



## Overlapping and parallel cerebello-cerebral networks contributing to sensorimotor control: An intrinsic functional connectivity study



Judy A. Kipping<sup>a</sup>, Wolfgang Grodd<sup>e</sup>, Vinod Kumar<sup>e</sup>, Marco Taubert<sup>a</sup>,  
Arno Villringer<sup>a,c,d</sup>, Daniel S. Margulies<sup>b,\*</sup>

<sup>a</sup> Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1a, 04103 Leipzig, Germany

<sup>b</sup> Max Planck Research Group: Neuroanatomy & Connectivity, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1a, D-04103 Leipzig, Germany

<sup>c</sup> Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

<sup>d</sup> Berlin School of Mind and Brain, Humboldt University, Luisenstrasse 56, 10117 Berlin, Germany

<sup>e</sup> Psychotherapy and Psychosomatics, University Hospital Aachen, Department of Psychiatry, Pauwelsstraße 30, 52074 Aachen, Germany

### ARTICLE INFO

#### Article history:

Accepted 9 July 2013

Available online 16 July 2013

#### Keywords:

Cerebellum  
fMRI  
Parietal  
Prefrontal  
Resting state

### ABSTRACT

In concert with sensorimotor control areas of the cerebrum, the cerebellum shows differential activation patterns during a variety of sensorimotor-related tasks. However, the spatial details and extent of the complex and heterogeneous cerebello-cerebral systems involved in action control remain uncertain. In this study, we use intrinsic functional connectivity (iFC) to examine cerebello-cerebral networks of five cerebellar lobules (I–IV, V, VI, and VIIIa/b) that have been empirically identified to form the functional basis of sensorimotor processes. A refined cerebellar seed-region selection allowed us to identify a network of primary sensorimotor and supplementary motor areas (I–V), a network of prefrontal, premotor, occipito-temporal and inferior-parietal regions (VI), and two largely overlapping networks involving premotor and superior parietal regions, the temporo-parietal junction as well as occipito-temporal regions (VIIIa/b). All networks involved the medial prefrontal/cingulate cortex. These cerebral clusters were used in a partial correlation analysis to systematically map cerebral connectivity throughout the entire cerebellum. We discuss these findings in the framework of affective and cognitive control, sensorimotor, multisensory systems, and executive/language systems. Within the cerebellum we found that cerebro-cerebellar systems seem to run in parallel, as indicated by distinct sublobular functional topography of prefrontal, parietal, sensorimotor, cingulate, and occipito-temporal regions. However, all areas showed overlapping connectivity to various degrees in both hemispheres. The results of both analyses demonstrate that different sublobular parts of the cerebellar lobules may dominate in different aspects of primary or higher-order sensorimotor processing. This systems-level cerebellar organization provides a more detailed structure for cerebello-cerebral interaction which contributes to our understanding of complex motor behavior.

© 2013 Elsevier Inc. All rights reserved.

### Introduction

Throughout the evolution of mammals, the cerebellum and the cerebral cortex have evolved in parallel. Their respective sizes have proportionally increased, and the connections between both have also substantially grown during phylogeny (Sultan, 2002; Sultan and Glickstein, 2007). The first combined cerebellar-cerebral function was coordination of movement involving both motor planning and execution (Holmes, 1939; Thach, 1997). In humans and great apes, the demands for sensory discrimination, sensorimotor integration and motor coordination have increased, requiring additional cerebellar contributions (Manto et al., 2012). The cerebellum contributes to diverse functions such as flexible motor action, execution of complex movements and successful learning

of new movement strategies (Smaers et al., 2011; Stein and Glickstein, 1992; Thach, 1998). One cerebellar role is to provide predictive values about the outcome of an intended goal, which allows for the preparation of neural systems in the cerebrum that are likely to be responsive to the task at hand (Courchesne and Allen, 1997). Both the estimated prediction of outcomes as well as the preparation of neural systems enable cost-optimal and goal-accomplishing movements.

In this study we specifically focused on widespread cerebral connectivity, which has been investigated in the primate brain using transsynaptic tract-tracing studies in the macaque monkey (Kelly and Strick, 2003; Lu et al., 2007; Middleton and Strick, 2000; Orioli and Strick, 1989). It has been demonstrated that the cerebellar output is composed of a number of separate but parallel “output channels” (Middleton and Strick, 1997). The underlying anatomical relationship of the sensorimotor system mainly comprises afferent connections of cerebellar lobules III–VI and VIIb–VIII via the deep cerebellar nuclei to the midbrain and thalamus, and subsequently to premotor and motor

\* Corresponding author at: Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1a, D-04103 Leipzig, Germany.

E-mail address: [margulies@cbs.mpg.de](mailto:margulies@cbs.mpg.de) (D.S. Margulies).

cortex. Efferent connections project back via the pontine nuclei to lobules V–VI and VIIIb–VIII in a closed-loop fashion (Kelly and Strick, 2003).

Anatomical connections established in the macaque monkey have been indirectly validated in humans by corresponding activation patterns in imaging studies using positron emission tomography and functional magnetic resonance imaging (fMRI). fMRI movement paradigms in humans, which involve simple and natural muscular flexion and extension, have revealed movement-related cerebellar representations which mapped foot, tongue and hand, which are restricted to the lobules IV, V, VI and VIII (Grodd et al., 2001; Rijntjes et al., 1999).

Lobules IV and V are consistently activated during the planning and execution of simple movements of body parts (Grodd et al., 2001; Schlerf et al., 2010). With respect to lower-level motor functions these areas appear to have somatotopic organization, which is similar in monkeys and cats (Snider and Eldred, 1952), as well as in humans (Grodd et al., 2001). However, in addition to the movement-related cerebral inputs, lobule V also receives proprioceptive information from spinal inputs, whose signals both converge on the same Purkinje cells as shown in cats (Allen et al., 1974). Consequently, lobule V has been found to be activated during passive and active movements (Jueptner et al., 1997; Thickbroom et al., 2003; Wiestler et al., 2011), tactile stimulation (Wiestler et al., 2011) and in the prediction of the sensory consequences of a movement (Blakemore et al., 1998), indicating an involvement in sensory as well as motor processes.

With increasing complexity of coordinated movements as evoked by higher rates of tapping (Jancke et al., 1999) or sequential movements (Schlerf et al., 2010), parts of lobule VI have been shown to accompany the motor-evoked activation in lobule V and more anterior lobules using fMRI in humans. Lobule VI has also been found to be specifically activated during the storage of acquired kinematic tool use (Imamizu et al., 2000). An index finger movement task with self-paced delay showed a temporal dissociation in sensorimotor processing (Hulsmann et al., 2003). Whereas lobule VI was recruited 3 s prior to movement onset, activation in lobule V followed close to and after movement onset. In contrast, Cui et al. (2000) report a lack of functional dissociation between preparation and execution of coordinated movements within bilateral lobules V–VII. These diverse fMRI results show that lobules IV, V, and VI may contribute to different phases of sensorimotor events.

Lobule VIII is activated during simple active and passive sensorimotor tasks, and therefore has been proposed to possess similar functions as lobule V, which is the representation of motor and sensory processes (Thickbroom et al., 2003). In both lobules, active performance as well as tactile stimulation reveal superimposed sensory and motor maps (Wiestler et al., 2011). However, despite this similarity, lobule VIII has been found to play a role in sensory feedback accompanying basic motor processing in lobule V (Habas and Cabanis, 2008) and in the timing of more complex and voluntary movements (Habas et al., 2004). Recent exploration of lobule VIII found a functional contribution of lobular segments VIIIa and VIIIb to finger tapping and verb generation (Stoodley et al., 2012).

The fMRI findings of overlapping cerebro-cerebellar networks involved in sensorimotor tasks complicate the functional assignments of cerebellar lobules IV, V, VI, and VIII. These cerebellar regions likely reveal differential involvement in domains involved in planning, execution, and control of movements and are thus engaged in various brain networks.

#### *Evaluating human cerebello-cerebral connectivity using iFC*

Three studies published in 2009 (Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010) used iFC to depict major cerebro-cerebellar iFC networks within the sensorimotor as well as non-motor domains in humans. In addition to dedicated cortical areas, subcortical components—including the midbrain and thalamus (Middleton and

Strick, 1997; Sommer, 2003)—have been shown to participate in various iFC networks (Habas et al., 2009). The sensorimotor nature of cerebellar lobules V, VI, and VIII (and particularly VIIIb; according to a peak cerebellar coordinate in Krienen and Buckner (2009)) has been validated using iFC (Krienen and Buckner, 2009; O'Reilly et al., 2010). Buckner et al. (2011) recently demonstrated a further differentiation. They show that lobules IV and V are sensorimotor related, lobule VI is part of the sensorimotor, ventral attention and fronto-parietal network, and lobule VIII is part of the sensorimotor and the ventral attention network. Very recently, Sang et al. (2012) investigated the cerebellar connectivity of the hemispheres and vermis. They found that lobules I–VI are connected to the visual and sensorimotor network; lobule VI to the auditory, the salience and sensorimotor network; and lobule VIIIb to the salience, sensorimotor, task-positive and the default mode network. However, if the cerebellum is connected to various regions within the cerebrum, the question remains as to what extent these cerebellar regions have overlapping or distinct connectivity patterns. The study by Buckner et al. (2011) applied a winner-take-all algorithm, which separates regions based on their strongest connectivity to large-scale cerebral resting-state networks, but does not allow for overlapping connectivity patterns. In contrast, the study by Sang et al. (2012) used one-sample *t*-tests for each lobule, which does not account for common variance across adjacent lobules, potentially introducing false positive overlapping connectivity results. Even though they quantified the connectivity maps of lobules VII and VIII, the more anterior cerebellar lobules were not addressed. Due to the variable methodology, it remains unclear whether the cerebellar regions have overlapping or separate connectivity patterns.

We therefore extended the examination of cerebellar lobules by introducing a refined seed definition for seed-based iFC analysis which addresses the false positive connectivity to adjacent cerebral and non-brain tissue (see also Buckner et al. (2011)). This refinement consisted of removing all voxels which were contaminated by adjacent non-cerebellar tissue. To enhance our understanding of the separate and overlapping cerebello-thalamo-cerebral pathways, we first investigated connectivity of cerebellar lobules I–IV, V, VI, and VIIIa/b with large-scale cerebral networks. This cerebello-centric approach was then complemented by a voxelwise iFC analysis beginning in the cerebrum. We were thus able to systematically identify overlapping and parallel functional regions on a sublobular level. We interpret the cerebellar mapping in the context of their associated cerebral functional subsystems.

## **Material and methods**

### *Participants*

We included 38 MR data sets from healthy participants (25 female; mean age of  $30.34 \pm 7.51$  years), distributed by the 1000 Functional Connectome Project ([http://fcon\\_1000.projects.nitrc.org/indi/pro/Berlin.html](http://fcon_1000.projects.nitrc.org/indi/pro/Berlin.html)). Two resting state scans were acquired during a single scanning session for each participant. Functional images were visually inspected to ensure that the ventral parts of the cerebellum (esp. lobule VIIIa/b) were acquired. Only those data sets that included the inferior portion of the cerebellum were included, thus restricting this study to 38 of 50 data sets.

### *Data acquisition*

MR images were acquired at a 3 T Magnetom Tim Trio Siemens scanner using a 12 channel phased-array head coil. In each of the two resting state scanning sessions, 200 whole brain volumes were acquired including the entire cerebellum using echo-planar image (EPI) pulse sequences with 34 axial slices (TR = 2300 ms, TE = 30 ms, flip angle 90°, slice thickness = 4 mm,  $3 \times 3 \times 4$  mm voxels, interleaved ascending slice acquisition, acquisition matrix =  $64 \times 64$ ,

Download English Version:

<https://daneshyari.com/en/article/6028272>

Download Persian Version:

<https://daneshyari.com/article/6028272>

[Daneshyari.com](https://daneshyari.com)