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Impaired working-memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit

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Abstract

A considerable body of evidence supports the notion that cerebellar lesions lead to neuropsychological deficits, including impairments in working-memory, executive tasks and verbal fluency. Studies employing functional magnetic resonance imaging (fMRI) and anatomical tracing in primates provide evidence for a cortico-cerebellar circuitry as the functional substrate of working-memory. The present fMRI study explores the activation pattern during an *n*-back working-memory task in patients with an isolated cerebellar infarct. To determine each patient's cognitive impairment, neuropsychological tests of working-memory and attention were carried out. We conducted fMRI in nine patients and nine healthy age-matched controls while they performed a 2-back task in a blocked-design. In both groups we found bilateral activations in a widespread cortico-cerebellar network, consisting of the ventrolateral prefrontal cortex (BA 44, 45), dorsolateral prefrontal cortex (BA 9, 46), parietal cortex (BA 7, 40), pre-supplementary motor area (BA 6) anterior cingulate (BA 32). Relative to healthy controls, patients with isolated cerebellar infarcts demonstrated significantly more pronounced BOLD-activations in the precuneus and the angular gyrus during the 2-back task. The significant increase in activation in the posterior parietal areas of the cerebellar patients could be attributed to a compensatory recruitment to maintain task performance. We conclude that cerebellar lesions affect remote cortical regions that are part of a putative cortico-cerebellar network.

Keywords: Verbal working-memory; Cerebellum; Cerebellar stroke; fMRI

1. Introduction

There is mounting evidence that the cerebellum participates in higher-order cognitive tasks such as executive processing, working-memory, verbal fluency and planning. Schmahmann and Sherman (1998) described for the first time a cognitive-affective syndrome following cerebellar lesions with executive, spatial, linguistic and affective symptoms. They postulate a disruption in a widespread cortico-cerebellar circuitry as a cause of impaired cognitive functions denoted as a fronto-cerebellar disconnection syndrome. An anatomical substrate for these functions is a cerebellar feedback loop through the thalamus to the prefrontal and parietal cortex (inferior parietal lobule) as it already has been reported for primates (Clower, West, Lynch, & Strick, 2001; Middleton & Strick, 1994, 2000, 2001; Schmahmann, 1991; Schmahman & Pandya, 1995; Schmahmann & Sherman, 1998). Several neuropsychological reports indicate the presence of working-memory impairments due to an isolated cerebellar lesion (Botez-Marquard, Bard, Leveille, & Botez, 2001; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Malm et al., 1998; Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000).

In a recent publication, Ravizza et al. (2006) investigated 15 patients with cerebellar damage and found selective impairments in verbal working-memory. Articulatory rehearsal strategies were unaffected thereby supporting non-motor causes for the impaired verbal working-memory. These clinical observations

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and above-mentioned anatomical findings in primates are compatible with the results of functional neuroimaging studies: Desmond, Gabrieli, Wagner, Ginier, & Glover (1997) and Chen and Desmond (2005) identified two cerebellar regions activated in verbal working-memory (a bilateral superior region and an inferior region on the right side) in addition to activations in the inferior parietal lobule (BA 40), Broca area (BA 6, 44) and anterior cingulum (BA 32). They propose two cortico-cerebellar networks for verbal working-memory: an articulatory control system with involvement of Broca's area (BA 6, 44) and the superior cerebellum (simplex lobule and crus I) and a phonological storage system connecting parietal areas (inferior parietal lobule) with the inferior cerebellum. Although the inferior parietal lobule is frequently mentioned as the likely locus of verbal short-term memory storage (Fiez et al., 1996; Smith & Jonides, 1998) this view has been recently challenged by Ravizza, Delgado, Chein, Becker, and Fiez (2004), who identified two regions of the intraparietal sulcus, one ventral and the other more dorsal, with the dorsal region responding to short-term memory load and the ventral region being involved in phonological encoding procedures. Neither of these two regions fulfilled, however, the requirements for proper phonological short-term storage. Majerus et al. (2006) deny this specific role of the parietal cortex in working-memory processes and describe its function as a more general superior attentional modulator, shifting focal attention to underlying subordinate networks, according to the cognitive process in question.

The VLPFC (BA 10, 47, 44 and 45) has been especially found to be activated in short-term maintenance (Owen, 2000) and in tasks that require selection, comparison and judgement of stimuli held in short-term and long-term memory (Petrides, 1994). On the other hand, the manipulation of information, reorganization and control of working-memory requires mid-DLPFC (BA 9, 46) (Bor, Duncan, Wiseman, & Owen, 2003; D'Esposito, Ballard, Aguirre, & Zarahn, 1998; Petrides, 1998). Neuropsychological studies support the view that the role of DLPFC activations in working-memory tasks is to increase task performance and facilitate memory, reducing the overall cognitive load with the help of structuring and categorizing information (Bor, Cumming, Scott, & Owen, 2004; Bor et al., 2003).

In our study, we test the hypothesis that impairments in working-memory can result from damage to this putative cortico-cerebellar network. Altered BOLD-activation in remote supratentorial brain regions underlying working-memory would point to a role of the cerebellum in human cognition.

2. Methods

The study was approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

2.1. Subjects

Nine patients with isolated cerebellar infarctions (five men, four women: mean age 46.2 years, S.D. = 8.1 years; range 38–63 years) were recruited from the Neurology Department of the University Hospital of Regensburg. All patients fulfilled the inclusion criteria of isolated stroke in cerebellum detected by MRI. Infarct size and location (specified on the basis of affiliation to arterial blood supply) were determined on the basis of T2-weighted and in cases of territorial infarcts as well on T1-weighted images by a neuroradiologist (Fig. 1). We included patients in an acute phase of stroke (2–8 days past infarction), as well as patients in a post-acute phase (2 month past infarction) or in a chronic phase (up to 6 years after cerebellar infarction).

A control group consisted of nine healthy controls matched for age and gender for each patient (mean age 44.2, S.D. = 9.6; range 35–63 years) (Table 1).

The average difference in age between matching pairs was 2.4 years (S.D. = 2.7; range 0–7 years). All study subjects were right handed according to the Edinburgh Handedness Inventory. Exclusion criteria were the use of psychotropic medication, vascular damage in other brain regions or a history of former strokes, cognitive impairment due to dementia, history of neurological and/or psychiatric illness, claustrophobia, pregnancy and the presence of ferromagnetic surgical pins.

2.2. Neuropsychological assessment

All patients were tested with a neuropsychological assessment battery. Verbal and non-verbal cognition was measured using a short form of the German version of the Wechsler Intelligence Scale for Adults Revised (WAIS-R; Tewes, 1994). Verbal long-term-memory was measured with the Logical Memory delayed free recall (LM II; Wechsler, 1987). Non-verbal long-term-memory was assessed with the Rey Complex Figure delayed free recall (Lezak, 1995). Verbal working-memory was measured with the digit span forward and backward (Tewes, 1994). Non-verbal working-memory was tested with the Corsi block span (Milner, 1971). The results of part B of the Trail Making Test (TMT-B) is reported as an attention measure (Lezak, 1995). The Ruff 2&7 Test (Ruff, Niemann, Allen, Farrow, & Wylie, 1992) was employed to measure attention. The Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989) provided a measure of lexical verbal fluency. Semantic verbal fluency was measured by

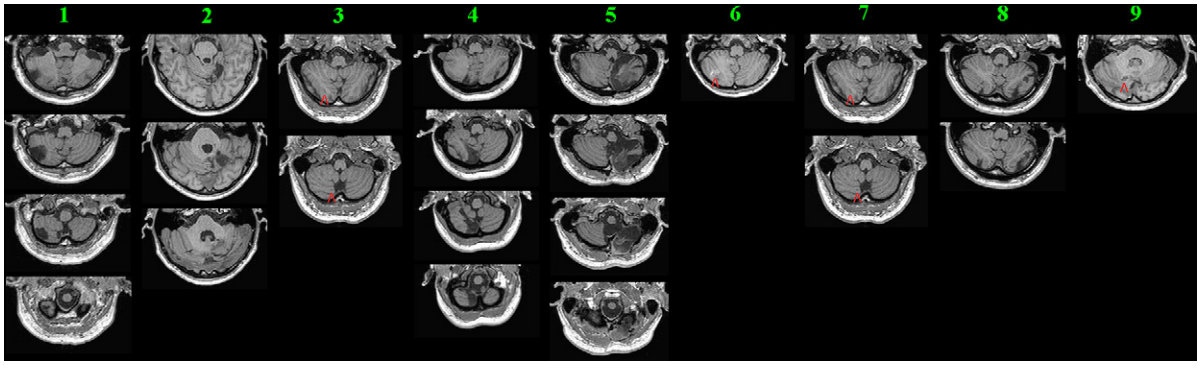

Fig. 1. Representative transversal slices of cerebellar infarcts. T1-weighted MRI at the level of maximal infarct volume for each patient, acquisition at time of the fMRI. Arrows denote location of lesions.