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Left cerebellar lesions may be associated with an increase in spatial neglect-like symptoms.

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Abstract:

Each cerebellar hemisphere projects to the contralateral cerebral hemisphere. Previous research suggests a lateralization of cognitive functions in the cerebellum that mirrors the cerebral cortex, with attention/visuospatial functions represented in the left cerebellar hemisphere, and language functions in the right cerebellar hemisphere. Although there is good evidence supporting the role of the right cerebellum with language functions, the evidence supporting the notion that attention and visuospatial functions are left lateralized is less clear. Given that spatial neglect is one of the most common disorders arising from right cortical damage, we reasoned that damage to the left cerebellum would result in increased spatial neglect-like symptoms, without necessarily leading to an official diagnosis of spatial neglect. To examine this disconnection hypothesis, we analyzed neglect screening data (line bisection, cancellation, figure copying) from 20 patients with isolated unilateral cerebellar stroke. Results indicated that left cerebellar patients (n=9) missed significantly more targets on the left side of cancellation tasks compared to a normative sample. No significant effects were observed for right cerebellar patients (n=11). A lesion overlap analysis indicated that Crus II (78% overlap), and lobules VII and IX (66% overlap) were the regions most commonly damaged in left cerebellar patients. Our results are consistent with the notion that the left cerebellum may be important for attention and visuospatial functions. Given the poor prognosis typically associated with neglect, we suggest that screening for neglect symptoms, and visuospatial deficits more generally, may be important for tailoring rehabilitative efforts to help maximize recovery in cerebellar patients.

Keywords: cerebellum, attention, visuospatial, spatial neglect, CCAS, cerebellar cognitive affective syndrome, fronto-parietal attention network, lateralization of function

Introduction:

Traditionally, the cerebellum has been viewed as a brain structure that plays a critical role in the coordination and timing of movements, as well as motor learning (Glickstein, Strata, & Voogd, 2009; Glickstein, Sultan, & Voogd, 2011). However, converging evidence from neuropsychology, functional brain imaging and studies in non-human primates over the past twenty-five years suggests that the cerebellum also plays a role in a variety of different cognitive and affective functions ranging from working memory, sensory processing, and language, to emotion, executive functions, and attention (e.g., Adamaszek et al., 2017; O. Baumann et al., 2015; Peterburs & Desmond, 2016; Schmahmann, Guell, Stoodley, & Halko, 2019; Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009; Strick, Dum, & Fiez, 2009). The cerebellum's role in an array of different cognitive functions is supported through its rich structural and functional connectivity with the cerebral cortex (Buckner, 2013; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Clower, West, Lynch, & Strick, 2001; Dum & Strick, 2003; Middleton & Strick, 2001; Strick et al., 2009).

There is also evidence that cognitive functions may be lateralized within the cerebellum in a manner that mirrors what is observed in the cerebral cortex, given that each cerebellar hemisphere projects to the contralateral cerebral hemisphere. For example, a meta-analysis of neuroimaging studies conducted by Stoodley and Schmahmann (2009) demonstrated that language functions were more strongly represented in the right cerebellum, whereas visuospatial functions were more strongly represented in the left cerebellum.

The known connectivity of the cerebellum with contralateral cerebral regions necessarily raises the question of whether damage to the left or right side of the cerebellum might result in deficits in attention/spatial processing or language (respectively). Although there is a good deal of evidence that language functions are more lateralized to the right cerebellum (for reviews see Marien & Borgatti, 2018; Stoodley & Stein, 2011), the role of the left cerebellum in attention and spatial functions is less established (e.g., Allen, Buxton, Wong, & Courchesne, 1997; Baier, Dieterich, Stoeter, Birklein, & Muller, 2010; Oliver Baumann & Mattingley, 2014; Brissenden, Levin, Osher, Halko, & Somers, 2016; Brissenden & Somers, 2019; Craig, Morrill, Anderson, Danckert, & Striemer, 2021; Gottwald, Mihajlovic, Wilde, & Mehdorn, 2003; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Molinari, Petrosini, Misciagna, & Leggio, 2004; Schweizer, Alexander, Cusimano, & Stuss, 2007; Starowicz-Filip et al., 2021; Striemer, Cantelmi, Cusimano, Danckert, & Schweizer, 2015; Striemer, Chouinard, Goodale, & de Ribaupierre, 2015; Wang, Yao, Lin, Hu, & Shi, 2022).

Lobules VI, VII, and Crus I and II of the left cerebellum are part of a network that is functionally connected with regions of the fronto-parietal attention network in the right cerebral hemisphere (Buckner, 2013; Buckner et al., 2011; Wang, Buckner, & Liu, 2013). Thus, a disconnection hypothesis would predict that damage to the left cerebellum may alter attention by disrupting its connectivity with right cerebral hemisphere attention networks (Craig et al., 2021). One of the most common outcomes following damage to the fronto-parietal attention network of the right cerebral hemisphere is spatial neglect – a disorder in which patients are unable to attend to people or objects on the contralesional (i.e., left) side (for reviews see Corbetta & Shulman, 2011; Danckert & Ferber, 2006; Esposito, Shekhtman, & Chen, 2021; Husain & Rorden, 2003). Spatial neglect is most often observed following damage to the temporo-parietal junction, superior temporal lobe, or ventral frontal cortex of the right hemisphere (Chechlacz, Rotshtein, & Humphreys, 2012; Karnath & Rorden, 2012; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Although spatial neglect was traditionally believed to be primarily a disorder of attention (e.g., Bartolomeo & Chokron, 2002; Driver & Mattingley, 1998), subsequent research has indicated that neglect is a disorder that is comprised of a constellation of symptoms, including deficits in temporal attention (Husain, Shapiro, Martin, & Kennard, 1997), time perception (e.g. Basso, Nichelli, Frassinetti, & di Pellegrino, 1996; Danckert et al., 2007), and spatial working memory (e.g., Ferber & Danckert, 2006; Husain et al., 2001; Malhotra et al., 2005; Pisella, Berberovic, & Mattingley, 2004; Striemer, Ferber, & Danckert, 2013).

Given the known connectivity between the left cerebellum and attention related regions of the right cerebral hemisphere (Wang et al., 2013), a disconnection hypothesis would suggest that damage to the left cerebellum may result in an increase in spatial neglect-like symptoms that are similar to what would be expected following injury to the fronto-parietal attention network of the right cerebral hemisphere, albeit with less severity. Although this increase in neglect-like symptoms may not be severe enough to warrant a formal diagnosis of spatial neglect, it would nonetheless provide additional evidence for the role of the left cerebellum in attention and visuospatial functions.

Although there have been single case reports of spatial neglect following focal cerebellar injury in adults (Geiser et al., 2022; Hildebrandt, Spang, & Ebke, 2002; Silveri, Misciagna, & Terrezza, 2001), there have only been a few group studies, and they have produced mixed results (Baier, Karnath, et al., 2010; Frank et al., 2010; Kim et al., 2008; Richter et al., 2007). Specifically, Kim and colleagues (Kim et al., 2008) observed neglect in 8/28 patients using a composite neglect score. In contrast, both Richter and colleagues (Richter et al., 2007) and Frank and colleagues (Frank et al., 2010) found little evidence of spatial neglect following cerebellar damage in groups of 21 and 22 patients, respectively. Thus, whether cerebellar lesions lead to an increase in spatial neglect-like symptoms, and, if so, which region(s) of the cerebellum might be associated with these symptoms, still requires further investigation.

In the current study, we conducted a retrospective analysis of neglect screening data from a group of patients (n=20) with isolated unilateral cerebellar stroke that were obtained from two different stroke databases. In addition, we conducted a lesion overlap analysis to determine which regions of the cerebellum might be responsible for any observed deficits. Our hypothesis was that, if the left cerebellum is important for attention and visuospatial functions, then lesions to the left cerebellum should lead to an increase in spatial neglect-like symptoms, without necessarily leading a diagnosis of spatial neglect.

Methods:

Participants

In order to be included in the current study each patient had to have an isolated unilateral cerebellar stroke, with no previous history of other neurological disorders, or dementia. A total of 20 patients met these inclusion criteria across the two databases. Data from nine of the patients was obtained from the Neurological Patient Database at the University of Waterloo, Canada (Dr. James Danckert). Data from the remaining eleven patients was obtained from the Rehabilitation, Stroke deficits and Robotic Technology (RESTART) database at the University of Calgary (Dr. Sean Dukelow). All patients provided informed consent at the time the data was collected. All protocols were approved by the MacEwan University Research Ethics Board, the University of Calgary Conjoint Health Research Ethics Board, the University of Waterloo Office of Research Ethics, and the Tri-Hospital Research Ethics Board.

For the University of Waterloo cohort (n=9; mean age = 61.35 years; SD = 10.53; range=48-79); 5 were male, and all were right-handed. Seven patients had a left cerebellar lesion, and two patients had a right cerebellar lesion. Note that all of the patients from the Waterloo cohort also appeared in a recent study examining the effects of cerebellar injury on spatial and non-spatial visual attention (Craig et al., 2021). Neglect screening for the Waterloo cohort included a line bisection task (see details below), as well as either the star cancellation (in 7/9) or Bells cancellation task (in 2/9), and a figure copying task (star, cube and flower from the Behavioural Inattention Test; Wilson et al., 1987).

For the University of Calgary cohort (n=11; mean age = 50.72 years; SD = 13.10; range of 31-68); 10 were male; and 9 were right-handed. Two patients had a left cerebellar stroke, and 9 patients had a right cerebellar stroke. Calgary patients were administered the conventional subtests of the Behavioural Inattention Test (BIT) which is commonly used to assess neglect (Wilson, Cockburn, & Halligan, 1987). Note that the BIT contains the same star cancellation and figure copying tasks completed by the patients in the Waterloo cohort.

Thus, our total sample comprised 20 patients (15 males, 5 females; mean age = 55.51 (SD = 12.90; 2 left-handed; age range: 31-79)). Of these patients, there were 9 left cerebellar patients, 11 right cerebellar patients.

In the current study we chose to focus our analysis on data from the line bisection, figure copying (star, flower and cube), and cancellation tasks (described below), as these were completed by all patients in our sample.

In addition to neglect screening data, we were also able to obtain scores on the Montreal Cognitive Assessment (MoCA) acquired at the time of neglect screening for 14/20 patients (10 from Calgary, 4 from Waterloo). The MoCA is a brief cognitive screening tool that is highly sensitive to the presence of Mild Cognitive Impairment (MCI) (Nasreddine et al., 2005).

Clinical, demographic, and neglect screening data for each patient including age, lesion volume, time post-stroke, and MoCA score, are available in Table 1.

-- insert Table 1 here –

Table 1: Clinical and demographic data for the cerebellar patient group (n=20). *Performed Bells cancellation; Days= Days post-stroke; MoCA=Montreal Cognitive Assessment; LB=line bisection, where negative values are left of center and positive values right of center; Left and Right % omissions refer to the percentage of omissions on the left and right sides of the cancellation task. [a] Outlier compared to normative sample (n=81).

ID:	Age:	Sex:	Hand:	Lesion:	Volume (cc):	Days:	MoCA:	LB % deviation:	Left % omissions:	Right % omissions:
29	67	F	R	L	14.61	65	26	1.22	0	0
61*	70	M	R	L	35.05	8	-	.66	0	**6.67[a]**
182*	60	M	R	L	8.36	45	-	-2.65	**6.67[a]**	0
309	67	M	R	L	25.99	1	-	.26	**11.11[a]**	**3.7[a]**
378	48	M	R	R	10.56	46	-	1.92	0	0
523	79	F	R	R	13.87	74	21	-2.31	**3.7[a]**	**3.7[a]**
564	51	F	R	L	1.99	32	-	1.57	**7.41[a]**	**3.7[a]**
678	59	M	R	L	10.35	4	23	-1.88	0	0
905	37	M	R	R	3.68	7	25	-.60	0	0
953	50	F	R	L	.62	566	27	2.86	**3.7[a]**	0
1037	63	M	R	R	22.63	12	23	1.21	0	0
1062	68	M	R	R	2.59	10	20	**-3.66[a]**	0	0
1071	58	M	R	R	.23	7	23	-.7	**18.52[a]**	**3.7[a]**
1299	31	M	L	R	3.11	2	24	1.04	0	0
1558	59	M	L	R	10.36	5	30	-1.23	0	0
1832	58	M	R	L	2.27	5	26	-.09	**3.7[a]**	0
1945	54	M	R	R	3.09	7	26	**-4.90[a]**	0	0
3163	58	M	R	L	.44	6	27	-1.58	**3.7[a]**	0
3185	39	F	R	R	10.03	2	28	.6	0	0
3334	33	M	R	R	2.89	4	-	.55	0	0
Mean:	**55.51**	**5F**	**2L**	**9L, 11R**	**9.14**	**45.40**	**24.93**	**-.38**	**2.93**	**1.07**
SD:	**12.90**				**9.47**	**124.51**	**2.75**	**1.98**	**4.86**	**2.00**

Neglect screening tasks.

Line bisection.

The Waterloo patient group bisected a set of 10 lines that were 234mm in length. Each line was presented on a separate sheet of 8.5” x 11” paper aligned with the patient’s body midline. Patients from the Calgary dataset completed the line bisection task from the BIT. This consisted of a single sheet of paper with three horizontal lines, each 192mm in length. The midpoint of the first line at the top of the page was positioned 33mm to the right of true center. The midpoint of the middle line was in the center of the page, and the midpoint of the third line at the bottom of the page was 33mm to the left of center. All patients were asked to bisect each line in half by marking the midpoint of the line with a pen. Each line was scored by calculating the deviation of the patient’s bisection point from true center in millimeters (mm) with negative values indicative of a leftward deviation and positive values indicative of rightward deviation. For each patient, these values were then averaged across the total number of lines bisected (i.e., 10 for the Waterloo patients, 3 for the Calgary patients).

Previous research has demonstrated that line bisection deviation can be influenced by line length (for a review see Jewell & McCourt, 2000). To attempt to control for differences in line length between the Waterloo (234 mm) and Calgary (192 mm) patient groups we calculated an average percentage deviation score (e.g., McIntosh, McClements, Dijkerman, Birchall, & Milner, 2004; Schenkenberg, Bradford, & Ajax, 1980; Schindler, Clavagnier, Karnath, Derex, & Perenin, 2006) by dividing the mean deviation score for each patient by the length of the line they bisected. We then multiplied this value by 100 to obtain a percentage. The resulting value represents the percentage deviation from center, while attempting to control for overall line length.[1]

Cancellation.

The majority of our patient sample (18/20) completed the star cancellation task from the BIT, while the remaining two patients completed the Bells Cancellation test (Gauthier, Dehaut, & Joanette, 1989). It is important to note that, although these two cancellation tests differ somewhat in their presentation, performance on the two tasks are highly correlated ($r(31)=.83$, $p<.001$) in patients with spatial neglect (Ferber & Karnath, 2001).

For the star cancellation task patients were asked to cross out all 54 small star targets (27 on the left and 27 on the right) while ignoring distracters consisting of 52 large stars, 13 letters, and 10 words interspersed on a horizontally oriented sheet of 8.5” x 11” paper that was placed at the patient’s midline. The total percentage of omissions on each side was calculated by dividing the number of misses by 27 and multiplying by 100.

Two patients in our sample completed the Bells cancellation test (Gauthier et al., 1989). This test consisted of a sheet of paper containing 35 bells hidden amongst 280 distractor shapes. The bells are distributed within 7 different columns within the sheet with each column containing 5 bells. One column is in the middle of the sheet with 3 columns of 5 bells on each side of the sheet resulting in 15 bells on each side. The sheet was positioned at the patient’s body midline. The total percentage of omissions on each side was calculated by dividing the number of misses by 15 and multiplying by 100.

[1] Note that previous studies have indicated that line bisection errors in patients with neglect do not increase in a strictly linear fashion with increases in line length (McIntosh, Ietswaart, & Milner, 2017). Given that this was a retrospective analysis of neglect screening data from two different sites using different line lengths, calculating percent deviation from center was our best option to attempt to control for differences in line length.

Figure copying.

All patients were asked to copy the star, cube, and flower from the BIT. Each figure was scored based on its completeness and any major omissions or distortions were noted.

Normative data.

In order to determine whether our cerebellar patients demonstrated any symptoms of neglect at the group or individual patient level, we compared their performance to a set of normative data previously published by Lee and colleagues (Lee et al., 2004). This normative dataset was comprised of 81 healthy adults (40 males, mean age=58.3 (SD=11.2; age range 42-81 years; all right-handed)) with no previous neurological history. It is important to note that there was no difference in age between our combined patient sample (55.5) and the normative sample (58.3) from Lee and colleagues (2004; $t(99)=0.97$, $p=.34$).

The normative sample from Lee and colleagues (2004) completed a number of different line bisection and cancellation tasks including a “solid” line bisection task and the star cancellation task from the BIT. These same norms were used by Kim and colleagues (2008) to determine whether cerebellar patients in their study demonstrated symptoms of neglect. Note that the same data analysis procedures noted above were applied to the normative data. Specifically, we converted their average mean deviation from center (in mm) for the line bisection task (10 lines in total) and divided it by the length of the line (242mm) to get a percentage deviation score while attempting to control for line length. The percentage of misses on the left and right side of the star cancellation task was also calculated.

Data analysis.

First, we carried out group level statistics comparing patients with left (n=9) or right (n=11) cerebellar lesions to the normative sample (n=81) for line bisection, as well as left and right omissions during cancellation performance. To examine the line bisection data, we used a one-way ANOVA to compare performance between the three groups. Effect sizes were calculated using partial eta squared (η^2_p). To analyze the cancellation data, we used non-parametric Mann-Whitney U-tests with a Bonferroni correction. Effect sizes for Mann-Whitney U-tests were calculated using rank-biserial correlation. All statistical analyses were carried out using JASP software (JASP-Team, 2022).

Following this group level analysis, we then compared the performance of each individual patient to the normative sample (n=81) using Z-scores (McIntosh & Rittmo, 2021). A patient was considered to be an outlier compared to the normative sample if their Z-score was ±1.96 or more.

Lesion analysis.

We obtained clinical MRI and/or CT medical imaging data for each of the 20 patients. These scans were acquired shortly after their stroke as part of their routine care. Each patient's lesion was traced by an experienced behavioural neurologist (Dr. Britt Anderson) who was blind to the behavioural performance of the patients. Lesions were manually traced using MRIcron software (http://people.cas.sc.edu/rorden/mricron/index.html). Individual patient cerebellar lesion maps are presented in Supplementary Figure 1. All patient anatomical and cerebellar lesion maps were then normalized into MNI space using the high-resolution CT template from the clinical toolbox in SPM 12 (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). We then extracted the cerebellar lesion volume for each patient from MRIcron. The normalized individual lesion maps were then combined to make a group lesion map in MRIcron which was overlaid onto the same high-resolution CT template. Next, the MNI coordinates were recorded for the areas where the largest number of patients had overlapping lesions for the left (n=9) and right (n=11) cerebellar groups. We then converted these MNI coordinates into Talairach coordinates and localized the lesioned areas using the Talairach Daemon Atlas (http://www.talairach.org/).

Results:

Line bisection.

Normative data.

The line bisection data from the normative sample from Lee and colleagues (2004) indicated that, on average, healthy older adults (n=81) bisected lines .06mm to the right of center with a SD=4.13mm. With a line length of 242mm, this amounts to an average rightward deviation of .025% (i.e., (.06/242) *100) with a SD=1.71%.

Cerebellar patient group performance.

For the line bisection data (Figure 1a), a one-way ANOVA indicated that there were no significant differences in line bisection performance between the patients with left (.061%) or right (-.73%) cerebellar lesions and the normative sample (.025%; $F(2,98)=1.32$, $p=.27$, $\eta^2_p=.013$).

Individual patient performance.

Although there were no overall group differences in line bisection, we examined individual patient performance to see if any patients in our group performed outside the range of the normative sample. To do this we calculated Z-scores for each patient based on the mean (.025%) and SD (1.71%) of the normative sample (n=81) from Lee and colleagues (2004). Based on these normative data, 2/20 patients had Z-scores that were larger than ± 1.96 (Table 1). Specifically, patient 1062 with a right cerebellar lesion had a mean line bisection deviation of -3.66% (Z= -2.16). In addition, patient 1945, also with a right cerebellar lesion, had a mean line bisection deviation score of -4.90% (Z= -2.88).

Cancellation.

Normative sample.

In the normative sample from Lee and colleagues (2004) the average percent misses for healthy adults in the star cancellation task was .18% on left (SD=0.81%) and .32% on the right (SD=1.33%).

Cerebellar patient group performance.

For the cancellation data (Figure 1b), Mann-Whitney U-tests with a Bonferroni correction (i.e., .05/6=.008) indicated that, for left cerebellar patients (n=9), there was a significant increase in left omissions (4.03%) compared to the normative sample (.18%; U=139.50, p=.006, corrected, r= -.62). However, there was no increase in right omissions (1.56%) compared to the normative sample (.32%; U=270.00, p=.06, corrected, r= -.26). In addition, the asymmetry in left vs. right omissions (i.e., left % omissions minus right % omissions) was significantly larger for left cerebellar patients (2.47%) compared to the normative sample (-0.14%; U=167.00, *p*=.006, corrected, r= -.54).

At the request of one of the reviewers we carried out an additional analysis examining whether the percentage of omissions in left cerebellar patients (n=9) was associated with whether the patient was less than 30 days post stroke (n=5), or more than one month post stroke (n=4). The results revealed that patients less than 30 days post stroke (mean=3.7%; U=93.00, *p*<.001, r= -54), and patients more than one month post stroke (mean=4.4%; U=46.5, *p*<.001, r= -.73), both made significantly more left omissions on cancellation, compared to the normative sample (mean=.18%).

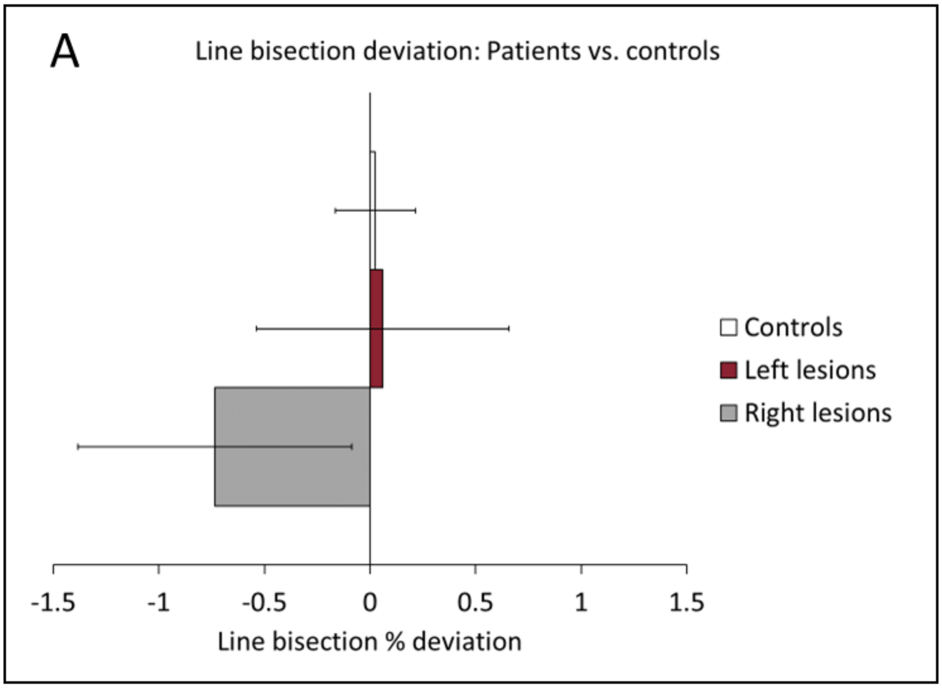
In contrast, there were no significant differences between right cerebellar patients and the normative sample for left omissions (patients=2.02 vs. controls=.18%; U=386.50, *p*=.10, uncorrected, r= -.13) or right omissions (patients=.67% vs. controls=.32%; U=397.00, *p*=.21, uncorrected, r= -.11).

Individual patient performance.

To examine individual patient performance for the cancellation task we calculated Z-scores separately for each patient for left and right omissions using the mean and standard deviation from the normative sample (left=.18%, SD=.81%; right=.32%, SD=1.33%). In the normative sample (Lee et al., 2004), only 4/81 participants (4.9%) missed a single target on the left side. Similarly, only 5/81 participants (6.2%) in the normative sample missed one or more targets on the right side. Given how rare it was for a participant in the normative sample to miss even a single target, a cerebellar patient missing only a single target on the left (Z=4.35) or the right (Z=2.53) would result in a cancellation score that fell well outside of the range of normal performance (Z= ±1.96). Based on this analysis, 6/9 (i.e., 67%) left cerebellar patients (182, 309, 564, 953, 1832, 3163) were outside of the normal range for left targets, and 3/9 (i.e., 33%) left cerebellar patients (61, 309, 564) were outside of the normal range for right targets. In contrast, only 2/11 (i.e., 18%) right cerebellar patients (523, 1071) were outside the normal range for left targets and the same two patients were outside the normal range for right targets.

--insert Figure 1 here—

Figure 1: Figure 1: A) Line bisection percentage deviation from center presented as a function of group (controls, left cerebellar patients, right cerebellar patients). Negative values represent a leftward deviation from center whereas positive values represent a rightward deviation from center. B) Percentage of omissions on the cancellation task presented as a function of group (controls, left cerebellar patients, right cerebellar patients) and side of omission (left vs. right). Error bars represent the standard error of the mean. * Indicates a statistically significant difference.



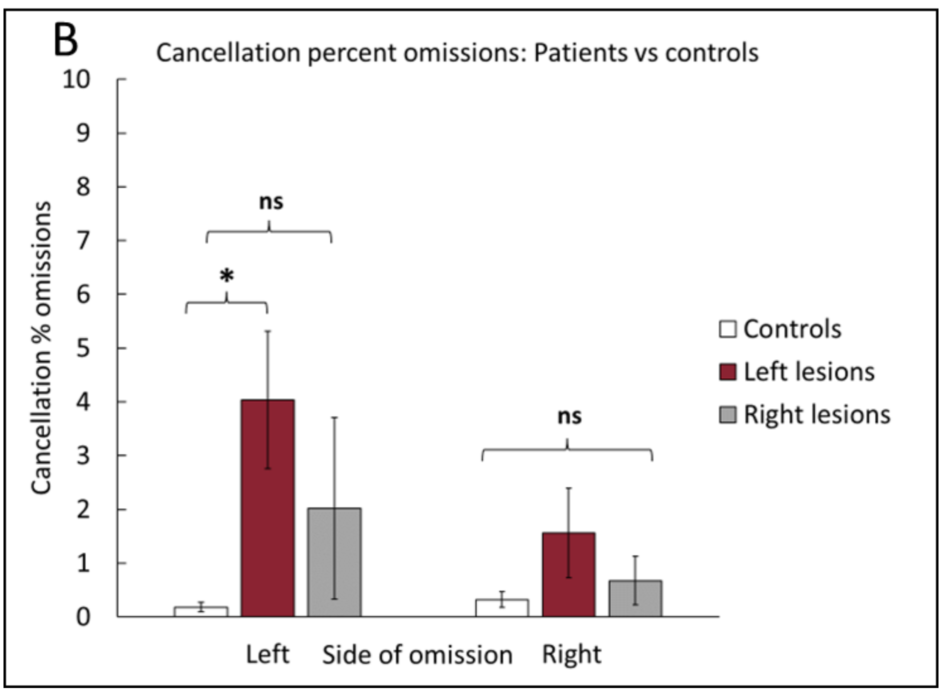


Figure copying.

All patients performed well on the figure copying tests and no major omissions or distortions were noted in any of the patients. Given that our patients did extremely well overall on figure copying, we did not analyze these data further.

Correlation analysis.

We conducted a correlation analysis to examine whether performance on the line bisection and cancellation tasks were related to clinical or demographic variables such as age, time post stroke, lesion volume, or MoCA score (available for 14/20 patients). There was a significant correlation between age at testing and lesion volume ($r(20)=.50$, $p=.024$) such that older age was associated with increased lesion volume. There were also significant correlations between age at testing and percentage of right omissions on the cancellation task ($r(20)=.45$, $p=.046$), lesion volume and percentage of right omissions ($r(20)=.54$, $p=.015$), and percentage of left omissions and percentage of right omissions ($r(20)=.48$, $p=.034$). However, the correlations between right omissions and age at testing, as well as right omissions and lesion volume, appeared to be driven by one patient (patient 61) with a large left cerebellar lesion. When this patient was removed these correlations were no longer significant ($p>.11$). Notably, there were no other significant correlations between age at testing, days post-stroke, MoCA, or lesion volume with either line bisection or cancellation performance (all *p*'s >.09).

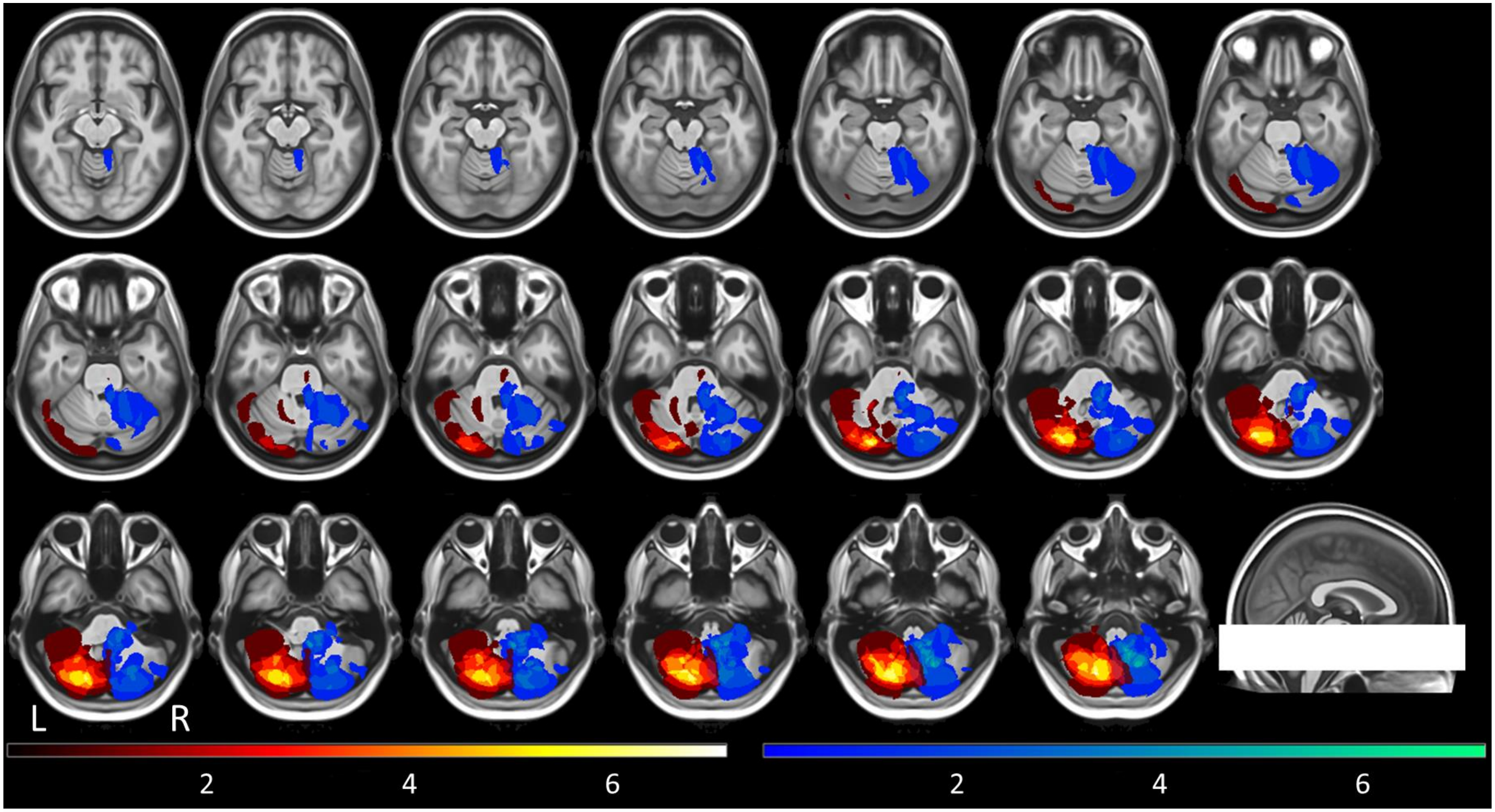
Lesion analysis.

As noted in the Methods, individual lesion maps for each patient are presented in Supplementary Figure 1.

The results of the lesion overlap analysis for the overall group (n=20) are presented in Figure 2. In the overall group of 20 patients, we examined the regions of greatest overlap for left and right cerebellar lesions. Based on this analysis the regions of maximum overlap in the left cerebellar group were Crus II in 7/9 patients (78% overlap; MNI: X= -17, Y= -73, Z= -49), and lobules VII (MNI: X= -28, Y= -78, Z= -37) and IX (MNI: X= -21, Y= -83, Z= -35) in 6/9 patients (66% overlap). For the right cerebellar group, the regions of maximum overlap were Crus II in 5/11 patients (45% overlap; X=20. Y= -64, Z= -49), and HIX (hemispheric lobule IX) in 4/11 patients (36% overlap; X=11, Y= -53, Z=-49). Note that we chose not to “flip” the lesions from one cerebellar hemisphere into the other and combine them into one lesion overlap map as this would have prevented us from being able to examine the relationship between side of lesion and changes in neglect like symptoms.

--insert Figure 2 here—

Figure 2: Figure 2: Group lesion overlay (n=20 total) for patients with left (n=9, in red/yellow) or right (n=11, in blue/green) cerebellar lesions. The scale indicates the number of patients in each group who had damage in a specific region. Based on this analysis the regions of maximum overlap in the left cerebellar group were Crus II in 7/9 patients (78% overlap; MNI: X= -17, Y= -73, Z= -49), and lobules VII (MNI: X= -28, Y= -78, Z= -37) and IX (MNI: X= -21, Y= -83, Z= -35) in 6/9 patients (66% overlap). For the right cerebellar group, the regions of maximum overlap were Crus II in 5/11 patients (45% overlap; X=20. Y= -64, Z= -49), and HIX (hemispheric lobule IX) in 4/11 patients (36% overlap; X=11, Y= -53, Z=-49).



Discussion

Overall, our results indicated that there were no significant impairments in figure copying following cerebellar damage. There were also no significant group differences in line bisection performance for left (n=9) or right (n=11) cerebellar patients (Figure 1A). Although, 2/11 patients with right cerebellar lesions demonstrated leftward deviations in line bisection scores that were outside the range of normal performance (Z= >±1.96).

Importantly, left cerebellar patients demonstrated a significant increase in the percentage of omissions on the left side of the cancellation task, and more left than right sided omissions overall, compared to the normative sample (Figure 1B). No significant effects were observed for right cerebellar patients. This observation is consistent with our disconnection hypothesis that the left cerebellum may play an important role in attention and spatial processing likely through its connections with the fronto-parietal attention network in the right cerebral hemisphere (Allen et al., 1997; Buckner, 2013; Craig et al., 2021; Stoodley & Schmahmann, 2009; Striemer, Chouinard, et al., 2015).

The results from the neglect screening data were supplemented by a lesion overlap analysis which indicated that the regions of maximum overlap in the left cerebellar group were Crus II in 7/9 patients (78% overlap) and lobules VII and IX in 6/9 patients (66% overlap). Previous research has demonstrated that Crus II and Lobule VII of the left cerebellum are functionally connected to regions of the fronto-parietal attention network in the right cerebral cortex (Buckner, 2013; Buckner et al., 2011; Wang et al., 2013). Thus, damage to these left cerebellar regions may result in a disconnection of these cortical regions in the right cerebral hemisphere that are known to play an important role in attention and spatial processing (Corbetta & Shulman, 2002; Husain & Nachev, 2007). In short, our results demonstrate that lesions to the left cerebellum may result in an increase in spatial neglect-like symptoms, even when the symptoms are not severe enough to result in a formal diagnosis of spatial neglect.

It is important to note that our results cannot be explained by visual field impairments or any other demographic factors. First, none of the patients in our sample had visual field defects. In addition, there were no significant correlations between line bisection or cancellation performance with lesion volume, MoCA score, or days post stroke, once a single outlier was removed (patient 61).

In addition, our results cannot be explained by non-specific factors resulting from stroke (e.g., general cognitive slowing, sensory or motor problems, fatigue, post-stroke depression). That is, non-specific deficits in each of these different domains cannot explain: 1) why patients missed significantly more targets specifically *on the left side* of cancellation tasks, or 2) why these results were only significant for those with *left*, but not right cerebellar lesions. If our results were due to non-specific effects of stroke, then one would assume that patients would be equally likely to omit targets on the left or right sides of the cancellation task following damage to either cerebellar hemisphere. However, this was not the case.

Although symptoms of spatial neglect following cerebellar damage have been observed in single-case studies (e.g., Geiser et al., 2022; Hildebrandt et al., 2002; Silveri et al., 2001), group studies in adults have provided contrasting results. Kim and colleagues (2008) found evidence of either ipsilateral or contralateral neglect in 8/28 patients using a composite neglect score comprised of performance across several different line bisection, cancellation, and figure copying tasks. Most of the patients were identified as having neglect through abnormal performance in line bisection tasks (6/28) whereas only two patients were identified as impaired in cancellation. In addition, there was no clear association between neglect symptoms and damage to the left or the right cerebellum. Based on these data, Kim and colleagues (2008) suggested that spatial neglect may be more common following cerebellar injury than previously thought.

The results from the current study are somewhat consistent with Kim and colleagues (2008) in that they noted that 6 of their 28 patients demonstrated abnormal line bisection scores. Although we did not see any overall group differences in line bisection performance, 2 of 11 patients with right cerebellar lesions had a leftward bias that was outside of the range of the normative sample. It should be noted, however, that there were differences in line length between our two patient cohorts (Waterloo cohort = 234mm, Calgary cohort = 192mm). Given that this was a retrospective analysis of neglect screening data from two different sites, we attempted to control for this by using percent deviation scores. As a result, this may have made our line bisection data less sensitive to detecting differences between our patient group and the normative data.

In addition, 2 of 28 patients examined by Kim and colleagues (2008) also demonstrated abnormal cancellation scores. Unfortunately, Kim and colleagues (2008) did not conduct any group-level comparisons to see if the cerebellar patient group(s) differed from controls for either line bisection or cancellation, and individual patient performance for each measure were not reported in their manuscript. This makes it difficult to directly compare their data to the current study.

It is interesting to note that, unlike patients in the study by Kim and colleagues (2008), patients in the current study were more likely to demonstrate an increase in neglect-like symptoms on *cancellation* but not line bisection. Previous research has suggested that, overall, cancellation tests seem to be more sensitive for detecting neglect compared to line bisection

(Azouvi et al., 2002; Ferber & Karnath, 2001). In addition, following lesions to the cerebral cortex, line bisection and cancellation performance are dissociable (Binder, Marshall, Lazar, Benjamin, & Mohr, 1992), and are thought to be related to different lesion locations (Mort et al., 2003; Rorden, Berger, & Karnath, 2006). This might also be the case for the cerebellum. Specifically, Kim and colleagues (2008) suggested that the lesion sites that were most often associated with neglect in their patient sample were regions near the vermis, but not the cerebellar hemispheres. However, in the current study, changes in cancellation performance were observed following damage to the left posterior-lateral cerebellum (i.e., Crus II and lobules VII, IX).

It is interesting to note that subsequent studies have demonstrated that line bisection deviation in cerebellar patients is correlated with the severity of upper limb ataxia symptoms (Frank et al., 2010). Note that the two patients in our study who exhibited a significant leftward deviation in line bisection (1062 and 1945) were both patients with right cerebellar lesions who were completing the task with their right (dominant) hand. Given that this was a retrospective analysis of neglect screening data, we were not able to obtain scores from any ataxia screening measures. However, cerebellar lesions typically result in problems with motor control on the ipsilateral side (Holmes, 1917). Thus, it is possible that these two patients' line bisection scores may have been caused by problems with motor coordination, thereby making it difficult to formulate the spatially precise response required in the line bisection task. In contrast, problems with motor coordination cannot explain the significant increase in left sided omissions on the cancellation task in left cerebellar patients for two reasons. First, each of these patients had a left cerebellar lesion which would affect motor control in their left hand. However, all of the patients completed the cancellation task with their right (dominant) hand. In addition, the cancellation task does not require the same spatially precise response as the line bisection task, as the patient simply needs to make a mark anywhere on the target. In short, it is unlikely that the differences in cancellation performance observed in left cerebellar patients in the current study were due to ataxia symptoms. However, the relationship between ataxia symptoms and scores on cognitive screening tasks that require a response with the ataxic limb is a topic that requires further investigation.

In contrast to Kim and colleagues (2008), Frank and colleagues (2010) found little evidence of spatial neglect following cerebellar stroke (n=22) using a combination of line bisection, letter cancellation, and extinction testing. However, some of their findings are also similar to ours. First, Frank and colleagues (2010) noted that left cerebellar patients omitted more targets in the cancellation task overall compared to right cerebellar patients and controls, although the difference was not statistically significant. In addition, similar to the current study (Figure 1a), Frank and colleagues (2010) noted that line bisection deviation was slightly rightward in left cerebellar patients, whereas deviation was leftward in right cerebellar patients. Another study by Richter and colleagues (2007) also found no evidence for neglect in a group of 21 patients with cerebellar stroke using line bisection, letter cancellation, and extinction testing.

What might explain the contrasting findings between these studies? One important factor could be differences in how long after the stroke patients were tested. Specifically, Kim and colleagues (2008) only tested patients who had a cerebellar stroke less than 60 days prior to the assessment (mean=14.28 days). Frank and colleagues (2010) tested their patients at a similar timeframe post stroke (mean=13.45 days). In contrast, the cerebellar patients examined by Richter and colleagues (2007) were tested an average of 46.7 months post-stroke (~1400 days). In the current study patients were tested an average of 45 days post stroke with a median of 7 days (Table 1). However, this was weighted by one extreme value (patient 953, tested 566 days post stroke). If this value is removed, then the mean number of days post stroke is 18 days, with a median of 7. Therefore, with the exception of one large value, the mean and median for days post stroke are within the subacute and acute stage, respectively (Bernhardt et al., 2017). It is interesting to note that, in the current study, there was no correlation between time post stroke and performance on either the line bisection or cancellation tasks. In addition, a subsequent analysis of cancellation performance in our left cerebellar patients indicated that there was a significant increase in left omissions regardless of whether patients were less than 30 days post stroke (n=5), or more than one month post stroke (n=4). However, it is possible that one could observe a correlation between time post stroke and performance in a larger sample of patients that were tested over a wider range of times following their injury. It is well-known that patients with cerebellar injury often recover more quickly from their injuries than patients with cortical lesions, a concept rereferred to as "cerebellar reserve" (Mitoma et al., 2020). Thus, it may be more difficult to observe symptoms of neglect (or other cognitive or motor deficits) in cerebellar patients several months following their injury.

Another important factor could be lesion volume. Specifically, although Kim and colleagues (2008) found more evidence of neglect in their cerebellar patient group (8/28 patients), the average lesion volume of their patients (n=28, mean=27.26cm^3, SD=22.64cm^3) was significantly larger than both Frank and colleagues (2010; n=22, mean=9.04cm^3, SD=6.92cm^3; $t(33)=4.02$, $p<.001$) and the current study (n=20, mean=9.14cm^3, SD=9.47cm^3; $t(38)=3.79$, $p<.001$). Kim and colleagues (2008) also noted that lesions were significantly larger in their neglect group (52.4cm^3) compared to their no-neglect group (17.2cm^3). Lesion volume data were not reported by Richter and colleagues (2007). In short, it may be harder to find symptoms of spatial neglect in cerebellar patients with smaller lesions. Although, other previous studies examining cognitive function following cerebellar injury have also failed to find a correlation between lesion volume and magnitude of impairment (e.g., Baier, Dieterich, et al., 2010; Craig et al., 2021). We did not observe any correlation between lesion volume and performance on the line bisection or cancellation tasks in the current study (once a single outlier was removed), but this may have been due to our relatively modest sample size (n=20).

Although we have found evidence that left cerebellar injury may lead to an increase in symptoms of spatial neglect, our study is not without its limitations. First, a sample of n=20 is relatively modest. However, it should be noted that our sample is similar in size to other recent group studies that have examined the effects of cerebellar injury on attention and spatial neglect symptoms (Craig et al., 2021; Frank et al., 2010; Kim et al., 2008; Richter et al., 2007). It is important to note that our study only included patients with isolated (unilateral) cerebellar stroke. Isolated cerebellar strokes comprise less than 3% of all stroke cases (Kelly et al., 2001; Macdonell, Kalnins, & Donnan, 1987; Tohgi, Takahashi, Chiba, & Hirata, 1993) which makes it challenging to recruit larger groups of these patients.

Another limitation of the current study is that we only have data from classic neglect screening tasks (i.e., line bisection, cancellation, and figure copying) that may be good at detecting relatively severe symptoms of neglect in patients with cortical injuries, but might not be sensitive enough to detect more subtle symptoms of neglect – like those revealed in the current study. For example, in a previous study that examined the sensitivity of different tasks in detecting neglect, Azouvi and colleagues (2002) noted that the most sensitive paper and pencil measure of neglect was the initial starting point during the cancellation task (typically to the right of center in patients with spatial neglect). In addition, the center of cancellation is another measure that could be examined in future studies (Binder et al., 1992; Rorden & Karnath, 2010). Given that the current study utilized a retrospective analysis of neglect screening data, these measures were not available to us.

Further to the point of test sensitivity, a recent case study by Geiser and colleagues (2022) also observed symptoms of left spatial neglect following damage to the left cerebellum. Notably, their patient sustained damage to Crus I, Crus II and Lobules IIIA, VI, VIIB and VIIIA of the left cerebellum, which is consistent with the lesion overlap results from the current study. Although their patient cancelled all the targets on the Bells cancellation task, their starting point was to the right of center, which is known to be a sensitive marker of neglect (Azouvi et al., 2002). However, the patient showed clearer symptoms of neglect using the five-point test – a more demanding non-verbal fluency task where the patient must produce as many different designs as possible within 40 separate squares on a single sheet of paper. In addition, eye tracking indicated that the patient's mean gaze position was also shifted rightward compared to controls, similar to patients with neglect. Geiser and colleagues (2022) results suggest that using standard paper and pencil measures to screen for neglect (such as those used in the current study) may be underestimating the number of patients who demonstrate neglect-like symptoms following cerebellar injury.

As noted in the introduction, spatial neglect is a complex disorder that is characterized by deficits in spatial attention (e.g., Bartolomeo & Chokron, 2002; Driver & Mattingley, 1998) as well as deficits in temporal attention (Husain et al., 1997), multi-second time perception (Basso et al., 1996; Danckert et al., 2007), and spatial working memory (e.g., Ferber & Danckert, 2006; Husain et al., 2001; Striemer et al., 2013). Previous studies in patients with neglect have also demonstrated difficulty with mental imagery (Bisiach & Luzzatti, 1978; Rode, Pagliari, Huchon, Rossetti, & Pisella, 2017). Given this, one might predict that lesions to the left cerebellum might also result in problems with some of these same processes. In a recent study, we demonstrated that damage to the left cerebellum was associated with deficits in both spatial and temporal attention (Craig et al., 2021). Furthermore, many previous studies have associated the cerebellum with an important role in timing, although mainly for shorter (sub second) intervals (for a review see Ivry & Spencer, 2004). A neuroimaging study by Brissenden and colleagues (2018) demonstrated that each cerebellar hemisphere plays a role in visual working memory in the ipsilateral visual field. Thus, lesions to the left cerebellum might be expected to result in difficulty with visual working memory in the left visual field. Finally, a previous patient study by Molinari and colleagues suggests a greater role for the left cerebellum in mental rotation as patients with left cerebellar lesions consistently completed fewer items in tests of mental rotation, compared to those with right cerebellar lesions (Molinari et al., 2004). Each of these areas remain open topics for future investigation regarding the possible lateralization of attention and spatial processing in the left cerebellum.

Conclusion.

In summary, the results of the current study demonstrate that lesions to the left cerebellum may be associated with an increase in omissions on the left side of cancellation tasks, similar to what is observed (albeit with less severity) in patients with spatial neglect following lesions to the right cerebral cortex (Danckert & Ferber, 2006; Ferber & Karnath, 2001; Husain & Rorden, 2003). A lesion overlap analysis indicated that Crus II and lobules VII and IX were the most commonly damaged regions in the left cerebellar group (n=9) with impaired performance. No deficits were observed at the group level following right cerebellar lesions (n=11).

This increase in neglect-like symptoms following damage to the left cerebellum is consistent with the notion that the left cerebellum may play an important role in attention and spatial processing (Allen et al., 1997; Buckner, 2013; Craig et al., 2021; Stoodley & Schmahmann, 2009; Striemer, Chouinard, et al., 2015), likely via its connections with the fronto-parietal attention network in the right cerebral hemisphere (Buckner, 2013; Buckner et al., 2011; Wang et al., 2013). Thus, it is possible to observe an increase in symptoms that are reminiscent of spatial neglect (i.e., increased misses on the left side of cancellation tasks) following left cerebellar injury, even if the symptoms are not clinically significant enough to lead to an official neglect diagnosis. Future studies should try to incorporate more sensitive measures when screening for neglect as well as attention and visuospatial deficits in patients with cerebellar injury to allow for a better estimation of the prevalence of these deficits in this population. It is well known that the presence of neglect symptoms following stroke is associated with poor functional recovery (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001; Nijboer, Van de Port, Schepers, Post, & Visser-Meily, 2013; Tarvonen-Schröder, Niemi, & Koivisto, 2020). If patients with cerebellar injuries are experiencing neglect-like symptoms following stroke, and these symptoms are not detected, then it could also negatively impact their functional recovery. Ultimately, a better understanding of the cognitive changes that occur following cerebellar damage will help scientists develop more accurate models of cerebellar function, and allow for improvements in diagnosis and rehabilitation following cerebellar injury.

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Declarations

Author contributions.

Conceptualization and study design: Christopher Striemer. Data collection: James Danckert and Sean Dukelow. Data analysis: Ryan Verbitsky and Christopher Striemer. Lesion tracing: Britt Anderson. The first draft of the manuscript was written by Ryan Verbitsky and Christopher Striemer. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing interests.

The authors have no relevant financial or non-financial interests to disclose.

Ethical approval and consent to participate.

All patients provided informed consent to participate at the time the data was collected in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All protocols were approved by the MacEwan University Research Ethics Board, the University of Calgary Conjoint Health Research Ethics Board, the University of Waterloo Office of Research Ethics, and the Tri-Hospital Research Ethics Board.

Consent to publish.

Not applicable.

Availability of data.

The authors confirm that the summarized group data supporting the findings of this study are available within the article and its Supplementary Material. Raw data and individual participant data cannot be made available because of ethical restrictions. Specifically, all participants in the study signed a consent form which indicated that only the researchers involved in the study would have access to individual participant data. Requests for access to individual participant data must be submitted to the corresponding author, and data sharing agreements must be submitted to the University of Waterloo Office of Research Ethics and the University of Calgary Conjoint Health Research Ethics Board.

Availability of materials.

The materials used in this study can either by easily be recreated from the descriptions provided in the Methods section (e.g., line bisection) or are copyrighted and cannot be freely shared (i.e., the line bisection, star cancellation and figure copying subtests of the Behavioural Inattention Test; Bells cancellation).

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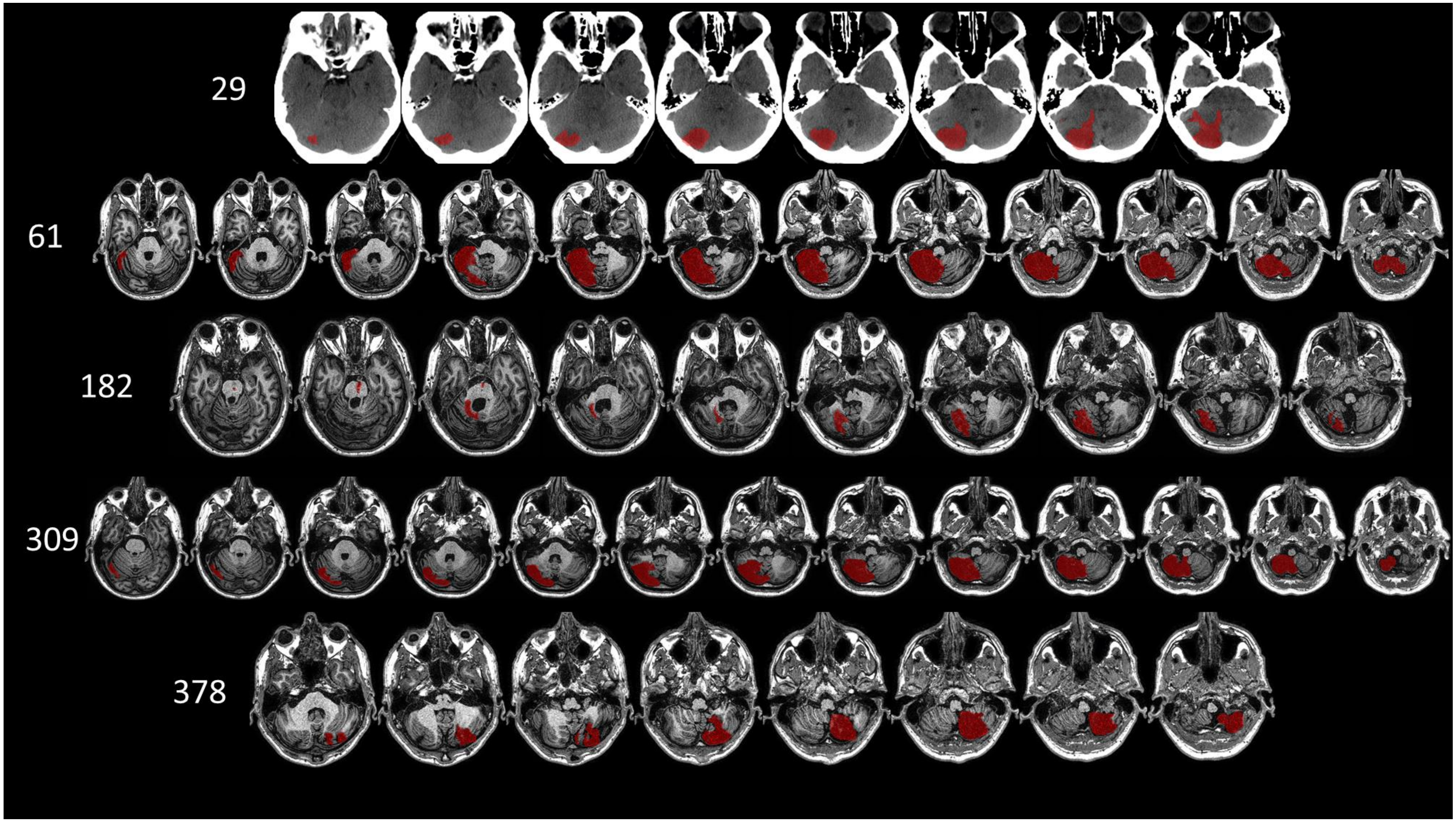
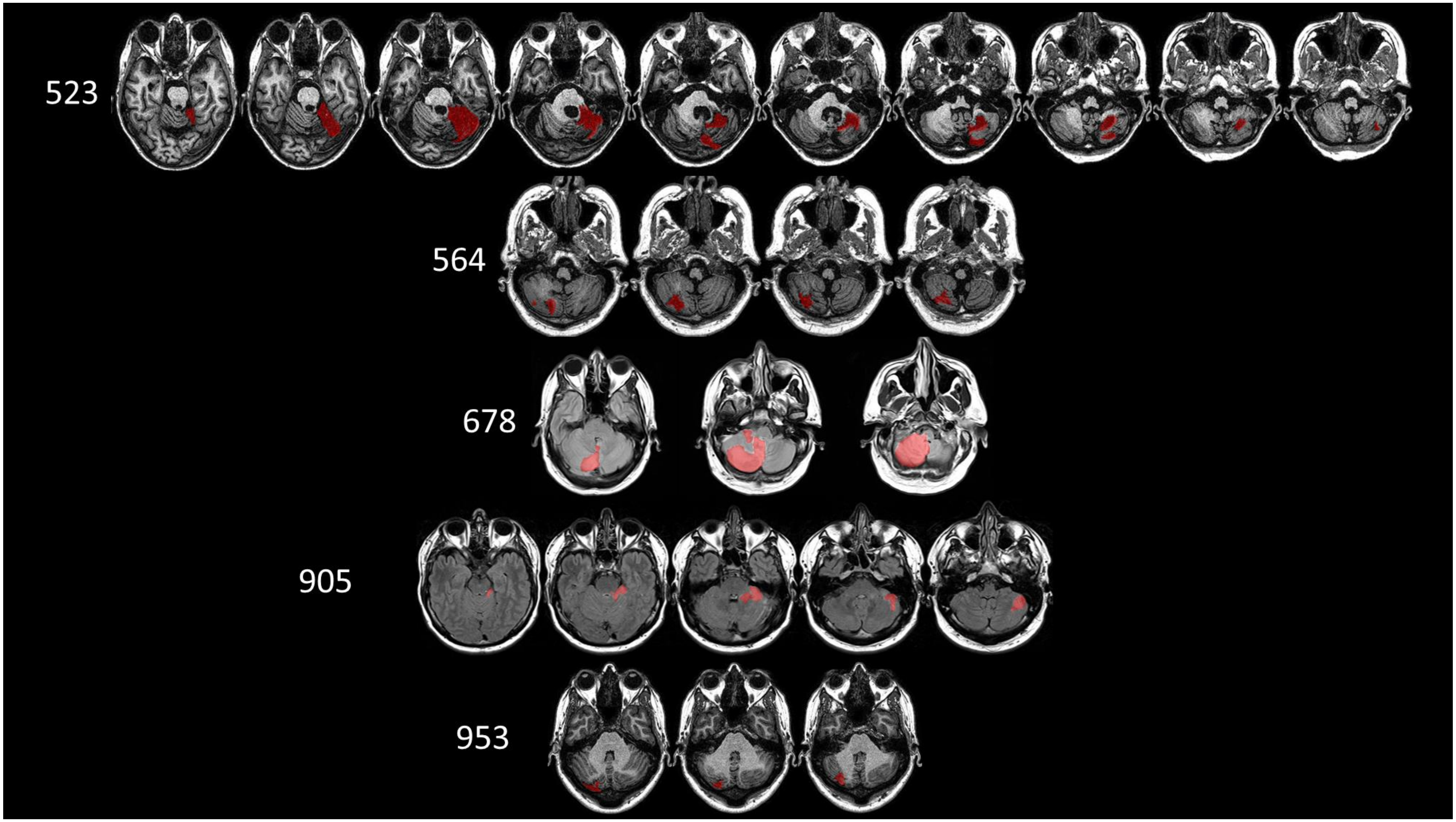
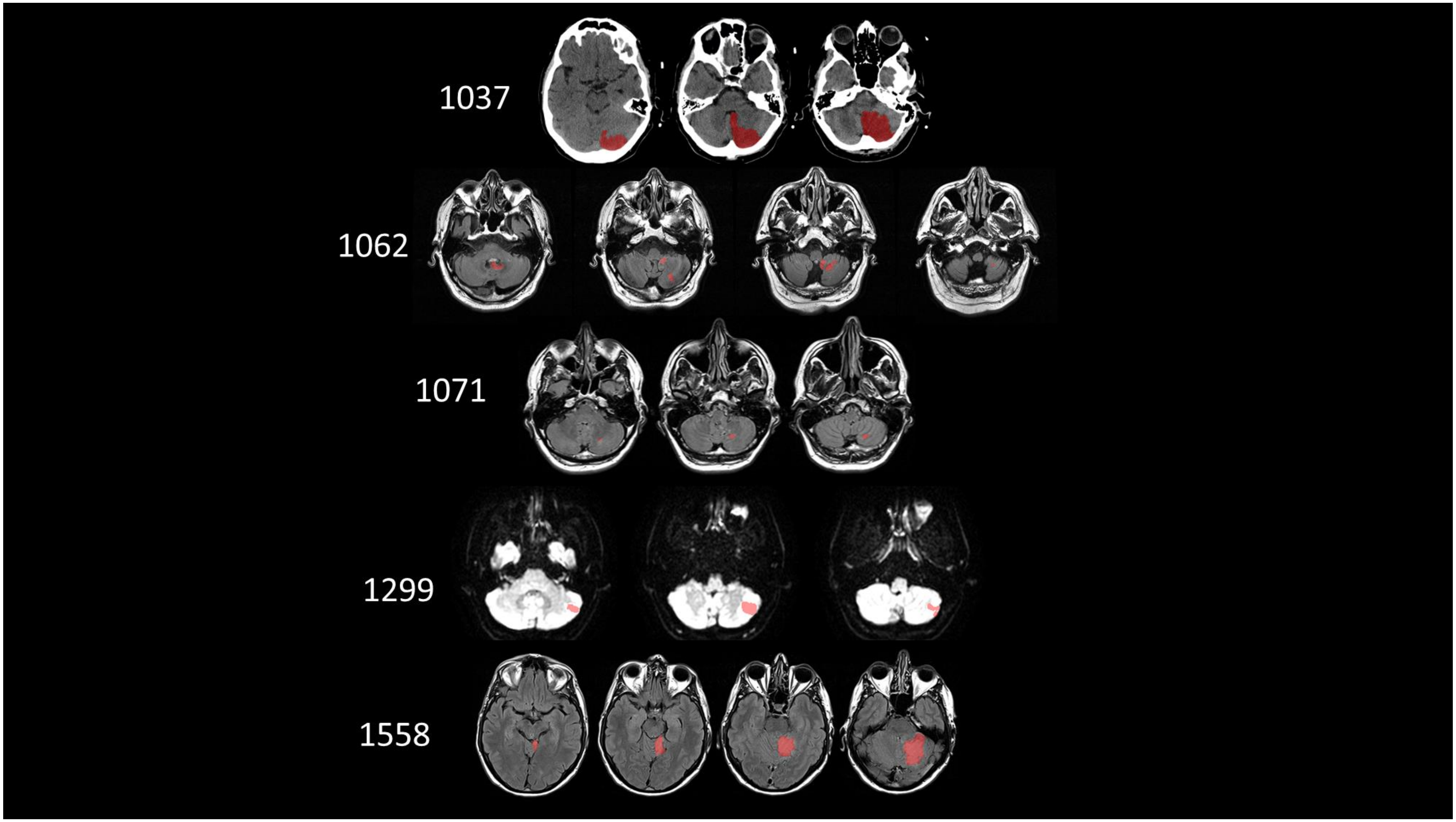
Supplementary Figure 1 Part 1: Individual patient lesion maps. Images are presented in neurological convention where left is on the left. Patient numbers in the Figure match those in Table 1 in the main manuscript.



Supplementary Figure 1 Part 2: Individual patient lesion maps.



Supplementary Figure 1 Part 3: Individual patient lesion maps.



Supplementary Figure 1 Part 4: Individual patient lesion maps.