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Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke

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ABSTRACT

Cerebellar lesions can cause motor deficits and/or the cerebellar cognitive affective syndrome (CCAS; Schmahmann's syndrome). We used voxel-based lesion-symptom mapping to test the hypothesis that the cerebellar motor syndrome results from anterior lobe damage whereas lesions in the posterolateral cerebellum produce the CCAS. Eighteen patients with isolated cerebellar stroke (13 males, 5 females; 20–66 years old) were evaluated using measures of ataxia and neurocognitive ability. Patients showed a wide range of motor and cognitive performance, from normal to severely impaired; individual deficits varied according to lesion location within the cerebellum. Patients with damage to cerebellar lobules III–VI had worse ataxia scores: as predicted, the cerebellar motor syndrome resulted from lesions involving the anterior cerebellum. Poorer performance on fine motor tasks was associated primarily with strokes affecting the anterior lobe extending into lobule VI, with right-handed finger tapping and peg-placement associated with damage to the right cerebellum, and left-handed finger tapping associated with left cerebellar damage. Patients with the CCAS in the absence of cerebellar motor syndrome had damage to posterior lobe regions, with lesions leading to significantly poorer scores on language (e.g. right Crus I and II extending through IX), spatial (bilateral Crus I, Crus II, and right lobule VIII), and executive function measures (lobules VII–VIII). These data reveal clinically significant functional regions underpinning movement and cognition in the cerebellum, with a broad anterior-posterior distinction. Motor and cognitive outcomes following cerebellar damage appear to reflect the disruption of different cerebro-cerebellar motor and cognitive loops.

1. Introduction

Until recently, the cerebellum was considered solely a sensorimotor structure, with gait ataxia, appendicular dysmetria, and dysarthria being the hallmark clinical symptoms of cerebellar damage (Holmes, 1939). However, in the past 20 years, multiple lines of evidence support a role for the human cerebellum in cognition and emotion, and clinically the Cerebellar Cognitive Affective Syndrome (CCAS, Schmahmann and Sherman, 1998; also known as Schmahmann's syndrome, Manto and Marien, 2015) is characterized by deficits in language, visual spatial, and executive functions, and affective dysregulation. Theoretically, the type of processing that underlies the cerebellar contribution to movement could also be applied to cognitive functions (Ito, 2008; Schmahmann, 1991, 1998), with damage leading to dysmetria of thought (Schmahmann, 1991) analogous to the dysmetric movements that characterize the cerebellar motor syndrome.

Anatomical connections link sensorimotor and association areas of the cerebral cortex in reciprocal loops with corresponding sensorimotor and cognitive regions of the cerebellum (Schmahmann and Pandya, 1997; Stoodley and Schmahmann, 2010; Strick et al., 2009). Primary and secondary sensorimotor homunculi in the cerebellar anterior lobe (lobules I/II through V) and lobule VIII, respectively, have been established through electrophysiological (e.g. Snider and Eldred, 1952) and human neuroimaging studies (e.g. Grodd et al., 2001). Predictably, these regions show resting state functional connectivity with somatomotor networks of the cerebral cortex (e.g. Buckner et al., 2011). The posterior lobes of the cerebellum (lobules VI through IX, which are greatly expanded in humans) interconnect with association cortices, supported by evidence from both tract-tracing (e.g. Middleton and Strick, 2001) and resting-state functional connectivity studies (Bernard et al., 2012; Buckner et al., 2011; Krienen

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and Buckner, 2009; O'Reilly et al., 2010). This functional topography is evident in task-based human neuroimaging data, in which sensorimotor tasks tend to engage the cerebellar anterior lobe and lobule VIII, and cognitive tasks activate the posterolateral cerebellar hemispheres (Keren-Happuch et al., 2014; Stoodley, 2012; Stoodley and Schmahmann, 2009; Stoodley et al., 2012).

Cerebellar functional topography may be critically important when considering clinical outcomes following cerebellar damage. For example, we have shown that the cerebellar motor syndrome is associated with damage to the anterior cerebellum (Schmahmann et al., 2009b), and other lesion-deficit studies have shown that limb and gait ataxia are more often associated with stroke involving the superior cerebellar artery as compared to posterior inferior cerebellar artery strokes (Kase et al., 1993; Timmann et al., 2008; Tohgi et al., 1993). Schoch et al. (2006) conducted detailed lesion-symptom mapping of ataxic signs in 90 patients, and also showed correlations between ataxia scores and anterior lobe damage (lobules II–V extending into VI). Dysarthria has been associated with damage to medial lobule VI, corresponding with the sensorimotor representation of the articulatory apparatus (Urban et al., 2003). In contrast, the CCAS is more likely to occur following cerebellar posterior lobe lesions (e.g. Levisohn et al., 2000; Schmahmann and Sherman, 1998). Several clinical studies have indicated an effect of lateralization of cerebellar damage on outcomes (e.g. Riva and Giorgi, 2000; Scott et al., 2001), reflecting the contralateral connections between the cerebellar hemispheres and the cerebral cortex. In particular, damage to right cerebellar regions results in a variety of language deficits, reflecting their interconnections with left cerebral hemisphere language areas (see Marien et al., 2014). The clinical consequences of cerebellar lesions on motor versus cognitive aspects of linguistic processing appear to be driven by cerebellar functional topography: ataxic dysarthria results from lesions in the cerebellar anterior lobe, whereas verbal fluency and working memory deficits are associated with posterolateral cerebellar damage (Bultmann et al., 2014; Ilg et al., 2013; Richter et al., 2007).

Here we further explore the structure-function correlation hypothesis within the human cerebellum by examining the relationship between the location of injury within the cerebellum and the motor versus cognitive outcomes. Patients with isolated cerebellar stroke completed a battery of motor and neuropsychological tasks to detect symptoms and signs of the cerebellar motor syndrome and the CCAS. Voxel-based lesion-symptom mapping was employed to determine which regions of the cerebellum were associated with behavioral deficits on a given task. We predicted that the cerebellar motor syndrome would be associated with damage to the sensorimotor representations in the anterior lobe and lobule VIII of the cerebellum, whereas impaired cognitive performance would be associated with damage to the cerebellar posterior lobe. These predictions, based on the established functional topography of the cerebellum and previous lesion mapping studies, enable us to assess whether damage to specific cerebellar regions are associated with cognitive subscores in a consistent manner. If cognitive deficits are indeed consistent with site of lesion, then these findings may be used to improve clinical diagnosis, management, and prognosis of cognitive outcomes following cerebellar stroke.

2. Materials and methods

2.1. Participants

Participants were 18 patients with a first ischemic stroke confined to the cerebellum admitted to the stroke service of the Massachusetts General Hospital during a four-year period. Exclusion criteria included age < 18 years, pregnancy, pre-existing neurological illness, underlying medical condition with active metabolic differences that may impair cognitive function, axis 1 or 2 psychiatric disorder, primary cerebellar hemorrhage, and cerebellar stroke showing signs of herniation requiring cerebellar excision with ventriculostomy placement. Patients with evidence (imaging or clinical examination) that the stroke involved brain areas outside the cerebellum, including the brainstem, were excluded. Patients provided written, informed consent and the study was approved by the Institutional Review Board of Partners Health Care.

Patients were thirteen males and five females (average age ± standard deviation of 46.8 ± 14.6 years; range 20–66 years). Each patient underwent a comprehensive medical and neurological examination and bedside mental state testing by a board certified neurologist (JDS). Neuroimaging, motor and neuropsychological testing were completed during the acute / subacute stage of recovery. The average times from date of stroke to behavioral assessment and MRI scan were 29.8 days (±18.1 days, range 8–67 days) and 38.8 days (±19.3 days, range 9–87 days), respectively. The average interval between behavioral assessment and MRI scan was 11.3 days (±16.2, range 0–65 days).

2.2. Behavioral assessment

The motor task battery included the modified International Cooperative Ataxia Rating Scale (MICARS; Schmahmann et al., 2009a; Trouillas et al., 1997); the grooved pegboard test (Lewis and Rennick, 1979); and finger tapping test (Bornstein, 1985). These tests tap both gross and fine motor skills that could be affected by cerebellar damage. The MICARS assesses posture and gait, kinetic limb function, speech, and eye movements based on a 120-point scale, with higher scores associated with greater impairment. In the grooved pegboard task, patients are asked to place pegs into notched holes, first with their dominant hand and then with their non-dominant hand; performance is based on time to completion for each hand. During the finger tapping test, participants tapped their index finger on a finger tapping board for five 10-second intervals. Patients complete this task first with their dominant hand and then with their non-dominant hand. Scoring is based on the average number of taps across each 10-second interval for each hand. For both the grooved pegboard and finger tapping tasks, patient scores were converted into z-scores based on published norms.

The neuropsychological test battery was designed to test the cognitive aspects of the CCAS, and included measures of IQ, language, spatial processing, executive function, and working memory (see below). Premorbid intelligence was estimated using the Barona index (Barona et al., 1984).

Neuropsychological testing was conducted at the Massachusetts General Hospital Psychology Assessment Center by clinical neuropsychologists and psychometricians (supervised by JCS). Unless otherwise noted, all scores were converted into age-adjusted z-scores using the published norms for each measure. Selected subtests from the Wechsler Adult Intelligence Scale, version 3 (WAIS-3; Wechsler, 1997) were used to evaluate current verbal (Vocabulary, Similarities) and visual (Matrix Reasoning) cognitive functioning. Language processing was assessed with the Boston Naming Test (Goodglass and Kaplan, 2000) and phonemic (F-A-S) and semantic (animals) verbal fluency (Controlled Oral Word Association Test [COWAT (Tombaugh et al., 1999)]). Spatial processing was assessed with the copy and organization scores of the Rey complex figure test (Osterrieth, 1944), and on motor-free tests including the Judgment of Line Orientation test (Benton et al., 1975), and the Mental Rotations test (Vandenberg and Kuse, 1978). The Wisconsin Card Sorting Test (WCST; Heaton et al., 1993), the Cognitive Estimation Test (Axelrod and Millis, 1994) and the Trail Making test (A and B; Tombaugh, 2004) measured executive function. Working memory was assessed with the Wechsler Memory Scale-III (WMS-III; Wechsler, 2009), using the digit span and spatial span measures.

Clinical classification of patients as having diagnoses of the cerebellar motor syndrome, CCAS, or both, was conducted based on the following parameters. Patients with MICARS scores of >13 out of a maximum of 120 were categorized as having the cerebellar motor syndrome on the basis of established cut-offs for that measure; patients with MICARS <4 were classified as in the normal range (Schmahmann et al., 2009a). As our participants had a mean