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Voxel-based lesion symptom mapping analysis of depressive mood in patients with isolated cerebellar stroke: A pilot study☆,☆☆

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ABSTRACT

Post-stroke depression (PSD) is the most common neuropsychological sequela of stroke and occurs in approximately one-third of all stroke survivors. However, there are no well-established predictors of PSD. Depression in stroke patients is correlated with unfavorable outcomes. Meta-analyses of the relationship between PSD and lesion location have yielded contradictory results and have not adequately addressed the impact of cerebellar lesions. Furthermore, other brain regions associated with depression in patients with cerebellar stroke remain a matter of debate. For these reasons, this cross-sectional study investigated the relationship between PSD and lesion location in patients with isolated cerebellar stroke.

Twenty-four patients in the subacute rehabilitative period following a first-ever isolated cerebellar stroke were enrolled in the study. Depressive mood were evaluated using the Geriatric Depression Scale. Regions of interest were drawn manually on T1-weighted magnetic resonance images using MRIcron software, and data were normalized to a standard brain template in order to examine the neural correlates of depression using voxel-based lesion-symptom mapping analysis.

Voxel-wise subtraction and χ (Ayerbe et al., 2014) analyses indicated that damage to the left posterior cerebellar hemisphere was associated with depression. Significant correlations were also found between the severity of depressive symptoms and lesions in lobules VI, VIIb, VIII, Crus I, and Crus II of the left cerebellar hemisphere ($P_{corrected} = 0.045$). Our results suggest that damage to the left posterior cerebellum is associated with increased depressive mood severity in patients with isolated cerebellar stroke.

1. Introduction

Post-stroke depression (PSD) has been reported to affect >30% of patients with stroke survivors (Hackett and Pickles, 2014). PSD can occur during the early or late phase after stroke and shows a high recurrence rate but a relatively short duration (Ayerbe et al., 2014). The influence of PSD on recovery from stroke is clinically significant, as it leads to increased functional dependence (Herrmann et al., 1998), poorer rehabilitation outcomes (Gillen et al., 2001), increased mortality, and lower quality of life (Ayerbe et al., 2013a). Moreover, recovery from PSD does not reduce the long-term risk of negative outcomes (Ayerbe et al., 2013b).

During the past few decades, a large number of studies have investigated the relationship between PSD development and stroke location. Several studies have suggested that left hemispheric stroke is related to the development of PSD, (Robinson et al., 1983; Robinson et al., 1984; Parikh et al., 1987) whereas MacHale et al. found a statistically significant association between PSD and right hemispheric lesion (MacHale et al., 1998). However, recent meta-analyses have failed to detect robust relationships between PSD and lesion location, (Carson et al., 2000; Hadidi et al., 2009; Wei et al., 2015) and thus this relationship remains inconclusive. Furthermore, most previous studies have focused on lesions to the cerebral hemispheres, and the potential role of the cerebellum in the development of PSD has been underexplored.

Since the definition of cerebellar cognitive affective syndrome by Schmahmann and Sherman (Schmahmann and Sherman, 1998), there has been growing concern regarding the role of the cerebellum in the control of emotional processing. Several studies have reported decreased cerebellar volume associated with mood disorders (Peng et al., 2011; DelBello et al., 1999; Escalona et al., 1993). Blood flow

Abbreviations: GDS, Geriatric Depression Scale; MBI, modified Barthel index; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PSD, post-stroke depression; ROI, regions of interest; SD, standard deviation; VLSM, voxel-based lesion-symptom mapping.

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abnormalities (Videbech et al., 2002; Dolan et al., 1992) and disrupted regional homogeneity in the cerebellum have been observed in subjects with major depressive disorder (Liu et al., 2010; Guo et al., 2011). Cerebellar stroke has also been associated with post-stroke emotional incontinence (Kim and Choi-Kwon, 2000). However, few studies have been conducted on the relationship between PSD and stroke-induced cerebellar lesions. Thus, the aim of the current study was to investigate the association between PSD and lesion location in patients with isolated cerebellar stroke using brain voxel-based lesion-symptom mapping (VLSM) analysis.

2. Methods

2.1. Subjects

From February 2005 to December 2014, we consecutively included 154 adult patients with cerebellar stroke from a tertiary inpatient rehabilitation hospital. Stroke diagnoses were made by clinicians who treated the patients at the time of admission, based on neurological examination and history of present illness. Diagnoses were confirmed by computed tomography or magnetic resonance imaging (MRI) findings during the acute period.

On MRI, we differentiated focal lesions in the supratentorial region, in respect to their signal intensities on T1-, T2- weighted and fluid attenuated inversion-recovery images, as well as their size, shape, symmetry and location (Longstreth et al., 1998). Hyperintense punctate lesions only on T2 images or lesions smaller than 3 mm were not regarded as evidences of cerebrovascular accidents, to exclude small unidentified bright objects (Kertesz et al., 1988) and enlarged perivascular spaces (Heier et al., 1989). Patients with evidence of old ischemic or hemorrhagic supratentorial lesions on imaging, but no previous diagnosis of stroke, were excluded from the study.

The inclusion criteria were as follows: 1) first-ever stroke restricted to the cerebellum, 2) age 18 years or older, 3) elapsed time of 3 months or less after stroke onset, 4) no history of neurological or psychiatric disorders, 5) no disorders of consciousness (vegetative or minimally conscious state, as defined by the JFK Coma Recovery Scale (Giacino et al., 2004)) and 6) no severe cognitive deficit (Mini-Mental Status Examination (MMSE) scores ≥15 points). Fifteen patients refused to proceed with the study. Twenty-four patients were enrolled in the study (Fig. 1).

The patients included 15 men and 9 women with a mean age of 55.04 years (standard deviation [SD], 17.79 years; range, 19–81 years). The mean elapsed time since stroke onset was 1.42 months (SD, 0.78 months; range, 0–3 months). All subjects or their family members gave informed consent, and all procedures were performed with the approval of Institutional Review Board for Clinical Studies of Yonsei University College of Medicine, Seoul, Korea.

2.2. Evaluation of cognitive function, depression, and functional status

Cognitive function was assessed using the MMSE, since Salter et al. reported increased sensitivity and specificity of the Geriatric Depression Scale (GDS) in patients with MMSE scores of 15 and higher (Salter et al., 2007). Patients with MMSE scores <15 were excluded from further assessment.

Patients were interviewed for depressive symptoms. A patient was considered depressed if he or she fulfilled the criteria of mood disorder due to stroke with major depression-like episode or minor depression (research criteria), as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (Unutzer et al., 2002), and had a GDS score > 16 points (Kim et al., 2008). We used GDS to quantify the severity of depressive symptoms. GDS is comprised of 30 questions with yes/no responses, and is a highly reliable and valid test for depression screening (Stiles and McGarrahan, 1998). Both MMSE and GDS were administered by a psychologist, who was unaware of the lesion location and detailed neurologic findings.

Performance on activities of daily living was measured with the modified Barthel index (MBI) (Shah et al., 1989). MBI scores range from 0 to 100; a lower score is associated with greater physical dependence.

2.3. Brain MR imaging acquisition

MRI was performed using a Philips 3T scanner (Intra Achieva, Philips Healthcare, Amsterdam, Netherlands). Brain MRI scans included high-resolution, 3-dimensional T1-weighted (axial plane, matrix = 224 × 256, field of view = 220 mm, voxel size = 0.875 × 0.875 × 1.0 mm^3, echo time = 4.6 ms, repetition time = 9.9 ms, flip angle = 8, 160 slices), T2-weighted (axial plane, matrix = 448 × 358, field of view = 230 mm, voxel size = 0.449 × 0.449 × 3.0 mm^3, echo time = 80 ms, repetition time = 4553 ms, 48 slices), and fluid attenuation inversion recovery scans (axial plane, matrix = 352 × 249, field of view = 230 mm, voxel size = 0.449 × 0.449 × 7.0 mm^3, echo time = 125 ms, repetition time = 11.000 ms, 20 slices).

2.4. Statistical analyses of demographic and clinical data

Demographic and clinical data were analyzed using SPSS Statistics software, Version 20.0 (IBM, Armonk, NY, USA). In subgroup analyses, the χ (Ayerbe et al., 2014) test and Fisher's exact test were used to analyze the effects of categorical variables (sex and stroke etiology). The Mann-Whitney *U* test was used to analyze the effects of continuous variables (age, lesion volume, time since stroke, and MMSE and MBI scores).

To assess possible confounding factors, correlations among age, lesion volume, and MBI and GDS scores were evaluated using Spearman's rank correlation coefficient. *P* values <0.05 were considered significant.

2.5. Lesion mapping and analysis

Lesions were manually drawn by a radiologist, who was blinded to all clinical information, on T1-weighted template MRI slices using MRIcron software (http://www.mricro.com; University of South Carolina, Columbia, SC, USA), and saved as regions of interest (ROI). Multiple images were compared to confirm lesion location and extent. The drawn lesions were inspected by a skilled neuroradiologist. Each ROI was registered, resampled to a voxel size of 2 × 2 × 2 mm^3, and normalized to a standard brain template using Statistical Parametric Mapping 12 software (http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology, London, UK).

Two types of analysis were conducted on the normalized lesions of our patients. First, we performed a group comparison study to recognize the lesions associated with PSD. Patients were classified into non-depressive (n = 16) and depressive groups (n = 8). The overlay map of ROIs for each group was created, and ROI data of the non-depressive group were subtracted from those of the depressive group. To avoid potential problems associated with subtraction analysis, we also performed a direct statistical comparison of lesions between depressive and non-depressive patient groups using voxel-by-voxel χ (Ayerbe et al., 2014) analyses for each voxel that was damaged in at least 1 patient (Rorden and Karnath, 2004). Statistical significance was defined as $P < 0.01$.

Second, a VLSM approach was applied to identify correlations between lesions and the severity of depressive symptoms using the VLSM 2.55 toolbox (http://neuroling.arizona.edu/resources.html; University of Arizona, Tucson, AZ, USA) for MATLAB (MathWorks, Natick, MA, USA) (Bates et al., 2003). A t-statistic for each voxel was calculated to compare the severity of depression in patients with and without a lesion in that voxel. Cluster size and the permutation method were used to correct multiple comparisons (Wilson et al., 2015). Only voxels that were lesioned in at least 10% of all patients were included in the analysis. Data were permuted 1000 times with a t-map threshold of