Hemispatial neglect in cerebellar stroke

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A B S T R A C T

Cognitive deficits can be associated with cerebellar injury. The purpose of this study is to learn: 1) if unilateral cerebellar injury might also cause hemispatial neglect, and if so, 2) if there is a left versus right asymmetry, 3) if the neglect is contralesional (CN) or ipsilesional (IN), and 4) if cerebellar injury might induce neglect by disruption of cerebellar–cortical networks.

Participants were 28 patients with unilateral cerebellar stroke who were assessed for neglect within 2 months after the onset of stroke. To investigate if the cerebellar–cerebral network dysfunction induced neglect, 12 patients received perfusion single photon emission computed tomography (SPECT). Eight of the participants demonstrated neglect (28.6%), four with left cerebellar strokes (three with CN and one with IN) and four with right cerebellar strokes (three with IN and one with CN). Among five patients with neglect who had undergone SPECT, only one with ipsilesional neglect showed crossed cerebello-cerebral diaschisis. Neglect induced by cerebellar stroke might be more common than previously reported. Based on the cerebellar–cortical network hypothesis we expected neglect to be more common with left than right cerebellar injury, but there was an equal number of patients with neglect from right and left sided strokes and the SPECT scan did not provide support of this hypothesis. Thus, this hypothesis cannot also explain the equal number of subject with ipsi- and contralesional neglect and in future studies alternative hypotheses such as vestibular hypothesis will have to be explored.

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1. Introduction

The major functions of the cerebellum appear to be motor and postural control as well as motor learning. However, many recent studies have suggested that the cerebellum also plays a significant role in non-motor functions such as memory, learning, thinking, verbal encoding, concept formation, planning, time estimation, emotion and judgment [12].

Each cerebellar hemisphere is reciprocally connected with the contralateral frontal and parietal association cortices, the thalamus, and the basal ganglia [3,4]. These reciprocal feedforward loops (cortico-ponto-cerebellar pathway) and feedback loops (cerebello-thalamic pathway) might provide an anatomical substrate for the cerebellum's influence on cognitive functions. Since projections from the cerebral cortex to cerebellum or from cerebellum to the cerebral cortex are contralateral, the right cerebellar hemisphere can be involved in cognitive functions mediated by the left hemisphere such as language, and left cerebellar hemisphere can be involved with right hemisphere functions including visuospatial analyses. A few clinical lesion and imaging studies appear to support the postulate that each side of the cerebellum influences hemisphere specific cognitive functions [5,6].

Hemispatial neglect refers to a syndrome in which patients with unilateral brain injury fail to report or respond to stimuli presented in a segment of space [7]. Although it is the contralesional half of viewer centered space that most often neglected (contralesional neglect, CN), some patients also demonstrate ipsilesional neglect (IN) [8]. Both of these forms of hemispatial neglect are more frequent and severe after the right or non-dominant hemisphere injury than the left [7]. Whereas neglect can be induced by a variety of lesions, both cortical and subcortical, that includes tempo-parietal or frontal association cortex, basal ganglia, and thalamus [7], IN is more often associated with frontal than tempo-parietal injuries and CN is more often associated with tempo-parietal injuries than frontal injuries [8]. Since the dentate nucleus in each hemisphere of the cerebellum is strongly connected to the frontal lobe of the contralateral cerebral cortex [9], as well as to the contralateral parietal lobe [10], and it is injury to the parietal and frontal lobes that most often induce neglect, it would be likely that unilateral left sided cerebellar lesions might cause ipsilesional (left sided)
hemispatial neglect. Although there have been several prior reports that hemispatial neglect can be induced by a cerebellar injury [11–15], these studies were based on a relatively small number of patients or case reports and their results were inconsistent.

Based on contralateral connectivity of the cerebellar–cerebral networks and preponderance of right versus left hemisphere injury associated with neglect, we predicted that cerebellar hemispheric injury would be associated with neglect and that neglect would be more common with left than right cerebellar injury. In the acute stage of hemispheric injury, CN is more common than IN, and since our subjects were in the acute stage we also predicted that we would observe more cerebellar IN than cerebellar CN. Finally, if neglect is induced by dysfunction of the cerebellar–cerebral networks, we would expect that those patients demonstrating neglect would demonstrate contralesional cerebral hyperperfusion on single photon emission computed tomography (SPECT) imaging.

2. Methods

2.1. Participants

Between June 2004 and October 2005, patients were consecutively recruited from two acute stroke care units (Samsung Medical Center in Seoul, Korea and Seoul National University Bundang Hospital in Gyeonggi-do, Korea). Patients were 28 individuals (11 women, 17 men; mean age of 61.5±14.7 years with range of 21–87 and mean education 8.9±5.8 years with range of 0–16) with an acute unilateral cerebellar stroke (right-sided lesion in 16/28, left-sided lesion in 12/28, Table 1). Cognitive functions were assessed in 25 out of these 28 patients by using the Mini-Mental State Examination (MMSE), and these patients had a mean MMSE score of 23.2±7.0 (range: 3–29). We included only patients whose stroke onset was less than 60 days prior to neglect testing, and those who were alert and cooperative enough to be able to perform neglect tests. There were three participants who completed only parts of neglect battery, but these subjects were also included. We excluded patients with prior stroke, significant diffuse cerebral white matter changes, bilateral cerebellar stroke, very small sized stroke (maximal diameter <0.5 cm), abnormal extracallosal movements (but patients with gaze evoked nystagmus were included) and accompanied severe upper limb coordination deficits (limb ataxia, intention tremor) which would preclude performing the neglect tests.

Initially 36 patients met these inclusion criteria, but eight patients were excluded for the following reasons: prior stroke (2/8), bilateral cerebellar infarctions (2/8), small sized stroke (3/8), and pre-stroke history of dementia (1/8). Out of 28 patients, three had cerebellar hemorrhage and the remaining 25 patients had cerebellar infarction. For the 28 experimental patients, the time from onset of cerebellar stroke to the neglect testing was 14.3±13.6 days. Brain MRI or CT scan were performed in all patients. The time interval from the acute stroke onset to brain MRI (25/28) or CT scanning (3/28) was an average of 5.7±8.3 days. Two patients were ambidextrous and the remaining 26 patients were right-handed as assessed by Edinburgh Handedness Inventory [16]. Twelve of the 28 patients who agreed to the physician’s request received brain perfusion SPECT. The time interval from the acute stroke onset to SPECT was average 13.9±10.2 days. All patients provided an informed consent for neglect tests and SPECT.

2.2. Apparatus–procedures

A psychomotorian who was unaware of the clinical data or imaging results administered a series of neglect tests to all subjects. The tests included: line bisection, cancellation, and figure copying. These tests have been previously demonstrated to be reliable and valid [17]. Of the 28 patients, 13 patients had upper limb dysmetria (left...
hand in 5/13 and right hand in 8/13), but these patients' dysmetria was not severe enough to interfere with tests performance. Thus, all the patients responded with the pen held in their right hand. The bisection tasks consisted of a “solid” line bisection task, and two versions of the Character Line Bisection Task (CLBT) which comprised the Letter-line and Star-line Bisection Tasks. Each subject bisected 10 solid-lines, 10 Letter-lines, and 10 Star-lines. Details of CLBT and their method of administration have been described previously [17]. The cancellation tasks consisted of a modified version of Albert’s line cancellation test [18] and the Star Cancellation Task [19]. There were two figure copying tasks: a modified Ogden Scene Test [20] and the Two Daisy Figure [21]. The scoring system of all tests also has been described [17]. Briefly, each score from three bisection and two cancellation tasks was converted to a 10 point scale and ranged from −10 to 10 with the plus and minus values representing leftward and rightward bias, respectively. Seven points were given to the two figure copying tasks. There are four objects in the modified Ogden Scene (i.e. left [pine] tree, fence, house, and right tree). For each object, we scored +1 for failure to reproduce objects on the left side of the patient’s drawing (i.e. left scene-based neglect), +0.5 for objects that have missing elements from the left side of the object (i.e. left object-centered neglect), and 0 for a complete figure. Conversely, subjects scored −0.5 for right-sided object-centered neglect and −1 for right scene-based omissions. Because the fence in the Ogden Scene is symmetric, the score of 0.5 or −0.5 was not applied; we scored this part as either 0 (complete drawing), +1 (complete omission of the left side of the fence), or −1 (complete omission of the right side of the fence). Similarly, we considered three objects within the Two Daisy Figure Test (i.e. left daisy, right daisy and pot) and applied the same scoring method described for the Ogden Scene to each object. A final score was obtained by summing scores of the two drawings, yielding scores that ranged from −7 to +7. Thus, when summing the score of all these tests, the scores could vary from +57 to −57. This score was again converted to a 100-point scale such that the possible scores can range from −100 to +100. Positive score denoted the rightward bias and negative leftward bias. As has been published previously [17], norms for this neglect battery were based on 81 normal subjects without previous history of neurological or psychiatric illness (40 men and 41 women with a mean age of 58.3 ± 11.2 years). Therefore, in right cerebellar stroke, CN was defined as a total score that exceeds +2SD of controls’ total score and IN as a total score that was less than −2SD of the controls’ total score. Likewise, CN in left cerebellar stroke was defined as a total score that was less than −2SD of controls’ total score and IN as a total score exceeds +2SD of the controls’ total score.

In addition to the tests for spatial neglect, a neurologist performed tests for visual, tactile and auditory extinctions and neglect dyslexia. To detect tactile, visual and auditory extinction, 20 unilaterals (10 right and 10 left) and 20 bilateral stimuli were presented in random order. Tests for tactile extinction were not performed when the pinprick or touch sense on affected side was 60% or less than the intact side. The presence of extinction was defined by the unawareness of being stimulated on one side for more than 30% of the 20 bilateral stimuli trials. The participants were tested for neglect dyslexia by having them attempt to read aloud 25 words of various lengths and syllables. Neglect dyslexia was considered present if the patient misread or omitted parts of words on the left or right end of the word in three or more of these 25 words.

2.3. Lesion analysis

2.3.1. Lesion location

The time interval from brain imaging to neglect assessment was a mean of 8.6 ± 8.3 days. Two neurologists who were unaware of the clinical findings plotted the vascular territories and lesion sites using the atlas provided by Tatu et al. [22] and Schmahmann et al. [23]. After developing a consensus as to the extent and location of each lesion, these investigators coded the lesion location according to vascular territories [superior cerebellar artery (SCA), posterior inferior cerebellar artery (PICA) and anterior inferior cerebellar artery (AICA) territories]. They also coded the lesion according to cerebellar topography system provide by Schmahmann et al. [23]: cerebellar hemisphere lobule [I, II, III, IV, V, VI, CrI, CrII, VIIB, VIIA, VIIB, IX, X] and vermian lobule [I, II, III, IV, V, VI, VIIA, VII, VIIIB, VIIIB, IX, X].

3. Results

3.1. Overall frequency of neglect

Out of the eight patients who demonstrated neglect, four had right cerebellar strokes and the other four had left cerebellar strokes. Four patients, one with a right cerebellar lesion and three with left cerebellar lesions showed CN. Four other patients, three with right cerebellar stroke and one with left cerebellar stroke, showed IN. The CN and IN groups did not differ in age (CN+: 60.1 ± 19.8 years, N−: 62.1 ± 12.7 years, p = 0.760), education (CN+: 7.5 ± 6.7 years, N−: 9.5 ± 5.4 years, p = 0.428), sex ratio (Male:Female) (N+: 5:3, N−: 12:8, p = 0.999), the interval between stroke and testing (N+: 21.0 ± 13.6 days, N−: 11.6 ± 12.9 days, p = 0.098), MMSE score (N+: 20.8 ± 8.0 in 8/8, N−: 24.4 ± 6.5 in 17/20, p = 0.240) and side of lesion (Left:Right) (N+: 4:4, N−: 8:12, p = 0.691).

3.2. Side of lesion and type of neglect: contralesional versus ipsilesional

Out of the eight patients who demonstrated neglect, four had right cerebellar strokes and the other four had left cerebellar strokes. Four patients, one with a right cerebellar lesion and three with left cerebellar lesions showed CN. Four other patients, three with right cerebellar stroke and one with left cerebellar stroke, showed IN. The CN and IN groups did not differ in age (CN: 63.8 ± 17.7 years, IN: 56.7 ± 14.3 years, p = 0.642), education (CN: 7.0 ± 6.6 years, IN: 8.0 ± 7.7 years, p = 0.851), sex ratio (Male:Female) (CN: 5:2, IN: 3:1, p = 0.999), the interval between stroke and testing (CN: 15.0 ± 7.8 days, IN: 27.0 ± 16.6 days, p = 0.238), MMSE score (CN: 19.0 ± 11.2, IN: 22.5 ± 4.0, p = 0.577), side of lesion (Left:Right) (CN: 3:1, IN: 1:3, p = 0.486) and total neglect scores (CN: −0.5 ± 2.3 IN: −0.8 ± 1.2, p = 0.117).

3.3. Lesions analysis

Overall, the mean lesion volume of all patients was 27.3 ± 22.6 cm³ (range: 0.9–72.0 cm³). When N+ and N− group were compared, the lesion volume was much greater in N+ (52.4 ± 17.9 cm³) than in N− (17.2 ± 15.4 cm³) group (p < 0.001). However, the lesion volume did not differ between the CN (48.2 ± 22.3 cm³) and IN (56.7 ± 14.3 cm³) groups (p = 0.546).

First, lesions were analyzed according to vascular territory. Lesions in patients with neglect involved SCA in 8/8, PICA in 8/8, and AICA in 5/8 (Fig. 1). However, SCA and AICA territories were less involved than PICA territory in N− group, thus both SCA and AICA territories tended to be more affected in N+ compared to N− (SCA: X² = 7.333, p = 0.075, AICA: X² = 4.732, p = 0.068). Second, lesions were coded as 13 cerebellar hemisphere regions and 13 regions of the vermis. Comparison of these lesions between N+ and N−, using univariate analyses, showed that injury to regions of the vermis was more often associated with neglect than injury to areas in the cerebellar hemispheres. More specifically, the lesions that were associated with neglect were in the superior
vermis (culmen (IV, $X^2 = 8.400, p = 0.009$), decilve (VI, $X^2 = 5.989, p = 0.030$) and folium (VIIAf, $X^2 = 6.400, p = 0.035$)), the inferior vermis [tuber (VIIAt, $X^2 = 9.707, p = 0.002$), pyramis (VIIIA and VIIIB, $X^2 = 8.400, p = 0.008$), uvula (IX, $X^2 = 6.222, p = 0.025$), nodulus (X, $X^2 = 5.673, p = 0.031$)], and parts of cerebellar hemisphere [tonsil (IX, $X^2 = 5.305, p = 0.029$), flocculus (X, $X^2 = 11.221, p = 0.003$)].

Further analysis included comparison of lesion sites between CN ($n = 4$) and N− ($n = 20$) groups or between IN ($n = 4$) and N− ($n = 20$) groups. The results showed that lesions of the vermis such as culmen (IV, $X^2 = 8.539, p = 0.018$), folium (VIIAf, $X^2 = 6.400, p = 0.035$), tuber (VIIAt, $X^2 = 9.600, p = 0.007$), nodulus (X, $X^2 = 5.305, p = 0.029$) were associated with IN compared to N−, and the folium (VIIAf, $X^2 = 6.400,$

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**Fig. 1.** Illustration of cerebellar lesions on the atlas provided by Tatu et al. [22]. IN attached to the case number indicates patients with ipsilesional cerebellar neglect while CN indicates patients with contralesional cerebellar neglect.
spatial neglect or visual extinction. There has been only one prior study in which no participant demonstrated clinically relevant signs of hypoperfusion in the infarcted areas with no distant or cortical hypoperfusion. Two of the three patients with CN (P21 and P23 in Fig. 1) had right-sided neglect from a right cerebellar infarction, but this patient’s hypoperfusion was limited to the areas damaged by the stroke. The one remaining patient with CN (P22 in Fig. 1), who had left-sided neglect from a right cerebellar infarction, showed both periventricular white matter hypoperfusion in addition to right cerebellar hypoperfusion.

Of the seven patients who had been imaged but showed no neglect, two patients (P1 and P2 in Fig. 1) showed hypoperfusion in the cerebral cortex of the hemisphere contralateral to the injured cerebellum, and another two (P8 and P27 in Fig. 1) showed hypoperfusion in the cerebral cortex that is ipsilateral to the cerebellar injury.

3.5. Task specificity of cerebellar neglect

We also analyzed the frequency of neglect based on individual test scores. The frequency was similar among the bisection tasks: the solid-line bisection (6/28, 21.4%), the Star-line Bisection (5/25, 20.0%) and the Letter-line Bisection (5/25, 20.0%) (p=0.989). Compared to bisection tasks, abnormal performances on cancellation tasks were rare: only one of 25 patients showed neglect on the star cancellation and another one of 26 patients showed neglect on the line cancellation. The frequency of neglect identified by at least one of bisection tasks was 39.3% (11/28) which was greater than the frequency identified by at least one of the cancellation tasks (7.1%, 2/26) (p=0.007). No patients demonstrated neglect in figure copying or neglect dyslexia tasks. Only one patient with IN demonstrated auditory extinction.

4. Discussion

4.1. Prevalence

Our study shows that neglect occurs in about 30% of patients after acute unilateral cerebellar stroke. Only three group studies so far have tested patients with cerebellar injuries for the presence of neglect. One of the two studies involved the removal of cerebellar tumors in 23 children who were assessed with line bisection and cancellation tests [13]. Post-operatively two children had “motor neglect” of the upper limb, but did not mention how this was determined by the tests they administered. They also analyzed the data after combining the results of line bisection with those of other visuospatial tasks such as copying the Rey–Osterrieth Complex Figure and Judgment of Line Orientation test. The authors described that the patients’ performances were weaker in comparison with the norms, but did not mention details and the frequency of neglect. A second study of children with cerebellar tumors recruited 12 children and adolescents who had undergone surgery for cerebellar astrocytoma and tested these children for components of the neglect syndrome using letter cancellation, line bisection and a test for visual extinction [15]. In this study no participant demonstrated clinically relevant signs of spatial neglect or visual extinction. There has been only one prior study that recruited adults with cerebellar strokes [14]. These investigators retrospectively analyzed a stroke registry and identified 37 patients with acute isolated cerebellar infarctions, but the patients in this registry demonstrated no evidence of significant neglect.

In contrast to these prior studies, we found that neglect from cerebellar stroke was fairly frequent. The discrepancy between the results of these former studies and our study has some possible explanations. First, while most of prior studies were performed in chronic stage after surgery [Aarsen et al.’s study; 3 years and 4 months, Richter et al.’s study; mean 5.7 years], our study involved patients in the more acute stage of stroke (mean 14.3 days). In many patients, neglect can be a transient sign observed primarily during the acute and sub-acute stages [24]. Second, while the participants from the tumor studies were children or adolescents with mean age of approximately 12–14 years, we recruited older patients (mean age of 61.5 years). In patients with hemispheric cerebral injuries, age appears to influence the prevalence of neglect, such that the older patients show greater frequency of neglect than do the younger patients [25]. In the Hoffmann and Schmitt study [14], however, the participants were stroke patients and the ages and chronicity of the patients were similar to those used in our study. Although these authors used a line bisection task, they did not provide details about the stimuli used to assess neglect (e.g., the length of the line used in the bisection task) and also provided no detailed information about lesion location and size. Thus, the comparisons that we can make between the Hoffmann and Schmitt study and our study are limited.

4.2. Lesion size

There have been conflicting reports as to the relationship between the lesion size of cerebellar injury and cognitive impairments. One study found a clear correlation between cognitive impairments and the CT-based estimates of infarct size [26]. A subsequent study, however, did not replicate these results, but rather found an inverse correlation between the lesion volume and the cognitive impairments [27]. Our results showed that the mean lesion size of the patients with neglect was much larger than those without neglect supporting Malm et al.’s result [26]. Although the reason for this discrepancy is not entirely clear, our patients’ lesions appeared to be larger than those of Kalashnikova et al.’s patients [27] and even larger than those of the cognitively normal group in their study. Thus, the results of the Kalashnikova et al.’s study might have been confounded by using participants with small cerebellar lesions.

4.3. Lesion loci

Since each cerebellar hemisphere projects to the contralateral cerebral cortex and cerebral hemispatial neglect is more frequent and severe with right (non-dominant) than left cerebral hemisphere injury, we expected that most patients with dysfunction in this cerebellar–cerebral network would have neglect ipsilateral to their cerebellar stroke (cerebellar ipsilesional neglect) and left cerebellar infarcts would be more likely to induce neglect than right cerebellar infarcts. However, only the half of patients with neglect (4/8) had ipsilesional neglect. Furthermore, although these 4 patients with IN were expected to have left cerebellar injury, contrary to our expectation, 3/4 had right cerebellar injury and only 1/4 had left cerebellar lesion. Thus, interruption of the cerebellar–cerebral networks cannot fully account for the neglect observed in our cerebellar injured subjects. Furthermore, the results of brain SPECT also failed to support this cerebellar–cerebral network dysfunction hypothesis of neglect.

Comparison of lesion sites between the patients with and without neglect showed that among many anatomic sites of cerebellar lesions, injury to the superior and inferior vermis seemed to be the lesion site that is most commonly associated with neglect. This finding is consistent with those of functional MRI studies that found activation of cerebellar
vermis during a line bisection judgment task [28] and the cerebellar vermis has a role in the mediation of object- and space-based visual attention [29]. Although the role of the vermis in the allocation of attention is not known, the vermis, via the deep cerebellar nuclei, project to the superior colliculus [30] and this input to the colliculus appears excitatory [31]. Although this cerebellar–collicular network might be important in saccadic eye movements, studies have revealed that injury to the superior colliculus can lead to neglect [32] and that a reduction of visual input to the colliculus by monocular eye patching can alter line bisection performance [33]. Continuous circling by a rat is a sign of neglect and collicular bicuculline-induced circling in rats can be blocked by GABA injections into the deep cerebellar nuclei [34].

4.4. Vestibular hypothesis

An alternative hypothesis that might account for the unexpectedly high frequency of contralesional cerebellar neglect is the vestibular hypothesis. Vestibular activation in normal subjects can induce a bias on the line bisection task [35]. Vestibular (caloric) stimulation can be used to reverse the spatial bias associated with neglect [36]. Finally, vestibular dysfunction and neglect have some similar signs, such as eye and head deviation, and several investigators have demonstrated that cerebellar strokes can mimic vestibular neurinotis [37]. The cerebellum, especially the flocculonodular lobe, is an important component of the vestibular system. Thus, a possible alternative mechanism that might account for presence of hemispatial neglect with cerebellar strokes is that neglect in these patients is being induced by alterations of the vestibular system. Spatial attention and actions require spatial computations and these computations are based on an egocentric (body–head centered) coordinate system. This spatial coordinate system is primarily based on three sources of sensory input: visual, vestibular and proprioceptive. Thus, the perturbations of the vestibular networks, induced by injury to portions of the cerebellum might induce a distortion of peoples’ spatial coordinate systems, resulting in hemispatial neglect. The flocculonodular lobe has reciprocal connection with ipsilateral peripheral vestibular organ and the vestibular nuclei. Therefore, in contrast to ipsilateral cerebellar neglect resulting from the posited crossed cerebral hemisphere dysfunction, unilateral cerebellar–vestibular dysfunction could induce an ipsilesional vestibular dysfunction and this dysfunction could produce the spatial ipsilesional orienting bias we observed in the four participants with contralesional neglect.

4.5. Neuropsychological deficits

Patients with right hemisphere stroke tend to show greater contralesional (left) hemispatial neglect in the Star Cancellation Task than in solid-line bisections or line cancellation tasks [38]. One explanation for this finding would be that the Star Cancellation Task has greater attentional demands than other tasks. In contrast, our patients’ performance on tests of neglect was characterized by greater impairment on line bisection than cancellation tasks. Thus, our results might provide further support against the cerebellar–cerebral hypothesis and the fact that our patients’ neglect is less likely driven by attentional demands might favor the vestibular hypothesis.

Acknowledgements

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (A050079), the Samsung Medical Center Clinical Research Development Program grant, # CRS-104-04-2, IN-SUNG Foundation for Medical Research.

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References