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Meta-analytic connectivity and behavioral parcellation of the human cerebellum

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ABSTRACT

The cerebellum historically has been thought to mediate motor and sensory signals between the body and cerebral cortex, yet cerebellar lesions are also associated with altered cognitive behavioral performance. Neuroimaging evidence indicates that the cerebellum contributes to a wide range of cognitive, perceptual, and motor functions. Here, we used the BrainMap database to investigate whole-brain co-activation patterns between cerebellar structures and regions of the cerebral cortex, as well as associations with behavioral tasks. Hierarchical clustering was performed to meta-analytically identify cerebellar structures with similar cortical co-activation, and independently, with similar correlations to specific behavioral tasks. Strong correspondences were observed in these separate but parallel analyses of meta-analytic connectivity and behavioral metadata. We recovered differential zones of cerebellar co-activation that are reflected across the literature. Furthermore, the behaviors and tasks associated with the different cerebellar zones provide insight into the specialized function of the cerebellum, relating to high-order cognition, emotion, perception, interoception, and action. Taken together, these task-based meta-analytic results implicate distinct zones of the cerebellum as critically involved in the monitoring and mediation of psychological responses to internal and external stimuli.

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Introduction

Functional neuroimaging has made significant progress toward advancing our understanding of the human cerebellum, yet a comprehensive understanding of this important structure remains a challenge. The cerebellum has long been assumed to act within the sensorimotor system and so its functions have been assumed to contribute to sensation and movement. Historically, this was based largely on studies of sensorimotor impairments following cerebellar lesions or atrophy, including impairments in coordination (Zwicker et al., 2011), eye movement (Miall et al., 2001), articulation (Wise et al., 1999), swallowing (Suzuki et al., 2003), tremor (Greco et al., 2002), or gait (the ataxia syndromes; Schmahmann, 2004). The anatomical connectivity of the cerebellum, which receives afferents from the spinal cord (Schweighofer et al., 1998), with the motor cortex (Chen, 2004) supports the region's significant involvement in motor functions. However, anatomical connectivity also suggests the cerebellum's association with non-motor, higher-level cognitive and affective functions. For example, tract-tracing studies in the macaque monkey have identified cortico–ponto–cerebellar connections originating from regions of the cortex associated with language, spatial, executive function, and affective processing (Middleton and Strick, 1994; Schmahmann and Caplan, 2006; Schmahmann and Pandya, 1989; Schmahmann and Sherman, 1998; Schmahmann et al., 1999; Stoodley, 2011).

Further evidence for the cerebellum's involvement in higher-level cognition comes from clinical findings. Specifically, localized cerebellar lesions lead to: 1) disturbances of executive function/cognitive control (e.g., planning, set-shifting, reasoning, working memory); 2) impaired visual–spatial processing and memory; 3) personality changes (e.g., flat affect and disinhibited/inappropriate behavior); and 4) disruptions of language and speech, including verbal fluency, dysprosodia,

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agrammatism and anomia (Schmahmann and Sherman, 1998). This specific neurophysiological profile following confined cerebellar lesions has been classified under the rubric of cerebellar–cognitive–affective syndrome (Schmahmann and Sherman, 1998; Schmahmann, 2004).

In addition to and consistent with these clinical findings, emerging neuroimaging evidence also has identified cerebellar contributions during the execution of cognitive and affective tasks (Schmahmann, 1991; Schmahmann and Sherman, 1998; Salmi et al., 2009; Stoodley et al., 2011, 2012; Strata et al., 2011). In a meta-analysis of 53 studies, Stoodley et al. (2009) demonstrated cerebellar activation during sensorimotor integration, language, spatial processing, verbal working memory, cognitive control, and emotional processing. Evidence from multiple studies also indicates that this diverse range of cerebellar functions relies on a broadly distributed system of cortical connections. That is, the cerebellum exhibits significant functional connectivity (FC) with frontal, parietal, temporal, and occipital cortices during resting-state and task-based functional neuroimaging studies (Allen et al., 2005; Buckner et al., 2011; Dobromyslin et al., 2012; Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010; Sang et al., 2012). The combined results of these experiments provide a preliminary framework for understanding the complexities of cortico–cerebellar connectivity and associated relations with cognition.

Despite the rapid increase in functional neuroimaging investigations, interpretations of cerebellar FC patterns and the accompanying behavioral implications has progressed more slowly. Large-scale meta-analytic methods now provide processing tools and heuristic frameworks to objectively assess convergent patterns of brain activity associated with specific behavioral domains. In particular, meta-analytic connectivity modeling (MACM) is used to comprehensively identify whole-brain co-activation patterns consistently reported across a number of published neuroimaging studies. This method has been employed to enhance understanding of the FC of the amygdala (Robinson et al., 2009), parietal operculum (Eickhoff et al., 2009) and regions of the default-mode network (Laird et al., 2009a, 2009b), and can be flexibly applied to the characterization of other brain regions. Although MACM previously has been utilized to investigate cerebellar co-activation, prior work has relied on defining regions of interest either by morphometric abnormalities (Reetz et al., 2012) or by aggregating across regions of a probabilistic atlas (Balsters et al., 2014). In accordance with literature reviews supporting differential cortical connectivity with distinct cerebellar zones, Balsters et al. (2014) investigated the preferential co-activation of a group of cerebellar structures contributing to motor performance, and a group of structures contributing to cognition. Their results demonstrated that a group of superior cerebellum structures exhibited preferential co-activation with the motor cortex, whereas a group of inferior cerebellar lobules demonstrated co-activation with prefrontal regions. Furthermore, Stoodley et al. (2009) modeled whole-brain co-activation profiles to demonstrate that separate behavioral domains were represented differently across the cerebellum. While these previous studies have provided new insight into the heterogeneous FC profile of the cerebellum, they were based on specific a priori hypotheses about cerebellar function and limited in that regions of interest were *subjectively* chosen. In contrast, the present study investigated both the large-scale meta-analytic connectivity and behavioral properties of the cerebellum through independent meta-analyses without assumptions regarding cerebellar behavior or functional organization.

Harnessing the accumulated volume of published neuroimaging results on the cerebellum, we sought to address two questions. First, is there a dissociable organization of connectivity within subregions of the cerebellum that can be observed employing meta-analytic tools? Second, can such FC architecture clarify the diverse behavioral functions that have been ascribed to the cerebellum? To address these questions, we performed a series of independent yet parallel meta-analyses (i.e., co-activation and behavioral) in the BrainMap environment using cerebellar regions of interest (ROIs) defined according to a probabilistic anatomical atlas (Diedrichsen et al., 2009). Resultant co-activation and behavioral profiles were examined to characterize meta-analytic congruency across these two parcellation schemes.

Materials and methods

Structural parcellation of the cerebellum

To investigate cerebellar functional organization, a reliable parcellation strategy is first needed. The most widely accepted current structural parcellation of the cerebellum is a normalized probabilistic atlas consisting of 28 structures (Diedrichsen et al., 2009) (Fig. 1) based on the Schmahmann cerebellum parcellation strategy (Schmahmann et al., 2000). This atlas has been used in various ways including confirmation and comparison of anatomical connectivity patterns (Rosch et al., 2010), identification of structural contributions across diverse tasks (Vahdat et al., 2011; Wu et al., 2011; Wildenberg et al., 2011; Moulton et al., 2011), examination of differential cortico–cerebellar co-activation (Balsters et al., 2014) and the longitudinal investigation of cerebellar morphometry (Tiemeier et al., 2010). Images delineating the volume of each cerebellar structure were obtained according to the Diedrichsen parcellation strategy in MNI space (http://www.icn.ucl.ac.uk/motorcontrol/imaging/propatlas.htm), with left and right structures treated independently (Diedrichsen et al., 2009). One structure (VIIa Crus I Vermis) occupying less than 0.1% of the total volume of the cerebellum was omitted from further analysis. The remaining 27 structures were seeded in the BrainMap database to identify functional experiments in which other brain areas were observed to co-activate with each of the cerebellar ROIs.

Co-activation meta-analyses

Meta-analytic connectivity modeling (MACM)

The first step in developing a functional organization of the cerebellum was to generate whole-brain co-activation profiles for each cerebellar ROI. We used the *Sleuth* software application (www.brainmap.org/sleuth) to search the BrainMap database for all experiments that reported one or more activation coordinates within a binarized mask for each of the 27 cerebellar ROIs analyzed. The number of coordinates reported in each structure (Table 1, *Metadata Foci*) indicates the strength of each region's representation within the database. We then downloaded whole-brain coordinates of regions which were simultaneously coactive with the coordinates observed in the cerebellar ROIs. Search results were limited to activation coordinates (not deactivations) reported in studies involving only healthy subjects. We converted coordinates reported in Talairach into MNI space (Lancaster et al., 2007; Laird et al., 2010). In addition to whole-brain co-activation coordinates, we also downloaded the corresponding metadata from the BrainMap taxonomy (Fox et al., 2005; Laird and Turner, 2012), which catalogues the experimental design, stimulus type (e.g., *Heat*, *Numbers*, *Objects*), paradigm class (e.g., *Face Monitor/Discrimination*, *Theory of Mind*), and behavioral domain (e.g., *Action*, *Emotion.Sadness*) of each study.

Once the whole-brain co-activation coordinates were identified for each of the cerebellar ROIs, we performed meta-analytic connectivity modeling (MACM) using *GingerALE* (www.brainmap.org/ale) (Laird et al., 2009a, 2009b; Robinson et al., 2009; Eickhoff et al., 2009). We derived a MACM image representing the above-chance probability that a given voxel co-activated with the cerebellar ROI seed. In *GingerALE*, an activation likelihood estimation (ALE) score is calculated at every voxel in the brain (Turkeltaub et al., 2002; Laird et al., 2005; Eickhoff et al., 2009; Turkeltaub et al., 2012; Eickhoff et al., 2012). These ALE scores were then transformed to *p*-values to identify voxels with significantly higher values than that expected under a null distribution. We thresholded each ALE map at a false discovery rate (FDR) threshold of $P < 0.05$, and a minimum cluster size of 250 mm^3. A

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