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BRIEF COMMUNICATION

The functional neuroimaging evidence of cerebellar involvement in the simple cognitive task

Olivera Šveljo · Milka Ćulić · Katarina Koprivšek · Miloš Lučić

Abstract Cerebellar involvement in cognitive functions has been revealed in numerous anatomical, clinical and neuroimaging studies and several hypotheses about potential the role of the cerebellum in higher level brain function have been established. The aim of this study was to show involvement of the cerebellum in simple cognitive tasks. For this matter, we contrasted two tasks from the same semantic domain with specific cognitive content and level of practice: counting forward and counting backward. Twelve volunteers participated in this fMRI study and they were asked to perform both tasks within the same number range (1 to 30 and vice versa). Results showed greater activation in the right cerebellum for the task of counting forward than for counting backward, while for counting backward greater activation was found in prefrontal cortex, supplementary motor area, and anterior cingulate of both hemispheres. Our results correlate with already established hypotheses about cerebellar role in precise and smooth control, not only in well-trained motor but in well trained cognitive tasks as well.

Keywords fMRI · Cognitive task · Cerebellum

Introduction

The motor role of the cerebellum in regulation and coordination of movement, posture, and balance, is highly recognized and widely accepted (Rappoport et al. 2000). Cerebellar disorders are usually manifested as ataxia – incoordination of movement, instability of gait, impairment of articulation, and difficulty with eye movement and swallowing. The basic deficit in motor capacity related to the cerebellar pathology is impairment of rate, rhythm, and force of contraction (Schmahmann 2004).

On the other hand, there are numerous clinical, anatomical, and functional imaging data (Davis et al. 2010; Ackermann et al. 2007; Leiner 2010; Stoodley 2012) that point out participation of the human cerebellum in different cognitive functions. Studies of the resting brain proved that besides functional networks related to motor control, the cerebellum is a part of "cognitive" networks with prefrontal and parietal association cortices (O'Reilly et al. 2010). Task related functional neuroimaging studies revealed cerebellar activation during a variety of cognitive tasks, related to language, visual-spatial, executive, and working memory processes (Chen and Desmond 2005; Ben-Yehudah et al. 2007; Hautzel et al. 2009; Richardson and Price 2009; Thürling et al. 2012; Stoodley 2012). Moreover, it has been noted that the posterolateral cerebellar cortex and dentate nucleus contribute to performance and learning of more functional behaviors such as the visually guided reach (Norris et al. 2011).

Hypotheses about cerebellar role in cognition are mainly postulated by the existence of anatomical connections between cerebellum and associative cortex (Leiner 2010). Connections between cerebellum and cerebrum are mainly via thalamus and lead to the brain areas (dorsolateral

O. Šveljo (✉) · K. Koprivšek · M. Lučić
Diagnostic Imaging Centre, Oncology Institute of Vojvodina,
Put Dr Goldmana 4, Sremska Kamenica, Serbia
e-mail: sveljo.olivera@onk.ns.ac.rs

M. Ćulić
Institute for Biological Research "Siniša Stanković", University of Belgrade, Bulevar Despota Stefana 142, Belgrade, Serbia

K. Koprivšek · M. Lučić
Medical Faculty, University of Novi Sad, Novi Sad, Serbia

prefrontal cortex, the medial frontal cortex, the parietal and superior temporal areas, the anterior cingulate cortex, and posterior hypothalamus) that are usually related to cognition and behavior (Dolan 1998; Middleton and Strick 1997). According to Ito (1993; 2006) cerebellar involvement in higher order brain functions is based on similar mechanisms as for motor functions and the role of the cerebellum could be explained from the viewpoint of control systems where the cerebellum acquires “dynamics” or “inverse dynamics” of a control object through repeated exercise and using “dynamics memory” it automates quick, precise, and smooth control of learned movement.

In the investigation of cerebellar role in motor practice, distinction should be made between well trained and untrained motor tasks (Friston et al. 1992; Doyon et al. 1996; Toni et al. 1998; Halsband and Lange 2006; Dirnberger et al. 2013). We hypothesized that a similar distinction should be made in the evaluation of cerebellar role in some cognitive processes as well. To test this hypothesis we contrasted two simple cognitive tasks with different cognitive content and a different level of practice: counting forward and counting backward. Although the same semantic domain task of counting forward is over learned and usually performed in a semiautomatic manner, the task of counting backward demands re-sequencing of word strings and is not commonly used in everyday practice.

Materials and methods

Participants, experimental protocol, and data acquisition

Twelve right-handed healthy volunteers between 24 and 46 years of age (mean age 35±7.55; 6 male) without a history of neurological or psychiatric diseases participated in this study. All subjects signed an informed consent and were scanned on a 3 T MR Unit (Magnetom TRIO, Siemens, Erlangen, Germany). The study has been approved by the Ethical Committee of the Oncology Institute of Vojvodina in Sremska Kamenica. Before scanning, subjects were instructed and rehearsed in the task and asked to remain still with closed eyes in the scanner during the scanning session. The functional images were obtained in axial planes at 3-second interval. Technical parameters for the images included TR 3,000 ms/TE 30 ms, matrix 64×64, flip angle 90°, field of view 240 mm, slice thickness 3 mm, with 36 slices per volume and gap 0.8 mm. Two trials were performed for each subject. Both trials consisted of alternating active (counting) and resting state (30 s each). In the first trial during active state subjects were asked to silently generate, without any lip movements or vocalization, about one number per second in their native language (Serbian), in forward order, starting with number 1. In the second trial subjects were asked to silently generate, also without any lip movements or vocalization, about one number per second, in backward order starting with number 30. There was no specific training of the task performance before scanning. To minimize adaptation effect to these simple cognitive tasks three blocks of alternated rest and active state were acquired for each trial. Start and stop instructions were given through headphones. There was a pause between two trials, and after each trial subjects were asked whether or not they performed tasks successfully and what number they reached during the active trial states.

Image processing

For the generation of an fMRI activation map for each subject as well as for comparison of the trials, the FSL software, (FMRIB’s Software Library Oxford, UK) was used (Smith et al. 2004).

In pre-processing, standard steps were applied: motion correction, non-brain removal, and spatial smoothing by a Gaussian kernel of FWHM 5 mm (Smith 2002). To remove low frequency artefacts, high pass temporal filtering was used (Gaussian-weighted least-squares straight line fitting, with sigma 30 s).

The general linear model as implemented in FSL was used for time-series statistical analysis of both trials for each subject. In this stage, images were registered to standard template (MNI 152) as a prerequisite for higher level analysis (Jenkinson and Smith 2001; Beckmann et al. 2003). The statistical images were initially corrected for multiple comparisons using a cluster threshold determined by $Z > 2.3$, and a corrected cluster significance of $P = 0.05$ (Worsley et al. 1992).

Higher-level statistics, i.e. analysis across trials, was carried out using a paired model test (Beckmann et al. 2003; Woolrich et al. 2004) and statistical images were generated using clusters determined by $Z > 1.5$ at the corrected cluster significance threshold of $P = 0.05$.

Results

All subjects performed the tasks successfully. For counting forward during the active state they finished the specified task in the number range from 26 to 30, while for counting backward during the active state they finished task in number range from 5 to 0.

Analysis across the trials showed that in the trial of counting forward compared to the trial of counting backward, greater activation was found in the right cerebellar hemisphere (crus I/II, VIIIB) (Fig. 1, Table 1). Active voxels were also found around the medulla and 4th ventricle, more expressed in the IX lobule of the right cerebellum and pontine nuclei (Fig. 1, Table 1).

For counting backward, greater activation was found in the prefrontal cortex bilaterally, anterior cingulate cortex (ACC) and supplementary motor area (SMA) (Fig. 2, Table 2).

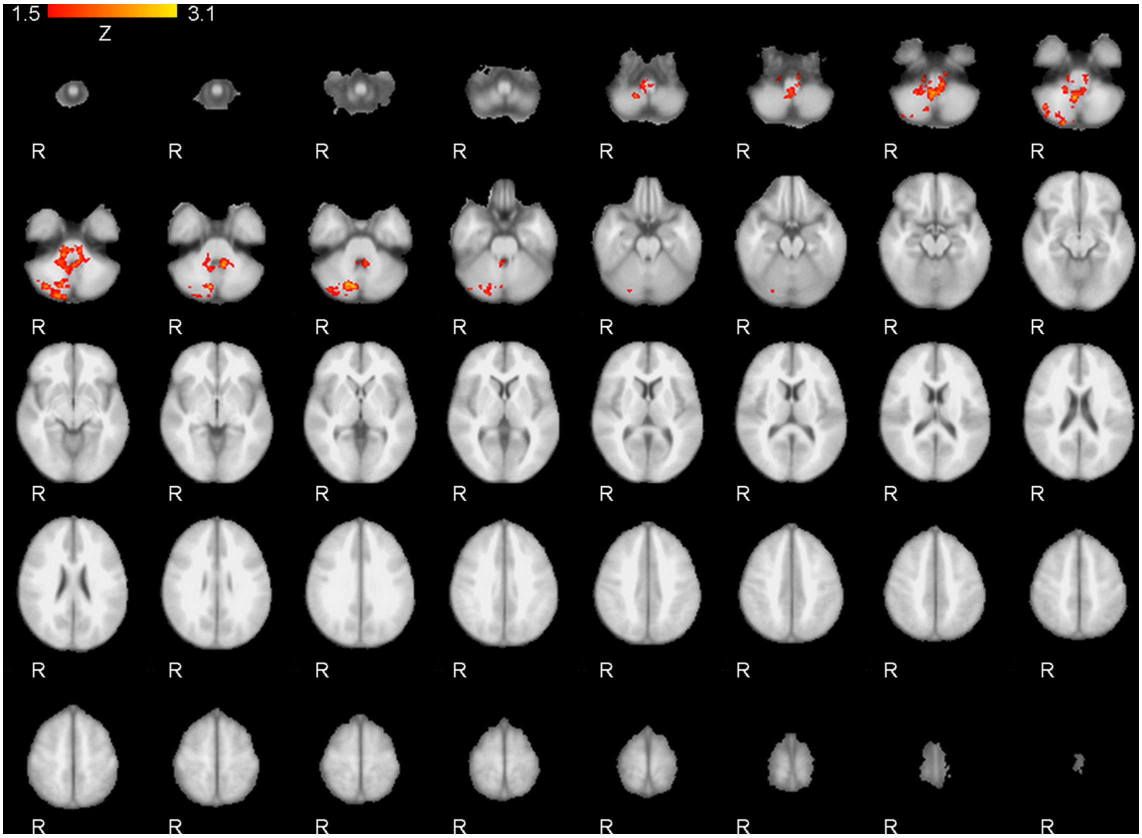

Fig. 1 FMRI maps (Z>1.5; *P*=0.05) showed greater activation for the task of counting forward than for counting backward in the pontine nuclei and right cerebellum

Discussion

Clinical studies revealed a variety of deficits in higher brain functions, especially speech, in patients with vascular cerebellar lesions (agrammatism, amnestic, or transcortical motor aphasia), or after the resection of cerebellar tumors in early childhood (Davis et al. 2010). Also, patients with focal cerebellar lesions show deficits in executive function and attention processes, such as working memory and divided attention. Patients with right-sided lesions were generally more impaired than those with left-sided lesions (Gottwald et al. 2004).

Table 1 MNI coordinates of the brain regions that were activated more for the task of counting forward than for the task of counting backward

Region	MNI			Z-score
	x	*y*	*z*	
Pontine nuclei	−2	−30	−40	2.04
Cerebellum r. lobule IX	8	−56	−46	2.40
Cerebellum r. lobule VIIIB	20	−46	−46	2.41
Cerebellum crus I/II right	8	−76	−34	3.15

r right

Resting state studies revealed that hemodynamic response function in the resting brain could be explained in terms of just a few (8–10) resting state networks (Damoiseaux et al. 2006) involved in executive control, episodic memory/self reflection, salience detection, and sensorimotor function. Furthermore, the only component that shows strong lateralization is the executive control network involved in attention, working memory, and response selection. Habas et al. (2009) found distinct cerebellar contributions in each of the intrinsic connectivity networks: the neocerebellum participates in the right and left executive control networks (contralateral crus I/II), the salience network (lobules V-VI), and the default mode network (lobule IX).

Our study of cerebellar involvement in simple cognitive tasks showed higher activity in the right cerebellum (crus I/II) for the over-learned task of counting forward than for the task of counting backward. It could be explained as cerebellar involvement in higher order brain functions through left executive network, which consists of right cerebellar areas and left prefrontal, left parietal cortex, and left angular gyrus (Habas et al. 2009). These brain areas are also active in language generation or arithmetic tasks in several neuroimaging studies (Price 2012; Dehaene et al. 2004; Sveljo et al. 2012). On the other hand, for the task of counting backward, higher activity was found in prefrontal areas of both hemispheres and anterior cingulate cortex, brain areas that are

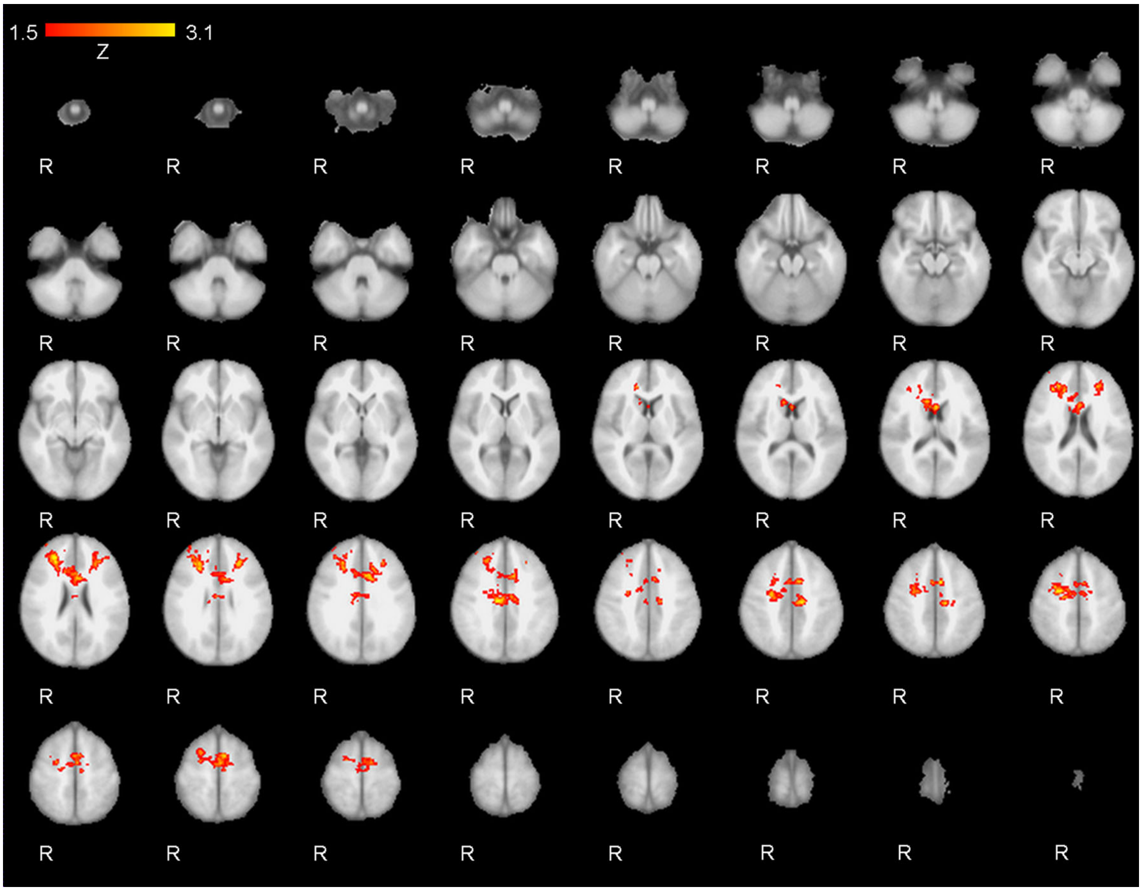

Fig. 2 Greater activations were found in the prefrontal cortex of both hemispheres, anterior cingulate cortex and supplementary motor area for the task of counting backward than for the task of counting forward (Z>1.5; $P=0.05$)

usually connected with processes related to working memory, stimulus representation and problem solving tasks (Baldo and Shimamura 2002; Lenartowicz and McIntosh 2005), and were consistently reported in imaging studies of motor learning (Halsband and Lange 2006).

However, the study of Wildgruber et al. (1999), showed greater activation in mesial and dorsolateral prefrontal areas, and anterior cingulate gyrus during continuous silent recitation of the months in reverse order compared to forward recitation. They also reported activation in the inferior frontal gyrus and parietal cortex, which is not observed in our study. Such a finding could be due to the difference in task performance, i.e. word production rates for forward recitation in this study was considerably higher than in reverse recitation, while in our study the word production rate in both conditions were similar.

Table 2 MNI coordinates of brain regions that are activated more extensively for the task of counting backward than the task of counting forward

Region	MNI			Z-score
	x	*y*	*z*	
SMA	0	−4	58	2.74
Prefrontal right	26	38	22	3.18
Prefrontal left	−24	30	26	3.19
ACC	-4	12	24	2.78

SMA Supplementary Motor Area; *ACC* Anterior Cingulate Cortex; *r* right

Language is usually defined as mental activity that we use for communication (with or without motor activity) while listening, speaking, thinking, reading and writing. Meaningful sound production in speech articulation involves about 80 muscles to realize rapid, highly coordinated and smooth movements which are synchronized to laryngeal and respiratory activity, while approximately 1,400 motor commands per second are assumed (Manto et al. 2012). Moreover, language generation demands a number of integrated processing steps, including encoding of the speech motor program and monitoring the spatiotemporal variations in auditory and somatosensory feedback (Golfinopoulos et al. 2010). A recent fMRI study (Stoodley et al. 2012) reflects the involvement of different cerebro-cerebellar circuits depending on the demands of the task being performed. For example: overt movement activates sensorimotor cortices along with contralateral cerebellar lobules IV-V and VIII; whereas more cognitively demanding tasks engage prefrontal and parietal cortices along with cerebellar lobules VI and VII, providing further support for a cerebellar role in both motor and cognitive tasks, and better establishing the existence of functional subregions in the cerebellum. They also spotted activation in right cerebellar lobules V and IX/VIIIB in contrasting finger typing and cognitive paradigms. Similarly, two distinct cerebrocerebellar verbal working memory networks: the frontal/superior articulatory control system and parietal/inferior cerebelar phonological storage system have been identified in contrasting articulatory rehearsal and verbal working memory tasks (Chen and Desmond 2005).

Although activation in medial cerebellum, i.e. the region of IX cerebellar lobule of both hemispheres, in our study could be caused by cerebrospinal fluid pulsations, the fact is that there is wider activation in the IX lobule of the right cerebellum, right lobule VIIIB, and pontine nuclei, areas that are usually related to vestibular and/or spinal reflexes as well as voluntary movement. This could lead toward hypotheses the about automation of a simple cognitive task through automation of motor program for this task. On the other hand, relatively weak forward counting activity that was found in the right lateral cerebellar nucleus (crus I/II), which is usually related to cognitive processes (Stoodley 2012; Manto et al. 2012), indicates higher cerebellar involvement in cognitive aspects of forward number recitation compared to backward number recitation. It should be noted that difficulties in detection of lateral cerebellar nucleus activity during verbal working memory task by fMRI, could be caused by the fact that at the level of single dentate neurons, the firing patterns of the cells cause insufficient change in the flow of oxyhemoglobin to produce stronger signals (Desmond et al. 1997).

Neuroimaging studies showed that cerebellar activity for motor tasks decreases with practice (Friston et al. 1992; Doyon et al. 1996; Toni et al. 1998) while the data from lesion studies in humans and experimental cerebellar inactivation in monkeys reported different motor and cognitive impairment as a consequence of cerebellar damage (Gottwald et al. 2004; Nagao and Kitazawa 2008; Leggio et al. 2008; Norris et al. 2011; Dirnberger et al. 2013). It has been noted that in evaluation of cerebellar contribution to motor processes, distinction should be made between motor performance, motor learning, sensory motor adaptation, and sequence learning (Seidler and Ashe 2009).

It was shown (Leggio et al. 2008) that patients with lesions of the left cerebellum performed defectively on sequence-based pictorial material while patients with lesions of the right cerebellum were impaired on sequences requiring verbal elaboration. This could indicate a prevalent role of cerebellar circuitry in recognizing event sequences, rather than planning and executing them. Moreover, the neuroimaging study of Seidler et al. (2002) showed significant cerebellar activation during the expression of learning rather than learning itself. Thus, the difference that we found between number recitation in forward and reverse order, could be analyzed from the point of the underlying memory processes. Our results might suggest that the task of counting forward compared to the task of counting backward depends predominantly on procedural knowledge, while the task of counting backward compared to the task of counting forward predominantly engage working memory processes. Further support for this hypothesis could be found in the fact that for the task of counting backward, higher activity was found in the anterior cingulate cortex that is usually reported in studies of learning and working memory processes and related to error correction and online monitoring of performance (Carter et al. 1998; Halsband and Lange 2006). Furthermore, it has been shown that cognitive rehabilitation in relapsing remitting multiple sclerosis patients was in correlation with increased functional connectivity of the anterior cingulate cortex (ACC), right middle frontal gyrus and inferior parietal lobule, while in the control group (without any cognitive rehabilitation) functional connectivity of the ACC with the right cerebellum and right inferior temporal gyrus decreased (Parisi et al. 2012). Also, a selective increase in associative priming size after transcranial magnetic stimulation of a lateral cerebellar site has been noted (Argyropoulos and Muggleton 2013) and these findings are discussed in the context of a cerebellar role in linguistic expectancy generation and the corticocerebellar “prefrontal” reciprocal loop.

Although our study was limited by the small sample size, our results correlated to the recent hypothesis of D’Angelo and Casali (2013) that the cerebellum operates as a general-purpose co-processor whose effects depend on the specific brain centers to which individual modules are connected.

Conflicts of interest statement Olivera Šveljo, Milka Ćulić, Katarina Koprivšek, and Miloš Lučić declare that they have no conflict of interest.

Informed consent statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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