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Which perseverative behaviors are symptoms of spatial neglect?

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Abstract

Spatial neglect is characterized by a failure to attend or make movements towards left-sided stimuli. Common paper-and-pencil tasks to diagnose spatial neglect are sensitive to perseverative errors, including additional marks over already cancelled targets and “scribbling” out a target. Here, we examine whether functionally distinct perseverative behaviors are related to spatial neglect. Line cancellation tasks of 45 healthy controls and 220 right-hemisphere stroke survivors were examined for recurrent marks (RM) and continuous marks (CM) perseverations. We found that RM perseveration correlated with neglect severity, while CM perseveration did not. Examination of lesion profiles for the two groups indicated distinct anatomical correlates, with RM lesions overlapping regions implicated in spatial neglect including the rolandic operculum, superior temporal gyrus, and inferior parietal lobule.

Keywords

Stroke; Neglect; Perseveration; Lesion mapping; Disengagement of attention; Barthel index; Activities of daily living; Functional disability; Motor disinhibition; Motor perseveration; Spatial representation; Spatial motor; Hyperkinesia; Allochiria; Working memory

1. Introduction

Spatial neglect is a failure to report, respond, or orient to stimuli in the side of space opposite a brain injury, causing functional disability (Barrett & Burkholder, 2006; Heilman, Watson, & Valenstein, 2011; Mesulam, 1999). To diagnose spatial neglect, it is common to use paper-and-pencil tasks that require manual responses, such as asking the participant to cancel all of the targets presented in an array (Albert, 1973). Individuals with spatial neglect often mark only those targets located on the ipsilesional side of the page, while failing to cancel those located on the contralesional side.

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In contrast to healthy adults, who typically cancel targets with a single line, participants with neglect may not cancel contralesional targets, and often mark an ipsilesional target more than once (Fig. 1A) or continuously mark it with a “scribble” (Fig. 1B). This unnecessary repetition or continuation of a response counter to instructions can be defined as *motor perseveration* (henceforth, *perseveration*). Co-occurrence of perseveration and spatial neglect is quite common, with rates of spatial neglect and perseveration reported from 30% to 90% (Pia, Ricci, Gindri, & Vallar, 2013; Toraldo et al., 2005). Perseverative ipsilesional behaviors may be functionally important, i.e. when they affect the type and direction of hand movements during wheelchair navigation. However, it remains unclear why perseveration and spatial neglect frequently co-occur. Attempts to explain why this relationship is so common fall largely under two theories: that perseveration is a symptom of spatial neglect (Manly, Woldt, Watson, & Warburton, 2002; Toraldo et al., 2005; Wansard et al., 2014) or that spatial neglect and perseveration are separate symptoms (Gandola et al., 2013; Ronchi, Algeri, Chiapella, Spada, & Vallar, 2012; Rusconi, Maravita, Bottini, & Vallar, 2002; Vallar, Zilli, Gandola, & Bottini, 2006). In past studies, conflicting evidence has been presented on the relationship between severity of neglect and severity of perseveration (Manly et al., 2002; Na et al., 1999; Nys, van Zandvoort, Van der Worp, Kappelle, & de Haan, 2006). Manipulating stimuli so that there are no left-sided targets reduced perseveration in some cases (Manly et al., 2002), but not others (Pia et al., 2013). Co-occurrence of perseveration and neglect severity was also not replicated in some studies (Ronchi et al., 2012; Rusconi, Maravita, Bottini, & Vallar, 2002; Vallar et al., 2006). These conflicting results come from studies that examine a single type of perseveration, or do not separate participants according to their distinct perseverative behaviors. Some forms of perseveration may be neglect-related while others may occur independently.

Perseveration can be categorized into two types. In one type of perseveration, the participant is unable to change to a new motor response, inappropriately repeating a prior motor response. This type of perseveration has been called *inertia of program action* (Luria, 1965), or *recurrent perseveration* (Sandson & Albert, 1984). In the context of the current study, we refer to this type of perseveration as *recurrent markings* (RM) perseveration. Other examinations of motor perseveration have termed this *Type I* (Na et al., 1999), *Simple* (Rusconi, Maravita, Bottini, & Vallar, 2002), *remarks* (Nys et al., 2006), and *Additional marks* (Gandola et al., 2013). RM perseveration is highlighted by the recurrence of a previous response after a delay and is manifest on a cancellation task as multiple distinct lines through a single target (Fig. 1A).

In the second type of perseveration, the participant continues to perform a movement even though the task is completed. Luria (1965) called this *effluent perseveration*, and Sandson and Albert (1984) referred to this as *continuous perseveration*. In the context of cancellation tasks, we refer to this as *continuous marking* (CM) perseveration (Fig. 1B). CM perseveration refers to the continuation of a response beyond the point of completion and is manifest as a “scribble” on a target. Other studies examining perseveration have described this form of perseveration as *Inkblot* (Torald et al., 2005) and *Scribble* (Gandola et al., 2013) perseveration. Recent research separating RM and CM perseverations by behavioral pattern found that these distinct types of perseveration differentially relate to spatial neglect (Gandola et al., 2013). In their study, RM errors, but not CM errors, were associated with

spatial neglect severity. RM perseveration is assumed to be related to spatial displacement of a motor response to uncanceled targets, which could be directly related to spatial neglect. CM perseveration, or scribble perseveration, is assumed, in contrast, to stem from failure to appropriately end or complete a motor task, which may not be spatially specific and thus may not be related to spatial neglect.

RM and CM perseveration are also associated with different functional neuroanatomy. Lesion profiles in RM include the inferior frontal gyrus (IFG), superior temporal gyrus (STG), and rolandic operculum – areas also typically associated with the presence of spatial neglect (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Gandola et al., 2013). CM perseveration, however, is reflective of lesions or dysfunctions of frontal and subcortical structures (Gandola et al., 2013; Luria, 1965; Sandson & Albert, 1984).

In the present study, we had three goals. The first goal was to confirm that RM relates to spatially biased behavior, while CM is not specific to spatial bias. Thus, we expected that RM, but not CM, would be correlated with measures of spatial neglect severity. The second goal was to examine lesion profiles in the two identified specific types of perseveration, and their relationship with spatial neglect. Based on recent research utilizing similar categories of perseveration (Gandola et al., 2013), we expected that RM would be associated with lesions of the IFG, STG, and rolandic operculum, and CM associated with frontal and subcortical lesions of the basal ganglia. Our third goal was to examine how co-occurring perseveration and spatial neglect related to reduced functional independence. Based on previous research indicating that spatial neglect is associated with many adverse stroke outcomes, including reduced functional independence, increased falls, and difficulties in mobility, we expected that spatial neglect and perseveration may be associated with increased functional disability. (Chen, Hreha, Kong, & Barrett, 2015; Jehkonen, Laihosalo, & Kettunen, 2006; Nijboer, Kollen, & Kwakkel, 2014; Nijboer, van de Port, Schepers, Post, & Visser-Meily, 2013).

2. Materials & methods

2.1. Participants

After giving written informed consent, 45 healthy controls (52.2% female) ages 49–88 years ($M = 64.56$, $SD = 9.42$) and 220 right brain stroke survivors (48.5% female) ages 19–93 years ($M = 65.36$, $SD = 14.34$) in an inpatient rehabilitation facility were assessed for this study (see Table 1). Participants who had a first right brain stroke, no history of neurological or psychiatric disorders, no uncorrected ocular disorders (e.g. near-sightedness or cataract), and used their right hand to write were enrolled in the study. Patients were tested as part of their participation in ongoing spatial neglect research ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00350012): NCT00350012. NCT00989430) during the period 2008–2015.

2.2. Neuropsychological and functional assessments

Healthy adults and stroke participants were assessed with the Behavioral Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987). The BIT is a widely used paper-and-pencil assessment of spatial neglect with scores from 0 to 146. Here, we used published cut-off

aggregate score for neglect of 129/146 as our criterion to define spatial neglect (Halligan, Cockburn, & Wilson, 1991). Additionally, stroke survivors were assessed for independence in everyday activities of self-care and mobility, using caregiver report on the Barthel Index (Mahoney & Barthel, 1965). Scores on the Barthel Index vary from fully dependent (0) to independent (100), with responses ranging from unable to independent in each of ten tasks.

2.3. Cancellation task: Measuring the center of spatial bias and perseveration

Of the subtests on the BIT, the line cancellation task (line crossing subtest; Albert, 1973), is a measure of neglect that also permits examination of motor perseveration. The task consists of 40 lines, each 25-mm long (“targets”), in varying orientations on an $8\frac{1}{2} \times 11$ in. sheet of paper (see Fig. 1). The lines are arranged into 7 columns, with columns 1–3 and 4–6 consisting of 6 lines. Each crossed line is scored as a point, and scores range from 0 to 36 (Wilson et al., 1987). To quantify the center of spatial bias, we computed a Center of Cancellation (CoC) using a method developed by Rorden and Karnath (2010) that utilizes the standard average position of the marked targets across the array. We then standardized each participant’s CoC score so that a score of –1 indicates extreme right neglect, 0 indicates no neglect, and +1 indicates extreme left neglect.

A perseverative error was scored if more than one mark was produced to cancel a target in the line crossing test. Perseverations were further coded for (1) recurrent markings (RM), defined as more than one separate line cancelling out a target, and (2) continuous markings (CM), defined as one continuous line repeatedly crossing over the target more than once in either a “V”, cross out, zigzag, or “scribble” pattern. We also calculated both the RM and CM perseveration ratio, which was the total number of targets with either RM perseverations, or CM perseverations, divided by the total number of targets cancelled.

2.4. Lesion mapping and localization

Clinical brain scans were obtained with participants’ authorization. When more than one scan was available, we used images obtained closest to the time of baseline neglect assessment (2–326 days from scan to assessment). We retrospectively identified brain lesion maps generated for 99 participants (44 CT and 55 MRI). The technique used for mapping these scans (e.g. Chen et al., 2014; Goedert, Chen, Boston, Foundas, & Barrett, 2013) was as follows. A “double-strain” lesion mapping method was performed. Reliability-trained technicians, blind to patients’ behavioral classifications, manually mapped individual lesions onto the axial plane of a standard brain template (Montreal Neurological Institute) using MRICron software (Rorden, Karnath, & Bonilha, 2007). A consensus conference led by an independent neurologist evaluated the normalized lesion maps and ensured accuracy. Lesion location was identified using an anatomical checklist and lesion volume (in cubic centimeters) was calculated from the lesion map and overlaid them for between-group comparisons.

3. Results

3.1. Perseveration and spatial neglect

To determine the cutoff score for abnormal perseverative behavior, we examined the responses of healthy control participants, using a 5th/95th percentile criterion. Two out of 45 (4.4%) healthy controls made more than one response on a given target, which calculated to 0–2.8% of cancelled targets. Therefore, we set a cutoff of >2.8% abnormally-cancelled targets as our criterion for perseveration. For the 205 stroke survivors with BIT scores, 115 (56.1%) had neglect and 64 (31.2%) had perseveration (Table 2). 53 of the 115 (46.1%) stroke survivors with neglect also had perseveration, and 11 of the 90 (12.2%) stroke survivors with no neglect had perseveration.

For BIT, there was a neglect by perseveration interaction ($F(1, 201) = 4.05, p = 0.046$). Post-hoc independent samples *t*-tests indicated the N+P+ group had significantly lower BIT scores than any other group (all *p*'s < 0.004). However, for the patients without neglect, there was no differences in BIT scores between the patients with (N–P+) and without perseveration (N–P–), $t(88) = 0.50, p = 0.618$. Thus, participants who had both neglect and perseveration had a more severe neglect than those who had neglect without perseveration. For the categorical variable of sex, we found no difference between groups ($X^2 = 2.18, p = 0.536$). For age, education, and BIT a 2 (Neglect: N+, N–) $\times$ 2 (Perseveration: P+, P–) ANOVA was conducted. There were no significant main effects or interactions for age and education (all *p*'s > 0.080).

The non-normal distribution of lesion volume could not be transformed. Therefore, we examined the difference of lesion volume among the four groups of participants (N+P+, N+P–, N–P+, N–P–) using a Kruskal-Wallis test. Results revealed significant differences of lesion volume among groups, ($H(2) = 21.79, p < 0.001$). Follow-up pairwise U tests with Bonferroni correction ($\alpha = 0.008$) resulted in two significant comparisons (both *p*'s < 0.001): the N+P+ group had greater lesion volume ($n = 26$; median = 100.95 cc, IQR = 29.69–181.12) than the N–P– group ($n = 39$; median = 20.92 cc, IQR = 6.79–83.7), and the N+P– group also had greater lesion volume ($n = 28$; median = 95.68 cc; IQR = 49.26–205.21) than the N–P– group.

3.2. Hypothesis 1: RM perseveration relates to spatially biased behavior, while CM is not specific to spatial bias

To address our first hypothesis, we separated those who perseverated into groups based on the type of perseveration. Here, participants could have no perseverations (P–), recurrent markings (RM+), continuous markings (CM+), or both recurrent and continuous markings (RM+CM+), see Table 3. We performed a 2 (Neglect: N+, N–) $\times$ 4 (Perseveration: RM+, CM+, P–, RM+CM+) ANOVA with the BIT score as the dependent variable. The result showed the significant main effect of neglect, $F(1, 198) = 59.42, p < 0.001$ with no significant effect of perseveration, $p = 0.234$ or interaction, $p = 0.261$. This indicated that the type of perseveration did not predict the severity of spatial neglect. Performance on cancellation tasks and perseveration ratios for the RM versus CM perseveration groups can be seen in Table 4 and Table 5.

It is possible that differences in RM+ from CM+ comes from its relationship to spatial bias, indexed by CoC and BIT. Spearman's rho was positive between the RM ratio and CoC, $r_s(62) = 0.334$, $p = 0.007$ but not between the CM ratio and CoC, $r_s(62) = -0.039$, $p = 0.759$. Thus, the higher the RM ratio the more rightward bias, but there was no correlation between the CM ratio and spatial bias. For BIT, there was a positive Spearman's rho for both BIT and RM ratio, $r_s(205) = -0.454$, $p < 0.001$, and BIT and CM ratio, $r_s(205) = -0.231$, $p = 0.001$.

3.3. Hypothesis 2: Lesion profiles of RM and CM reflect distinct underlying brain areas

We compared lesion maps of the N+RM+ and N+CM+ groups, confirming our hypothesis that lesion profiles of RM and CM were distinct. An independent samples *t*-test confirmed that N+RM+ ($n = 16$) and N+CM+ ($n = 6$) groups were not different in number of days from stroke incident to testing ($p = 0.55$) and from scan date to testing ($p = 0.558$). Lesions for each group were then overlapped and subtracted between RM and CM groups (Fig. 2). Panel A represents where N+RM+ was lesioned more than N+CM+ (e.g. [N+RM+] – [N+CM+]), and Panel B represents where N+CM+ was lesioned more than N+RM+ (e.g. [N+CM+] – [N+RM+]). Subtraction analyses indicate areas specific to each form of perseveration, see Table 6. Due to the insufficient sample size, the voxel-based lesion-symptom analysis was not performed.

In addition to the primary question, we asked a secondary question to examine whether there was a common location of brain lesion shared among patients with spatial neglect and perseveration, but absent in other spatial neglect patients. Overlapping N+P+ and N+P– images are presented in Fig. 3, indicating that lesions in the N+P+ were more medial, centralized around the putamen, portions of the inferior parietal lobule, supramarginal gyrus, and white matter tract of the superior corona radiata. On the other hand, lesions of the N+P– group were more lateral, affecting regions of the insula, parietal operculum, and portions of the inferior parietal lobule. We contrasted these groups in a voxel-based comparison with Liebermeister quasi-exact test following 4000 permutations (Rorden et al., 2007) and included voxels with lesions in at least 4 participants. Using corrected family-wise error statistical thresholds, we found significant clusters in the right putamen that were lesioned in the N+P+ group, statistically differentiating lesions in this group from those in the N+P– group, $p < 0.05$ (Fig. 4). This finding is consistent with our hypothesis that lesion profiles of RM and CM reflect different underlying brain areas.

3.4. Hypothesis 3: Individuals with both neglect and perseveration have greater difficulty in functional activities than those with neglect alone

To examine this hypothesis, we performed a 2×2 factorial ANOVA on the score of the Barthel Index. We retrospectively identified 181 who had completed the Barthel Index at screening. We could not determine conclusively why the Barthel Index was not collected in the other patients, but in most cases this missing data appeared to be related to time constraints or inability to identify an appropriate caregiver to validate the performance self-report. The result showed a significant neglect by perseveration interaction, $F(1, 177) = 5.84$, $p = 0.017$, as well as significant main effects of neglect ($F(1, 177) = 39.62$, $p < 0.001$) and perseveration ($F(1, 177) = 6.58$, $p = 0.011$). Follow-up pairwise comparisons resulted in significant differences between the N+P+ group and all other groups (Bonferroni corrected

pairwise comparisons all p 's < 0.001), and between the N+P- group and the N-P- group ($p < 0.001$; Fig. 5). Comparisons of the N-P+ and N-P- group were not significant, $p = 0.999$. These results are consistent with a combination of neglect and perseveration causing greater disability, than the disability caused by the presence of neglect or perseveration alone.

We further examined if perseveration type related to disability. We separated perseveration type into four groups: no perseveration (P-), RM+, CM+, and those with both RM and CM perseveration (RMCM+). Using these groups we performed a 4×1 factorial ANOVA on the score of Barthel Index. The result showed a significant effect of perseveration type, $F(3, 181) = 17.405$, $p < 0.001$. Follow-up Bonferroni corrected pair-wise t -tests resulted in significant differences between the P- group and the RM+ group ($p < 0.001$), and between the P- group and those with both types of perseveration ($p < 0.001$). No other comparisons reached significance, all p 's > 0.592 . This analysis indicates the presence of RM perseveration, either in isolation or combined with CM perseveration increases disability. This is consistent with our hypothesis that the presence of perseveration will decrease functional independence in stroke survivors.

4. Discussion

We utilized a large data set of healthy participants and inpatient stroke survivors to retrospectively examine perseveration on a simple cancellation task. Our data suggests that recurrent markings (RM), a perseverative behavior, may represent an additional symptom of spatial neglect while continuous markings (CM) may be independent of neglect. In the current sample, RM was associated not only with lesions in the inferior frontal gyrus and the superior temporal gyrus, but also with parietal lesions. Perseverative behaviors with continuous markings (CM) were not associated with spatial neglect while lesions linked to CM included brain regions of the orbitofrontal cortex and caudate. Finally, a significant increase in functional disability was related to the combined presence of perseveration and spatial neglect. Below, we discuss our findings in the context of ongoing research in this area.

4.1. Theories of perseveration

In the past, an ongoing debate why perseveration and spatial neglect frequently co-occur is largely between two ideas. One possibility is that perseveration is a symptom of spatial neglect and may arise from deficient spatial processing at several stages. Failure to disengage/inhibit return may occur due to perceptual-attentional spatial "Where" dysfunction (Barrett, Schwartz, Crucian, Kim, & Heilman, 2000; Mannan et al., 2005; Na et al., 1999; Posner & Cohen, 1984). It is also possible that "Where" representational dysfunction may contribute to perseverative behaviors. For example, patients with allochiria may perceive objects located in the neglected space as though those objects were on the unaffected side (Halligan, Marshall, & Wade, 1992). Awareness of the presence of uncanceled lines on the left may increase a tendency to orient to right-sided lines. Here, recurrent marks may not really be perseverative behaviors, but may be errors resulting from an ineffective attempt to cancel targets in the contralesional space, which are perceived either implicitly or even explicitly (Manly et al., 2002; Toraldo et al., 2005). This explanation does

not rule out, however, the presence of Spatial Aiming (directional hypokinesia). Another possibility is that deficient spatial working memory makes it difficult for patients with spatial neglect to track their performance accurately (Wansard et al., 2014). If patients also have spatial Aiming bias (a preference for moving or orienting toward the ipsilesional side), this could lead to returns to previously cancelled targets, or recurrent perseverations after leaving the target (Kim et al., 2009).

Lastly, a pure pathologically asymmetric motor-intentional spatial Aiming bias (Goedert et al., 2013) may cause subjects to make multiple cancellations of the same ipsilesional target. Aberrant, increased rightward directional kinesis, or increased propensity to move in the right space (hemispatial hyperkinesia) in Aiming neglect could in isolation produce spatially-asymmetric perseveration errors.

Perseveration and spatial neglect, while often associated, may also be independent disorders, with distinct functional and neuroanatomical underpinnings (Na et al., 1999). Here, perseverations may be due to an unrelated disruption of attentional and motor systems, causing a generalized (non-spatial) disinhibition of motor activity. Such motor response disinhibition may be brought about by a number of types of brain lesions including those that involve the frontal, parietal, and temporal cortex, as well as the basal ganglia (Allison, 1966; Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009; Sandson & Albert, 1987). Neglect and perseveration may co-occur in these cases because the brain lesions cause more than one symptom, with different functional mechanisms may be responsible for the two sets of symptoms.

4.2. Lesion profile associated with perseveration

Lesion profiles of RM and CM in our study were consistent with Gandola et al. (2013), but we identified additional regions as potentially related to RM perseveration in neglect. Although there were differences in our methodology and theirs, it is also possible that we identified additional lesions associated with perseveration; a larger, prospective, controlled study is needed to clarify this issue. N+RM+ lesions overlapped with many regions implicated in spatial neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Karnath & Rorden, 2012; Karnath, Rorden, & Ticini, 2009). Like Gandola et al. (2013), we identified lesions in the superior temporal gyrus, inferior frontal gyrus, supramarginal gyrus, and rolandic operculum. In addition, we also identified lesions in the inferior parietal lobule, including the angular gyrus, specifically associated with RM perseveration and spatial neglect. This result is of particular interest as the inferior parietal lobule has been implicated in spatial neglect (Mattingley, Husain, Rorden, Kennard, & Driver, 1998), and it may support spatial Aiming and leftward directional kinesis, suggesting that RM perseveration may be closely related to spatial Aiming neglect.

Toraldo et al. (2005) and Gandola et al. (2013) also found patients with spatial neglect will make “flying marks” errors while completing line cancellation. Here, marks were made in blank areas that did not touch or cancel a line in the array. Others have observed these errors and combined them with RM errors (Na et al., 1999). We did observe flying marks errors in our sample, however, we chose not to interpret these errors as perseverations. Flying marks may be due to any number of underlying causes unrelated to perseveration. In our

retrospective study, we were unable to observe marks as they were made and understand the behavior producing perseverations; this is a limitation of our current study.

Mannan et al. (2005), Wansard et al. (2014) and others (Gandola et al., 2013) investigated the possibility that different types of perseverative errors may be associated with different neglect mechanisms. As discussed above, spatial perceptual-attentional Where errors, spatial representational (working memory or allochiria-related) Where deficits, or spatial motor Aiming (directional or hemispacial hyperkinesia) may explain RM errors. Wansard et al. (2014) demonstrated that brain regions associated with Where, representational errors are different than those associated with errors related to defective response inhibition. Although the target clicking task they used is not exactly the same as a line cancellation task, they reported inferior parietal sulcus lesions associated with spatial representational deficits. This suggests that spatial working memory deficits and allochiria might contribute to RM errors in our neglect patients. Further research examining tasks assessing these functions in isolation, together with tasks eliciting perseveration, will help elucidate this relationship.

The specific relationship between CM perseveration and neglect has been examined using case series to assess whether CM marks can be altered by the presence of targets on the contralesional (neglected) side of an array (Bottini & Toraldo, 2003; Toraldo et al., 2005). In one case, eliminating left-sided targets significantly reduced CM perseveration in a patient with frontal and insula lesions (Bottini & Toraldo, 2003). However, CM marks were not altered by changes in the number of targets on the left side in another case with extensive lesions including the frontal, parietal, and occipital lobes as well as the insula (Toraldo et al., 2005). Another study examined the effects of contralesional background movement, which can reduce symptoms of spatial neglect, to reduce perseverations in patients with spatial neglect (Kim et al., 2009). In this prospective approach, the authors were able to compare continuous perseveration with return perseveration, where a patient would return to previously cancelled targets to remark them. In their study Kim et al. (2009) found that background movement during a cancellation task reduced both perseveration and neglect in a patient with return perseveration, but not patients with continuous perseveration, suggesting a relationship between return perseveration and spatial neglect. Unfortunately, the present study is retrospective, and therefore we were unable to examine the relationship between return perseveration and lesion profile in spatial neglect.

Examinations of lesion profiles provide insight into the underlying neural correlates that may be critical for perseveration. Voxel-based lesion-symptom mapping analysis of perseveration (RM and CM combined) revealed that areas within the right putamen were spared in the neglect-only group in comparison to the group with both neglect and perseveration, suggesting that this brain area may play an important role in the development of perseveration after stroke.

Separating groups by form of perseveration can provide a clearer idea of which brain areas relate specifically to perseverative behaviors. In the present study, we found that lesions of the N+CM+ group were relatively centralized in subcortical areas in comparison to the N+RM+ group, suggesting a relation between CM perseveration and motor control (Hotz & Helm-Estabrooks, 1995; Sandson & Albert, 1984; Sandson & Albert, 1987). In the only

other study to our knowledge that examined lesion profiles of specific types of perseveration in spatial neglect, Gandola et al. (2013) found that CM perseveration was related to lesions of the caudate and orbitofrontal cortex. We confirmed these findings in our results, which converged on the orbitofrontal cortex and caudate as a key region involved in CM perseveration. We did not observe the extent of frontal lesions (middle and medial frontal gyrus) that we expected to see in continuous perseveration, as previously reported (Gandola et al., 2013; Sandson & Albert, 1984). This may be due to the limited nature of our sample, whose lesions were mostly in areas other than the frontal lobe (selection bias), or it may be due to the small number of CM participants in our sample. Future studies sampling from a broader range of stroke survivors, and including a representative group of patients with and without both perseveration and spatial neglect, is needed.

4.3. Perseveration and functional disability

It is presently unclear how perseveration impacts everyday functioning. This study provides new evidence on how co-occurring perseveration and neglect might relate to functioning in everyday tasks. Given relationships between functional outcomes and neglect (Chen et al., 2015; Nijboer et al., 2013; Nijboer et al., 2014), it is not surprising those participants with spatial neglect overall had poorer functional independence than stroke survivors with no neglect or perseveration. However, those with co-occurring neglect and perseveration (N+P+) were significantly more dependent to complete everyday tasks than those with neglect only (N+P-). It should be noted that lesion volume between these two groups is not significantly different. Future prospective studies to confirm the relationship between neglect-associated perseveration and functional disability are needed. It will be helpful, in these studies, to understand whether different functional errors occur when neglect and perseveration occur together.

4.4. Conclusions

We categorized perseverations into two types, and confirmed that co-occurring neglect and perseveration may be associated with brain regions participating in spatial cognitive processing, and that it may be associated with spatial representational deficits. Neglect-associated perseveration was also related to reduced ability to perform everyday functional tasks. It would be important to learn whether perseverative errors are present in activities of daily living in spatial neglect, and whether they have a unique effect on patient care and caregivers. Future research utilizing prospective methods and measures sensitive to perseverative behaviors in everyday activities will be useful.

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Fig. 1.

The Albert Cancellation Task of the BIT assesses for the presence of spatial neglect (left sided omissions) as well as repetitive behaviors on cancelled targets. The participants below both demonstrate severe spatial neglect. Panel A demonstrates recurrent marking (RM) perseveration and Panel B demonstrated continuous marking (CM) perseveration.

Fig. 2.

Contrast of lesion maps for N+RM+ and N+CM+. The top (A) shows lesions that were present patients with neglect and RM+ compared to CM+ including the inferior frontal gyrus, superior temporal gyrus, rolandic operculum, inferior parietal lobule, and supramarginal gyrus. The bottom panel (B) shows areas lesioned in patients with neglect and CM+ compared to RM+, highlighting the orbitofrontal cortex and more subcortical regions involving the hippocampus and putamen. The maps are presented with the right hemisphere showing on the left and numbers above each slice correspond to MNI z coordinates of each transverse section.

Fig. 3. Overlapped lesion maps for the (A) Neglect and Perseveration, (B) Neglect Only, and (C) Perseveration only groups. The maps are presented with the right hemisphere showing on the left and numbers above each slice correspond to MNI z coordinates of each transverse section.

Fig. 4.

Brain regions significantly associated with neglect and perseveration (N+P+). Voxels that survived the statistical threshold of FWE $p < 0.05$ are shown. The color illustrates corresponding Z-score values. Zoomed in image demonstrating cluster of voxels that are intact in the neglect without perseveration group (N+P-) and lesioned in the neglect and perseveration group (N+P+). The maps are presented with the right hemisphere showing on the left and numbers above each slice correspond to MNI z coordinates of each transverse section. Abbreviation: FWE, family wise error.

Fig. 5.

Follow-up pair-wise *t*-tests indicates that neglect reduces functional independence following stroke, with the greatest impact in those with both perseveration and neglect. Error bars represent standard error of the mean.

Table 1

Mean demographic information of healthy and stroke groups.

	Healthy (n = 45)	Stroke (n = 205)	p value
Sex (females)	24 (52.2%)	100 (48.8%)	0.566
Age, yrs	64.56 (9.42)	64.91 (13.70)	0.640
Education, yrs	16.15 (2.74)	14.27 (3.15)	0.002
BIT (n = 250)	144.91 (1.26)	106.51 (47.26)	<0.001
MMSE (n = 220)	29.60 (0.86)	26.37 (27.36)	<0.001

Values in parenthesis represent standard deviations. *BIT* Behavioral Inattention Test. *MMSE* Mini Mental State Examination. *p* values resulted from two-tailed independent samples *t*-tests or chi square for sex.

Table 2

Demographic and neuropsychological characteristics of stroke survivors in neglect and perseveration groups.

	Neglect		No neglect	
	Perseveration (N:P+)	No perseveration (N:P-)	Perseveration (N:P+)	No perseveration (N:P-)
n	53	62	11	79
Females	26 (49.1%)	32 (51.6%)	3 (27.3%)	39 (49.4%)
Age	65.96 (14.88)	60.29 (14.20)	70.60 (7.13)	64.74 (13.66)
Education	13.54 (2.48)	13.63 (2.91)	13.40 (3.13)	14.45 (2.23)
BIT (n = 205)	44.46 (35.57)	70.33 (38.86)	137.40 (5.94)	139.74 (4.93)
MMSE (n = 175)	24.63 (5.52)	28.04 (5.24)	27.20 (2.59)	28.80 (1.66)
Barthel (n = 181)	29.17 (20.41)	42.59 (24.07)	57.00 (20.79)	62.26 (27.17)
Lesion Volume cm ³ (n = 99)	126.81 (93.17)	133.51 (113.59)	18.07 (20.00)	49.88 (62.11)

Values in parenthesis represent standard deviations. *BIT* Behavioral Inattention Test, *MMSE* Mini Mental State Examination.

Table 3

Neuropsychological characteristics of perseveration groups. Counts (%) and means (SD).

	No perseverations (P-)	Recurrent (RM+)	Continuous (CM+)	Recurrent & continuous (RM+CM+)
Total (n = 205)	150 (73.2%)	29 (14.1%)	11 (5.4%)	15 (7.3%)
Neglect (n = 115)	65 (56.5%)	26 (22.6%)	9 (7.8%)	15 (13.1%)
Non-neglect (n = 90)	85 (94.4%)	3 (3.3%)	2 (2.2%)	0 (0.0%)
BIT (n = 205)	112.3 (41.5)	52.9 (40.6)	75.7 (52.2)	59.3 (43.9)
MMSE (n = 175) ^a	27.6 (4.8)	24.3 (5.3)	26.6 (6.6)	25.0 (4.9)
Barthel (n = 181) ^a	55.7 (26.8)	24.8 (19.8)	38.2 (34.6)	28.6 (21.4)
Lesion volume cm ³ (n = 99)	45.3 (107.0)	128.3 (133.1)	39.2 (64.8)	29.7 (264.6)

Values in parenthesis represent standard deviations. *BIT* Behavioral Inattention Test, *MMSE* Mini Mental State Examination.

^aOut of the 205 total participants not all completed the MMSE or Barthel Index due to time constraints during screening.

Table 4

Cancellation task performance for each perseveration group.

	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Color Key– Total Number Cancelled
							0–1
							1.1–2
							2.1–3
							3.1–4
							4.1–5
							5.1–6
Total Targets Cancelled RM group (out of 6)	1.3	1.9	2.0	3.6	3.9	5.3	
Total Targets Cancelled CM Group (out of 6)	4.2	4.5	4.5	4.7	5.3	5.8	

Table 5

Percent of targets cancelled for each group.

<i>Color Key – % targets with perseveration</i>						
50.1–60+%						
40.1–50%						
Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	
% Cancelled Targets with RM	16.7	22.4	22.6	21.1	33.3	45.1
						30.1–40% 20.1–30%
% Cancelled Targets with RM	16.7	29.6	33.3	50.4	53.3	60.6
						10 1–30% 0–10%

Table 6

Brain regions associated with RM and CM perseveration. X = at least 2 patients' lesions involved a given region.

Brain region (right)	RM	CM
Precentral gyrus	X	
Postcentral gyrus	X	
Inferior frontal gyrus	X	
Superior frontal gyrus		
Orbitofrontal cortex		X
Insula	X	X
Heschl gyrus	X	
Superior temporal gyrus	X	
Middle temporal gyrus	X	X
Inferior temporal gyrus		
Rolandic operculum	X	
Inferior parietal lobule	X	
Supramarginal gyrus	X	
Hippocampus		X
Caudate	X	X
Putamen		X
Superior occipital		X
Middle occipital		X