Mapping the Human Cerebellum

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Abstract:

Thirty years of research have provided compelling evidence that the human cerebellum is engaged in a wide array of cognitive tasks. Understanding the functional contributions of this structure to cognition remains a subject of considerable debate. Previous studies have generally taken a piecemeal approach, employing a limited number of tasks to test specific hypotheses. Here we take a different approach, seeking to identify a detailed characterization of functional subdivisions across the extent of the cerebellar cortex. During fMRI scanning, 24 participants performed a large task battery designed to tap into a broad range of cognitive processes (e.g., attention, memory, social cognition). These heterogeneous task patterns were leveraged to derive a multi-task parcellation of the cerebellum. We then developed a novel tool to evaluate the strength of functional boundaries, employing out-of-sample generalization. We tested our novel, multi-task parcellation, along with existing resting state and anatomical parcellations. We find that the multi-task parcellation successfully identifies functional sub-regions within the cerebellum, and provides a significant improvement over boundaries identified with resting state data. Surprisingly, lobular boundaries, the current standard for assigning functional activations, do not coincide with functional boundaries. The multi-task parcellation offers a novel functional map for analyzing and reporting cerebellar activations.

Keywords: Cerebellum; fMRI; Parcellation; Cognition

Introduction

Over the past three decades, converging lines of evidence have demonstrated the engagement of the cerebellum in a broad range of cognitive tasks, extending well beyond the domain of motor control (e.g., Sokolov et al. 2017). Much of this work has involved functional magnetic resonance imaging (fMRI), with an explosion of papers demonstrating robust cerebellar activation, even when experimental and control conditions are well-matched in terms of overt motor requirements (Stoodley & Schmahmann, 2009). The fMRI signal is mostly reflective of mossy-fiber input (Mathiesen, Casear, & Lauritzen, 2004); as such, fMRI provides a high-resolution view of the inputs to the cerebellum, the majority of which come from the cerebral cortex. The organization of these inputs within the cerebellum should prove useful for understanding and testing functional hypotheses of how this subcortical structure interacts with the rest of the brain to support cognition.

A plethora of tasks have been employed in fMRI to explore non-motor functions of the cerebellum, typically designed to test specific functional hypotheses (e.g., prediction, language retrieval, working memory). Although this approach has expanded our understanding of the functional domain of the cerebellum, it is limited in providing a comprehensive view of cerebellar function and organization. An alternative to this piecemeal approach is to use a broad task battery designed to produce activation across the extent of the cerebellum. This approach has been successfully employed to derive in-vivo functional parcellations of the human neocortex (Glasser et al. 2016; Yeo et al. 2011).

To this end, we adopted a data-driven approach to derive a comprehensive parcellation of human cerebellar function. Participants were tested on a large battery of cognitive tasks expected to evoke functionally heterogeneous activity patterns. We developed a novel measure to evaluate how strongly a boundary reflects a real discontinuity in the functional profiles of voxels. We used this tool to assess our task-based functional parcellation, comparing it to existing resting-state (Buckner et al. 2011; Spronk et al. 2018) and lobular parcellations (Diedrichsen et al. 2009) of the cerebellum. Finally, our large task battery enabled us to characterize the activity profiles of the functional regions in terms of latent cognitive features.

Methods

Approach

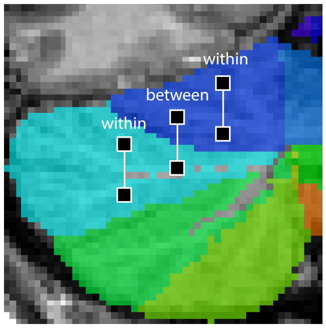

Figure1.*Spatial Evaluation Criterion: Correlations between voxel-pairs "within" and "between" regions are calculated. In this example, voxels are assigned to regions demarcated by lobular boundaries. Voxel-pairs are binned according to spatial distance. Each black square represents a 3mm^3 voxel and is exaggerated in size for illustrative purposes.*

To evaluate the functional organization of the human cerebellum, 24 participants were tested on a broad range of tasks (27 tasks encompassing 47 conditions) spanning cognitive, motor, affective, and social domains (~5.5 hours of fMRI scanning per subject). The tasks were organized into two sets, A and B, each composed of 8 shared tasks and 9 unique tasks. Participants were scanned four times, twice while performing Set A and twice while performing Set B. The inclusion of shared tasks was useful for assessing reliability; the inclusion of unique tasks was exploited to evaluate out-of-sample generalization of the maps.

General Procedure

fMRI data were acquired on a Siemens 3T Prisma system, using an accelerated 2D-EPI sequence (2.5x2.5x3mm resolution, TR=1s, 48 slices, MB acceleration 3x, in plane acceleration 2x). Each scanning session consisted of eight 10-min imaging runs with a given set (A or B), and each of the 17 tasks was presented once in each run. Tasks were tested in blocks of 35s. An instruction screen was presented for the first 5s of each block, specifying the task and instructions (e.g., 'Theory of Mind Task!' User your LEFT hand. 1= false belief. 2 = true belief), followed by 30s of continuous task performance. Most tasks consisted of a continuous stream of trials, each 2-5s long. Other tasks (movie watching, spatial navigation) lacked a discrete trial structure. The participants completed a 3-day training protocol prior to the scanning sessions to minimize the effects of learning. Eye-tracking data were obtained during the final training session.

General Linear Model

A univariate linear model was employed to extract task-related activity. When appropriate, tasks were divided into sub-conditions; for example, congruent and incongruent trials of the Stroop task were modeled as two separate regressors. A first-level model yielded 29 (Set A) and 31 (Set B) activation estimates for each imaging run. All activity estimates were expressed relative to the mean activity of the voxel across tasks.

Parcellations

Currently, there is no task-based parcellation of the cerebellum. Thus, the heterogeneous activity patterns elicited by the multi-task battery provided an opportunity to derive a novel parcellation. Semi, nonnegative matrix factorization was used to identify latent dimensions across all activity patterns. This approach expresses the activation profile of each voxel across conditions as a (non-negative) weighted sum of latent functional components. A "winner-take-all" approach was then computed so that each vertex of the cerebellar surface was assigned to the network that explained the largest amount of variance. We compared this multi-task parcellation with two other maps, one based on resting state data archived as part of the Human Connectome Projects (Buckner et al. 2011; Spronk et al. 2018) and an anatomical parcellation based on the lobular organization of the cerebellum. We note two important differences between the multi-task and resting state parcellations. First, each resting state parcellation was predicated on a parcellation derived from the cerebral cortex while the multi-task parcellation was computed from cerebellar activity patterns alone. Second, the resting state parcellations involved a small amount of data per subject (~12 min) obtained in a large sample (n=1000), whereas the multi-task parcellation was assessed on a large task battery (~5.5 hours) obtained from a small set of subjects (n=24). The lobular parcellation was based on a spatially unbiased probabilistic atlas (Diedrichsen et al. 2009).

Spatially Unbiased Evaluation Criterion

Presently, few methods exist to rigorously evaluate functional maps. To address this issue, we developed a novel tool with the goal of quantitatively evaluating the correspondence between boundaries defined by a particular parcellation to real functional subdivisions. The core assumption of this approach is that, if a boundary between two regions is dividing two functionally heterogeneous regions, then two voxels that lie within each region ("within voxel-pairs") should be more functionally homogeneous than two voxels that are separated by the boundary ("between" voxel-pairs). To control for spatial distance between two voxels, correlations were calculated for spatial distances (4mm-35mm) and then the corresponding difference for the within- and between- regions for each distance was taken (Fig 1). For the multi-task parcellation, boundaries were always established on data from Set A and evaluated with the data from the unique tasks of Set B (and vice versa), ensuring out-of-sample generalization. The criterion was always cross-validated across sessions (within each set) to assess reliability and the evaluation was computed separately for each individual.

Feature-Based Encoding

Feature-based encoding was employed to characterize the task-evoked activity patterns latent to each cerebellar network. Specifically, a feature space was computed by representing each of the task conditions as a vector of cognitive and motor features. The value for the motor features was based on task performance (left and right hand presses, saccadic eye movements) and the cognitive features were sourced from an online cognitive ontology (cognitiveatlas.org). Forty-six features were chosen from a possible 815, creating a feature matrix (task conditions x features). For example, movie watching and action observation were associated with a "dynamic view" feature, whereas the emotional processing and the theory of mind tasks were associated with "social cognition." Each of the cerebellar networks were projected into task space to

compute a task loading matrix (task conditions x regions). To characterize each region in terms of features, the feature matrix was correlated with the task loading matrix. The three highest correlations for each network were selected for visualization purposes.

Results

The activation maps for the tasks were highly diverse and replicable. Considered as a whole, the maps activated the extent of the cerebellar cortex with most regions activated by multiple tasks. A clustering approach was used to parcellate the cerebellar cortex into ten discrete regions.

There are True Functional Boundaries in the Human Cerebellum

Our boundary evaluation metric provided a tool to quantify the similarity in the activation profiles within and between cerebellar sub-regions. We restricted the analysis to data from the unique tasks that were not used in deriving the multi-task parcellation. Consistent with the idea that the parcellation defines true functional boundaries, the activity profiles for voxels within a region were more similar than the activity profiles for voxels spanning the boundary (Fig 2). This advantage was observed across a range of spatial distances. Although we depict the results for a multi-task map composed of 10 regions, a similar pattern is observed for maps with fewer or more regions (range tested, 5 – 25).

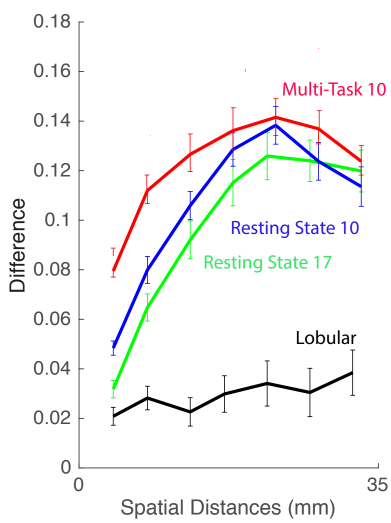

Figure 2. *Difference between voxel-pairs "within" and "between" regions across spatial distances derived either from resting state data (blue-10 networks; green-17 networks) or multi-task data (red-10 networks) yield true functional boundaries in the cerebellum while the lobular parcellation (black) does not.*

We applied the same metric, asking if parcellations based on resting state data would also capture functional relationships in our multi-task data sets. Here, too, we observed stronger correlations between voxels within a region compared to voxels spanning (resting-state) boundaries. In a direct comparison of the two parcellation schemes, the multi-task parcellation yielded significantly better predictions than resting state parcellations, independent of the number of regions in a particular parcellation.

Lobular Boundaries do not coincide with Functional Boundaries

We also applied our metric to a parcellation based on lobular boundaries, asking if this anatomical map predicts functional differences. Surprisingly, the correlation between voxels within a lobule was only weakly better than the correlation between voxels that spanned a lobular boundary. In comparison to the multi-task or resting state parcellations, the lobular boundaries were much poorer predictors of functional differences. The fact that lobular boundaries fail to account for functional differences is rather unexpected. Methodologically, the current observation is important given that lobular divisions have been the most prevalent heuristic in the neuroimaging literature for describing specialization within the cerebellum (Fig 2).

The Majority of the Cerebellum is best characterized by Cognitive Features

Unlike resting-state maps, a task-based map can be related to putative cognitive processes that may be driving the activation patterns. To exploit this opportunity with the current data set, the task conditions were characterized by a vector of motor and cognitive features. Somatotopic regions of the cerebellum (networks 4, 8, 10) were best explained by motor-related features (left hand presses, right hand presses, saccadic eye movements). Beyond these three motor regions, cognitive features such as "response selection", "narrative", "lexical processing" best accounted for prominent regions that spanned Crus I/II and lobule VIIb (Fig. 3, see networks, 3, 5:9). These regions are typically associated with higher-level cognitive functions, as well as pronounced asymmetries between the left and right cerebellum (Fig 3).

Discussion

The aim of this study was to develop a comprehensive map of the human cerebellum. This was done in a data-driven manner, testing a group of participants on a diverse task battery across multiple scanning sessions. The battery provides the most exhaustive data set obtained from the same set of subjects, a resource that should prove useful for researchers interested in the functional topography of the

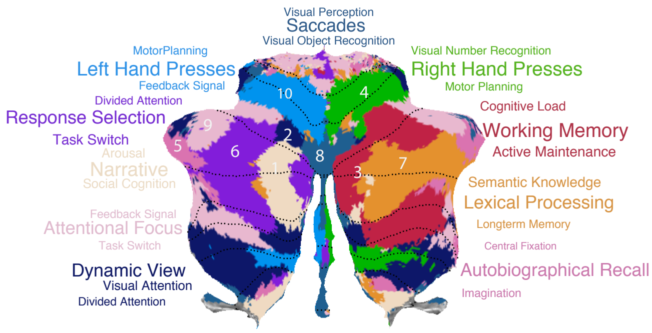

Figure 3. *Assigning semantic meaning to the multi-task parcellation. Each network is described by the three cognitive features that best explain the activity profiles in this region. The features are weighted according to the amount of variance they explain within a region. Larger font indicates strongest weights. Networks are labelled in white from 1-10.*

human cerebellum (and cerebral cortex, data yet to be analyzed in detail). Moreover, we developed a novel tool to rigorously evaluate if boundaries defined from any mapping procedure define functionally-relevant subdivisions. We found that both task-based and resting state parcellations defined true functional boundaries. To our surprise, lobular boundaries were quite poor in defining functional boundaries.

The current results provide a first-pass depiction of the functional organization of the cerebellum across a diverse set of cognitive and motor tasks. By using a feature-based encoding method, we can provide a semantic characterization of the cerebellar subregions. We recognize that the question remains about how to describe computational specialization within regions and differences between regions. This comprehensive functional parcellation of the cerebellum can provide a guide in deriving and evaluating computational hypotheses.

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