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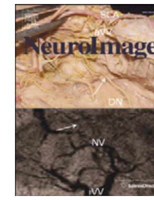

Involvement of the cerebellar cortex and nuclei in verbal and visuospatial working memory: A 7 T fMRI study

M. Thürling [a,b], H. Hautzel [c,d], M. Küper [a], M.R. Stefanescu [a,b], S. Maderwald [b], M.E. Ladd [b,e], D. Timmann [a,*]

[a] Department of Neurology, University of Duisburg-Essen, Germany
[b] Erwin L. Hahn Institute for Magnetic Resonance Imaging, University of Duisburg-Essen, Germany
[c] Department of Nuclear Medicine (KME), Medical Faculty, Heinrich-Heine-University Düsseldorf, at Forschungszentrum Jülich, Germany
[d] Department of Nuclear Medicine, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany
[e] Department of Diagnostic and Interventional Radiology and Neuroradiology, University of Duisburg-Essen, Germany

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ABSTRACT

The first aim of the present study was to extend previous findings of similar cerebellar cortical areas being involved in verbal and spatial n-back working memory to the level of the cerebellar nuclei. The second aim was to investigate whether different areas of the cerebellar cortex and nuclei contribute to different working memory tasks (n-back vs. Sternberg tasks). Young and healthy subjects participated in two functional magnetic resonance imaging (fMRI) studies using a 7 T MR scanner with its increased signal-to-noise ratio. One group of subjects (n = 21) performed an abstract and a verbal version of an n-back task contrasting a 2-back and 0-back condition. Another group of subjects (n = 23) performed an abstract and a verbal version of a Sternberg task contrasting a high load and a low load condition. A block design was used. For image processing of the dentate nuclei, a recently developed region of interest (ROI) driven normalization method of the dentate nuclei was applied (Diedrichsen et al., 2011). Whereas activated areas of the cerebellar cortex and dentate nuclei were not significantly different comparing the abstract and verbal versions of the n-back task, activation in the abstract and verbal Sternberg tasks was significantly different. In both n-back tasks activation was most prominent at the border of lobules VI and Crus I, within lobule VII, and within the more caudal parts of the dentate nucleus bilaterally. In Sternberg tasks the most prominent activations were found in lobule VI extending into Crus I on the right. In the verbal Sternberg task activation was significantly larger within right lobule VI compared to the abstract Sternberg task and compared to the verbal n-back task. Activations of rostral parts of the dentate were most prominent in the verbal Sternberg task, whereas activation of caudal parts predominated in the abstract Sternberg task. On the one hand, the lack of difference between abstract and verbal n-back tasks and the lack of significant lateralization suggest a more general contribution of the cerebellum to working memory regardless of the modality. On the other hand, the focus of activation in right lobule VI in the verbal Sternberg task suggests specific cerebellar contributions to verbal working memory. The verbal Sternberg task emphasizes maintenance of stimuli via phonological rehearsal, whereas central executive demands prevail in n-back tasks. Based on the model of working memory by Baddeley and Hitch (1974), the present results show that different regions of the cerebellum support functions of the central executive system and one of the subsidiary systems, the phonological loop.

Introduction

The human cerebellum contributes to specific cognitive tasks (Beaton and Mariën, 2010; Stoodley and Schmahmann, 2009; Strick et al., 2009 for reviews). One of the best studied examples is working memory. Neuroanatomical, human cerebellar lesion and neuroimaging studies provide convincing evidence that the cerebellum plays a role in verbal working memory, which in turn may influence performance in a range of other cognitive domains (Bellebaum and Daum, 2007; Ben-Yehudah et al., 2007; Marvel and Desmond, 2010a, for reviews). The cerebellar contribution is most obvious in functional brain imaging studies. On the behavioural level, verbal working memory dysfunction is generally mild, and cerebellar patients, at least with chronic disease, frequently perform within the normal range (Ravizza et al., 2006; Timmann and Daum, 2010 for review).

The specific contributions of the cerebellum to working memory have not been conclusively resolved. Based on their extensive neuroimaging studies of verbal working memory, Desmond and colleagues (Chen and Desmond, 2005; Desmond et al., 1997; Kirschen et al.,

* Corresponding author at: Department of Neurology, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany. Fax: +49 201 723 5901.
E-mail address: Dagmar.Timmann-Braun@uni-due.de (D. Timmann).

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2005, 2010; Marvel and Desmond, 2010b) suggest that different regions of the cerebellum are involved in different phases within the phonological loop: the superior cerebellum and dorsal dentate nuclei in phonological encoding, and the inferior cerebellum and ventral dentate nuclei in retrieval and maintenance of the phonological store (Marvel and Desmond, 2010a for review). The phonological loop is one of the two "slave" systems of working memory according to the still popular model introduced by Baddeley and Hitch (1974); the visuospatial sketch pad is the other. Whereas the phonological loop is responsible for short-term storage of phonemes, visual and spatial information is stored in the visuospatial sketch pad. The superordinate component of working memory is the central executive system, which is thought to be the central coordinator and integrator of working memory regardless of the modality. Later, Baddeley added a third slave system to his model, the so-called "episodic buffer" (Baddeley, 2000).

A recent fMRI study by one of the authors suggests that the cerebellum contributes to the central executive system (Hautzel et al., 2009). Cerebellar cortical activations were compared in verbal and visuospatial working memory tasks. Lack of significant differences between tasks supported a more general role of the cerebellum in working memory that is an amodal contribution to the central executive system (Hautzel et al., 2009). No clear conclusions could be drawn on the cerebellar nuclei, most likely because of limitations in spatial resolution and signal-to-noise ratio using 1.5 T MRI and in the normalization methods available at the time.

Findings of specific contributions of the cerebellum to the different phases of the phonological loop on the one hand and a more general contribution of the cerebellum to working memory independent of stimulus modality on the other are not mutually exclusive. Cerebellar contributions may differ depending on the demands of the working memory task. Desmond's group examined the Sternberg task, whereas in the Hautzel et al. study n-back tasks were used. Demands on verbalization are notably higher in the Sternberg task, whereas central executive demands prevail in n-back tasks. In the Sternberg task subjects are required to maintain a list of verbal stimuli (most commonly letters) in short-term memory to be able to decide whether a test stimulus is part of the list or not. The experimental design of a Sternberg task emphasizes the sole stimulus maintenance via phonological rehearsal. Additionally, this effect is intensified by presenting considerably large numbers of stimuli at a time close to the capacity limits of working memory (Miller, 1956). In contrast, in n-back tasks fewer verbal stimuli have to be stored in working memory concurrently. Verbal stimuli are presented one after the other, and subjects need to decide whether the present stimulus is the same as the n-to-last stimulus, for example the second-to-last in a 2-back task. Thus, stimuli change more quickly in n-back tasks and additionally need to be tagged, ordered and updated in terms of sequence.

The aims of the present study were twofold. First, we wanted to extend the previous findings of similar cerebellar areas being involved in verbal and spatial working memory to the level of the cerebellar nuclei. We took advantage of ultra-high-field MRI (7 T MRI) and its increased signal-to-noise ratio, and of a recently developed ROI-driven normalization method of the dentate nucleus (Diedrichsen et al., 2011). Recent studies have shown that reliable activations of the dentate nucleus, in particular of its ventral part in more cognitive tasks, are feasible based on these advanced techniques (Küper et al., 2011a; Thürling et al., 2011). Histological data in monkey and recent structural and functional MRI connectivity studies suggest that the more ventral and caudal parts of the dentate nuclei contribute to more cognitive tasks, whereas motor function may be primarily located in the more dorsal and rostral dentate nucleus (Dum and Strick, 2003; Strick et al., 2009). We hypothesized that verbal and visuospatial n-back tasks would lead to activations within the ventral and caudal dentate bilaterally. Based on the previous findings in the cerebellar cortex, we hypothesized that these areas were similarly activated by both modalities.

Second, we asked the question whether different areas of the cerebellar cortex and nuclei contribute to different working memory tasks. In addition to verbal and visuospatial versions of the n-back tasks, a verbal and a newly developed visuospatial version of the Sternberg task were used. Regions related to both tasks were expected in the posterolateral cerebellar hemisphere and ventrocaudal dentate nucleus, that is in those regions thought to contribute to cognitive functions. The regions, however, may only partially overlap because the focus is more on the central executive in n-back tasks and on one of the subsidiary systems in Sternberg tasks. Whereas cerebellar regions related to n-back tasks were hypothesized to be largely the same in both the cerebellar cortex and nuclei, it was expected that regions in the Sternberg task may show different laterality depending on the stimulus modality. Verbal Sternberg task-related activations were expected to be more prominent on the right, given that the right cerebellum (which is connected with the left cerebrum) has been shown to contribute to language (Fiez et al., 1992; Justus, 2004; Thürling et al., 2011). On the other hand, cerebellar cortical and dentate regions related to abstract (visuospatial) stimulus materials may be more prominent on the left (Stoodley and Schmahmann, 2009). The left cerebellum is connected with the right cerebrum, which is known to be more strongly involved in visuospatial function. Findings of lateralization of visuospatial tasks in the cerebellum, however, are less consistent than lateralization of language function to the right cerebellum (Frank et al., 2007 for review).

Materials and methods

Participants

N-back tasks: Initially, 25 healthy subjects (mean age 26.6 ± 5.5 years, range 21–45 years, 14 males, 11 females) underwent the n-back tasks. Four participants were subsequently excluded due to technical problems (n = 2) or insufficient task performance below the statistically derived cut-off threshold of 66% correct responses (n = 2). The data from 21 subjects (mean age 25.5 ± 3.9 years, 11 males, 10 females) were further analysed.

Sternberg tasks: 27 healthy subjects (mean age 27.4 ± 4.8 years, range 20–43 years, 18 males, 9 females) participated in this study. Four participants had to be excluded due to insufficient task performance below the statistically derived cut-off threshold of 66% correct responses (n = 3) or intense head movements more than 2 mm or 2° (n = 1). Data from 23 participants (mean age 27.0 ± 3.8 years, 15 males, 8 females) were subjected to the subsequent analyses.

All participants were right-handed as measured by the Edinburgh handedness scale (Oldfield, 1971). Informed consent was obtained from all participants. The study was approved by the local ethics committee.

Description and implementation of the paradigms

Verbal and abstract n-back, as well as verbal and abstract Sternberg tasks, were performed in separate fMRI runs. Generation and triggering of the visual stimuli as well as collection of behavioural data were done using E-PRIME software (http://www.pstnet.com/eprime.cfm). The visual stimuli were projected onto a screen and were viewed via a mirror mounted on a head coil inside the MR scanner.

N-back tasks

A total of 20 stimuli were visually presented one at a time over a total interval of 30 s. The stimulus presentation time was 1300 ms, with an inter-stimulus interval (ISI) of 200 ms in which a central