significant. Not surprisingly, both forward and backward digit span significantly correlated with all language variables (*all* $r = 0.49–0.81$, all $p < .01$). This smaller sample size did not allow for a VLSM analysis of digit span, but interestingly, there were two patients with large temporal lobe lesions and conduction aphasia who showed a striking dissociation of robust spatial span (up to 9 spatial locations), but highly impaired digit span performance (0–2 digits). Consistent with the VLSM results above, these two patients' lesions spared left frontal cortex and most of left parietal cortex.

In short, we found evidence of a clinical impairment on spatial working memory in individuals with LHD. It should be emphasized that we are not claiming that spatial span is globally affected by LHD, as only a subset of individuals scored in the clinically-impaired range. Our correlational and VLSM findings show that this impairment is not related to patients' language deficits, but rather point to the involvement of a left hemisphere fronto-parietal network as playing a significant role in distinguishing which patients have impaired versus spared spatial spans. This network has been implicated in domain-general attentional control and working memory processes (e.g., Majerus et al., 2016; Todd & Marois, 2004). The current findings have implications for the clinical assessment and rehabilitation of individuals with left hemisphere damage. Visuospatial impairments, such as those identified in the current study are often overlooked in the assessment and rehabilitation of individuals with LHD (Schendel, Dronkers, & Turken, 2016). Following a left hemisphere stroke, cognitive rehabilitation efforts understandably focus on the most salient and disruptive cognitive deficits, such as language dysfunction. However, deficits in spatial working memory and attentional control more generally, may negatively impact everyday functioning and have the potential to influence rehabilitation strategies. Clinical assessment of putatively non-verbal cognitive domains in LHD individuals is clearly needed to evaluate potential deficits that may be amenable to remediation.

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References

Baddeley AD (1986). Working memory New York: Oxford University Press.

Baddeley AD (1992). Working memory. Science, 255(5044), 556–559. [PubMed: 1736359]

Baddeley AD (2003). Working memory: Looking back and looking forward. Nature Reviews Neuroscience, 4(10), 829–839. [PubMed: 14523382]

Baddeley AD, & Hitch G (1974). Working memory. Psychology of Learning and Motivation, 8, 47–89.

Baldo JV, Bunge SA, Wilson SM, & Dronkers NF (2010). Is relational reasoning dependent on language? A voxel-based lesion symptom mapping study. Brain and Language, 113(2), 59–64. [PubMed: 20206985]

Baldo JV, Dronkers NF, Wilkins D, Ludy C, Raskin P, & Kim J (2005). Is problem solving dependent on language? Brain and Language, 92(3), 240–250. [PubMed: 15721957]

Baldo JV, Katseff S, & Dronkers NF (2012). Brain regions underlying repetition and auditory-verbal short-term memory deficits in aphasia: Evidence from voxel-based lesion symptom mapping. Aphasiology, 26, 338–354. [PubMed: 24976669]

Baldo JV, Paulraj SR, Curran B, & Dronkers NF (2015). Impaired reasoning and problem-solving in individuals with language impairment due to aphasia or language delay. Frontiers in Psychology, 6, 1523 10.3389/fpsyg.2015.01523. [PubMed: 26578991]

Baldo JV, & Shimamura AP (2000). Spatial and color working memory in patients with lateral prefrontal cortex lesions. Psychobiology, 28(2), 156–167.

Barrouillet P, Bernardin S, & Camos V (2004). Time constraint and resource sharing in adults' working memory span. Journal of Experimental Psychology: General, 133(1), 83–100. [PubMed: 14979753]

Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, et al. (2003). Voxel-based lesion-symptom mapping. Nature Neuroscience, 6(5), 448–450. [PubMed: 12704393]

Beeson PM, Bayles KA, Rubens AB, & Kaszniak AW (1993). Memory impairment and executive control in individuals with stroke-induced aphasia. Brain and Language, 45(2), 253–275. [PubMed: 8358599]

Bor D, Duncan J, Wiseman RJ, & Owen AM (2003). Encoding strategies dissociate prefrontal activity from working memory demand. Neuron, 37(2), 361–367. [PubMed: 12546829]

Bor D, & Owen AM (2006). A common prefrontal–parietal network for mnemonic and mathematical recoding strategies within working memory. Cerebral Cortex, 17(4), 778–786. [PubMed: 16707737]

Brett M, Leff AP, Rorden C, & Ashburner J (2001). Spatial normalization of brain images with focal lesions using cost function masking. NeuroImage, 14(2), 486–500. [PubMed: 11467921]

Bruce CJ, & Goldberg ME (1985). Primate frontal eye fields. I. Single neurons discharging before saccades. Journal of Neurophysiology, 53(3), 603–635. [PubMed: 3981231]

Burgio F, & Basso A (1997). Memory and aphasia. Neuropsychologia, 35(6), 759–766. [PubMed: 9204483]

Chao LL, & Knight RT (1996). Prefrontal and posterior cortical activation during auditory working memory. Cognitive Brain Research, 4(1), 27–37. [PubMed: 8813410]

Collins DL, Neelin P, Peters TM, & Evans AC (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. Journal of Computer Assisted Tomography, 18(2), 192–205. [PubMed: 8126267]

Colonna A, & Faglioni P (1966). The performance of hemisphere-damaged patients on spatial intelligence tests. Cortex, 2(3), 293–307.

Corsi PM (1972). Human memory and the medial temporal region of the brain Montreal: McGill University.

Cowan N (1995). Attention and memory: An integrated framework New York: Oxford University Press.

Cowan N, Li D, Moffitt A, Becker TM, Martin EA, Saults JS, et al. (2011). A neural region of abstract working memory. Journal of Cognitive Neuroscience, 23(10), 2852–2863. [PubMed: 21261453]

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, & Grossman M (1995). The neural basis of the central executive system of working memory. Nature, 378, 279–281. [PubMed: 7477346]

De Renzi E, Faglioni P, & Previdi P (1977). Spatial memory and hemispheric locus of lesion. Cortex, 13(4), 424–433. [PubMed: 604009]

De Renzi E, & Nichelli P (1975). Verbal and non-verbal short-term memory impairment following hemispheric damage. Cortex, 11(4), 341–354. [PubMed: 1222578]

DeArmond SJ, Fusco MM, & Dewey MM (1976). A photographic atlas: Structure of the human brain Oxford: Oxford University Press.

Harnish SM, & Lundine JP (2015). Nonverbal working memory as a predictor of anomia treatment success. American Journal of Speech-language Pathology, 24(4), S880–S894. 10.1044/2015_AJSLP-14-0153. [PubMed: 26383918]

Heilman KM, Watson RT, & Valenstein E (1993). Neglect and related disorders. Clinical Neuropsychology, 3, 279–336.

Hester RL, Kinsella GJ, & Ong B (2004). Effect of age on forward and backward span tasks. Journal of the International Neuropsychological Society, 10(4), 475–481. [PubMed: 15327726]

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, & Mintun MA (1993). Spatial working memory in humans as revealed by PET. Nature, 363, 623–625. [PubMed: 8510752]

Kasselimis DS, Angelopoulou G, Simos P, Petrides M, Peppas C, Velonikas G, et al., Working memory impairment in aphasia: The issue of stimulus modality, Journal of Neurolinguistics, (in press).

Kasselimis DS, Simos PG, Economou A, Peppas C, Evdokimidis I, & Potagas C (2013). Are memory deficits dependent on the presence of aphasia in left brain damaged patients? Neuropsychologia, 51(9), 1773–1776. [PubMed: 23770384]

Kertesz A (1982). Western aphasia battery New York, NY: Grune &Stratton.

Kessels RP, Kappelle LJ, de Haan EH, & Postma A (2002). Lateralization of spatial-memory processes: Evidence on spatial span, maze learning, and memory for object locations. Neuropsychologia, 40(8), 1465–1473. [PubMed: 11931950]

Kessels RP, Postma A, Wijnalda EM, & De Haan EH (2000a). Frontal-lobe involvement in spatial memory: Evidence from PET, fMRI, and lesion studies. Neuropsychology Review, 10(2), 101–113. [PubMed: 10937918]

Kessels RC, van Zandvoort MJE, Postma A, Kappelle LJ, & De Haan EHF (2000b). The Corsi block-tapping Task: Standardization and normative data. Applied Neuropsychology, 7(4), 252–258. [PubMed: 11296689]

Kimberg DY, Coslett HB, & Schwartz MF (2007). Power in voxel-based lesion-symptom mapping. Journal of Cognitive Neuroscience, 19(7), 1067–1080. [PubMed: 17583984]

Lang CJ, & Quitz A (2012). Verbal and nonverbal memory impairment in aphasia. Journal of Neurology, 259(8), 1655–1661. [PubMed: 22258478]

Luciana M, Burgund ED, Berman M, & Hanson KL (2001). Effects of tryptophan loading on verbal, spatial and affective working memory functions in healthy adults. Journal of Psychopharmacology, 15(4), 219–230. [PubMed: 11769814]

Mackey WE, Devinsky O, Doyle WK, Meager MR, & Curtis CE (2016). Human dorsolateral prefrontal cortex is not necessary for spatial working memory. Journal of Neuroscience, 36(10), 2847–2856. [PubMed: 26961941]

Majerus S, Attout L, D'Argembeau A, Degueldre C, Fias W, Maquet P, et al. (2012). Attention supports verbal short-term memory via competition between dorsal and ventral attention networks. Cerebral Cortex, 22(5), 1086–1097. [PubMed: 21765184]

Majerus S, Cowan N, Péters F, Van Calster L, Phillips C, & Schrouff J (2016). Cross-modal decoding of neural patterns associated with working memory: Evidence for attention-based accounts of working memory. Cerebral Cortex, 26(1), 166–179. [PubMed: 25146374]

Martin N, & Ayala J (2004). Measurements of auditory-verbal STM span in aphasia: Effects of item, task, and lexical impairment. Brain and Language, 89(3), 464–483. [PubMed: 15120538]

Milner B (1971). Interhemispheric differences in the localization of psychological processes in man. British Medical Bulletin, 27(3), 272–277. [PubMed: 4937273]

Nys GMS, van Zandvoort M, Worp HVD, Kappelle LJ, & Haan ED (2006). Neuropsychological and neuroanatomical correlates of perseverative responses in subacute stroke. Brain, 129(8), 2148–2157. [PubMed: 16870885]

Postma A, & de Haan EHF (1996). What was where? Memory for object locations. Quarterly Journal of Experimental Psychology, 49A(1), 178–199.

Potagas C, Kasselimis D, & Evdokimidis I (2011). Short-term and working memory impairments in aphasia. Neuropsychologia, 49(10), 2874–2878. [PubMed: 21704643]

Ratcliff G (1979). Spatial thought, mental rotation and the right cerebral hemisphere. Neuropsychologia, 17(1), 49–54. [PubMed: 431809]

Rausch R, & Ary CM (1990). Supraspan learning in patients with unilateral anterior temporal lobe resections. Neuropsychologia, 28(2), 111–120. [PubMed: 2314569]

Ricciardi E, Bonino D, Gentili C, Sani L, Pietrini P, & Vecchi T (2006). Neural correlates of spatial working memory in humans: A functional magnetic resonance imaging study comparing visual and tactile processes. Neuroscience, 139(1), 339–349. [PubMed: 16324793]

Rorden C, & Brett M (2000). Stereotaxic display of brain lesions. Behavioural Neurology, 12(4), 191–200. [PubMed: 11568431]

Schall JD (2009). Frontal eye fields. Encyclopedia of neuroscience (pp. 1635–1638). Springer Berlin Heidelberg.

Schendel K, Dronkers NF, & Turken U (2016). Not just language: Persisting lateralized visuospatial impairment after left hemisphere stroke. Journal of the International Neuropsychological Society, 22(7), 695–704. [PubMed: 27329557]

Shimamura AP (1995). Memory and the prefrontal cortex. Annals of the New York Academy of Sciences, 769(1), 151–160. [PubMed: 8595022]

Smith EE, Jonides J, & Koeppe RA (1996). Dissociating verbal and spatial working memory using PET. Cerebral Cortex, 6(1), 11–20. [PubMed: 8670634]

Todd JJ, & Marois R (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. Nature, 428(6984), 751–754. [PubMed: 15085133]

Tsujimoto S, & Postle BR (2012). The prefrontal cortex and oculomotor delayed response: A reconsideration of the “mnemonic scotoma”. Journal of Cognitive Neuroscience, 24(3), 627–635. [PubMed: 22098265]

Vandierendonck A, Kemps E, Fastame MC, & Szmalec A (2004). Working memory components of the Corsi blocks task. British Journal of Psychology, 95(1), 57–79. [PubMed: 15005868]

Warrington EK, & Rabin P (1970). Perceptual matching in patients with cerebral lesions. Neuropsychologia, 8(4), 475–487. [PubMed: 5522574]

Wechsler D (1997). WMS-III: Wechsler memory scale administration and scoring manual Psychological Corporation.

Wilde N, Strauss E, & Tulsky DS (2004). Memory span on the Wechsler scales. Journal of Clinical and Experimental Neuropsychology, 26(4), 539–549. [PubMed: 15512941]

Xu Y, & Chun MM (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. Nature, 440(7080), 91–95. [PubMed: 16382240]

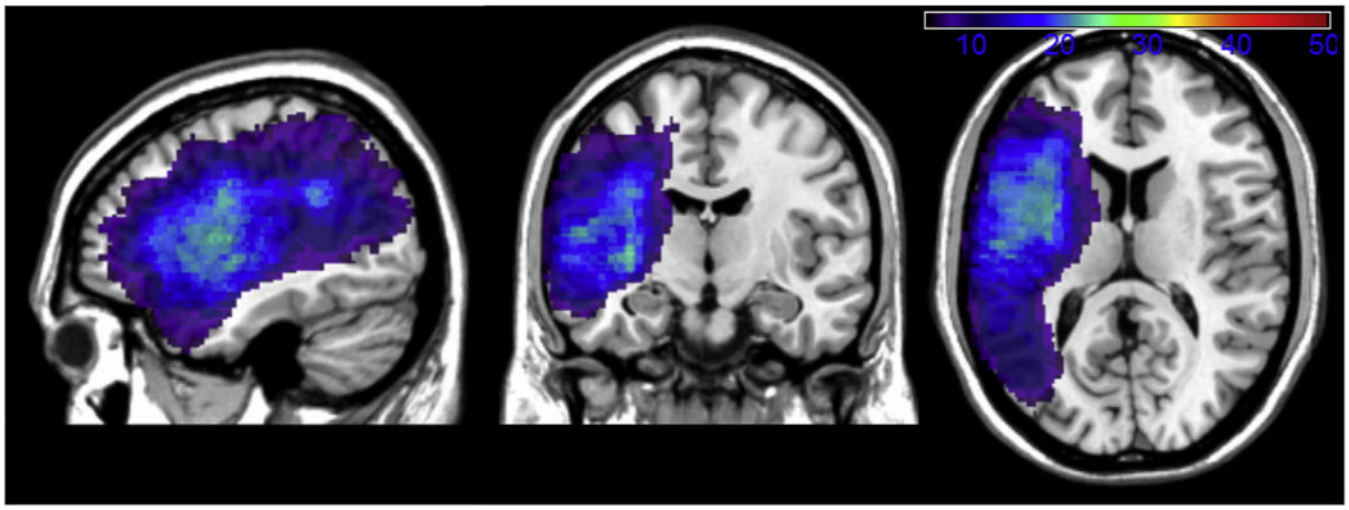

Fig. 1.

Overlay of participants' normalized lesion reconstructions on a common brain template, with a minimum of five participants in each voxel to be consistent with the VLSM analyses.

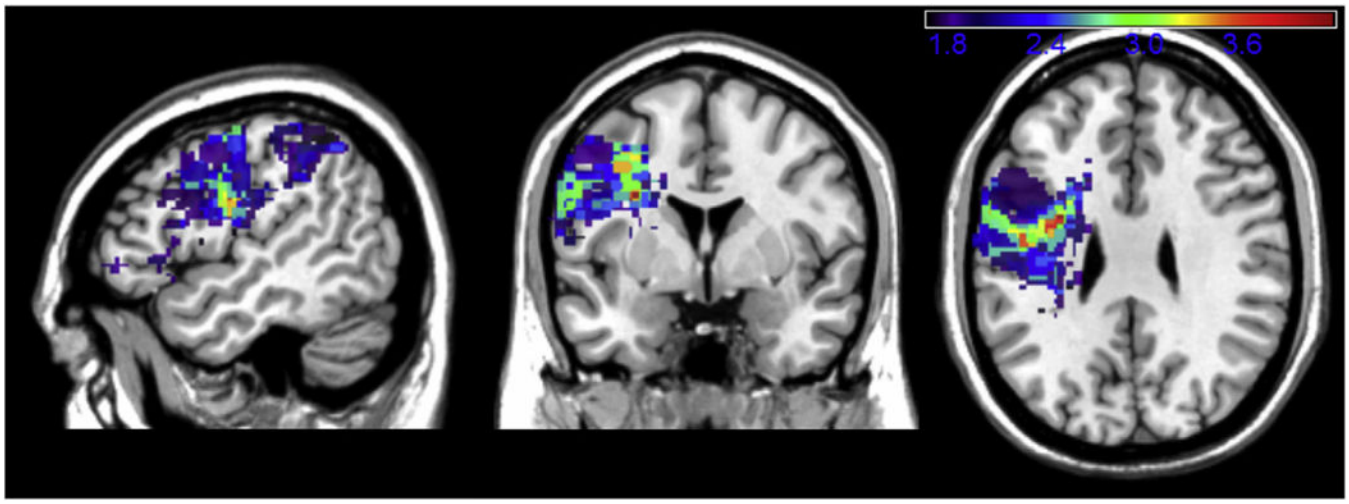

Fig. 2.

VLSM map showing regions significantly associated with backward spatial span. The peak voxel was located in the white matter medial to the precentral gyrus (−32, −4, 30) and is shown in red in the center (coronal) slice.

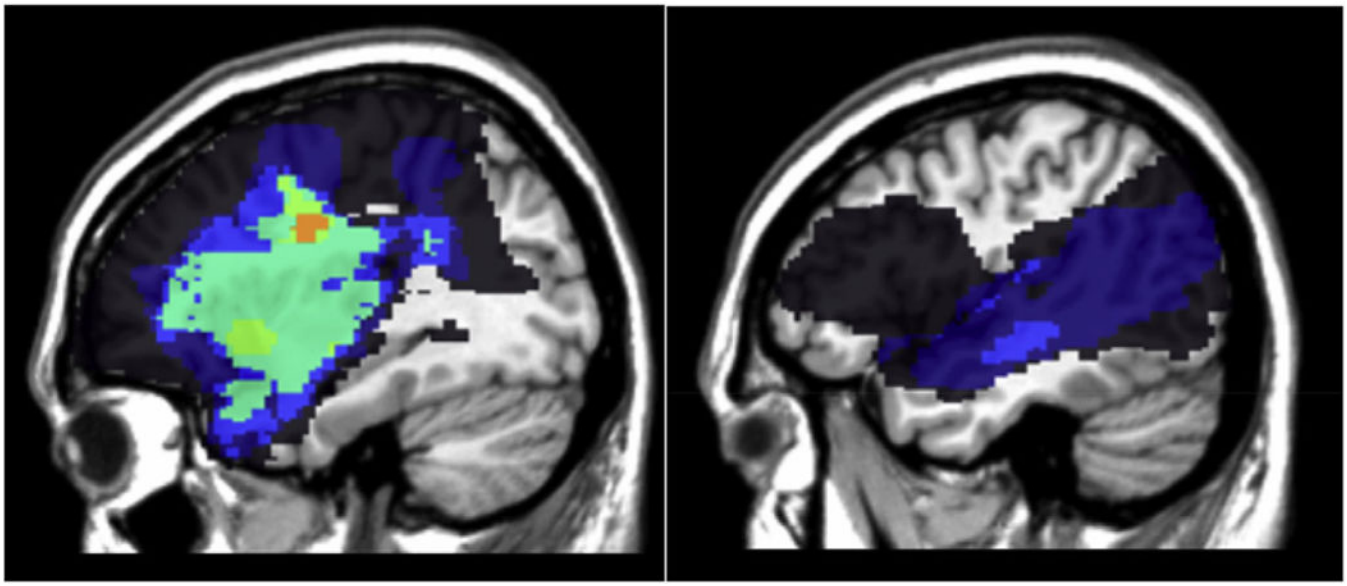

Fig. 3.

Lesion overlays of individuals with backward spatial span in the clinically-impaired range (left, n = 8) versus those in the superior range and above (right, n = 8). Brighter areas (green, orange) are regions of greater overlap and darker areas (black, dark blue) are regions of lesser overlap.

Table 1

Descriptive statistics for the variables of interest.

	N	M	SD	Range
WMS-III Spatial Span				
Forward spatial span raw score	50	6.8	1.7	3–10
Backward spatial span raw score	50	6.2	2.1	2–13
Western Aphasia Battery				
Overall WAB score	50	77.3	24.6	13.9–100
Comprehension	50	8.5	1.9	2.1–10
Fluency	50	7.6	2.8	0–10
Repetition	50	7.5	3.1	0–10

Note. WMS-III – Wechsler Memory Scale – Third Edition; N = sample size; M = mean; SD = standard deviation.

Table 2

Two-tailed pearson correlations between spatial span and language measures.

	Forward Spatial Span	Backward Spatial Span
Overall WAB Score	.21 ns	.19 ns
Comprehension	.17 ns	−.02 ns
Repetition	.14 ns	.16 ns
Fluency	.10 ns	.26 ns

Note. *ns* – non-significant.