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Navigating the "little brain": Comprehensive Mapping of Functional Organisation

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Abstract

Two decades of neuroimaging research suggests that the cerebellum is functionally involved in a range of cognitive and motor processes. However, missing from the literature is a comprehensive map detailing a clear functional organisation of the cerebellum. Previous studies have used a restricted task-mapping approach to localise task-specific functional activation to cerebellar lobules. However, this approach, which is often limited to one or two functional domains within individual subjects, fails to characterise the full breadth of functional specialisation within the cerebellum. To overcome this restricted task-mapping problem, we tested 17 subjects on a condition-rich task battery (61 task conditions) across 4 scanning sessions. We then adopted a bottom-up approach, which allowed us to characterise functional activations in terms of latent features, rather than tasks. In this way, we were able to describe a broad spectrum of heterogeneous activity patterns using 11 latent features (rather than 61 task conditions). In deriving a functional map, we found that functional boundaries did not coincide with a lobular assignment, challenging the validity of the standard lobular nomenclature. This work offers two novel contributions to the field. First, the task battery that we designed is the most comprehensive to date, making this work the veritable "look-up table" for functional topography of the cerebellum. Second, we show that functional and lobular boundaries do not align. Thus, we challenge the field to revise the standard lobular nomenclature, to include functional subdivisions. In addition, we encourage the community to use the rich dataset generated by this expansive task battery with the aim of advancing the field towards a unified and testable theory of cerebellar function.

Keywords

Cerebellum, Functional Topography, Bottom-Up Modelling, Multivariate Analysis, Functional Parcellation, Condition-Rich Task Battery

Acknowledgements

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1.Introduction

1.1 The Cerebellum is Functionally Heterogeneous

The cerebellum, otherwise known as the "little brain' is located on the back of the brainstem at the midbrain-hindbrain junction. Although it may be "little", it contains roughly 50 billion neurons, approximately half the total number of neurons in the human brain (Azevedo et al. 2009). Traditional views of the cerebellum hold that the processing power of this structure is dedicated exclusively to sensorimotor control and learning, with important roles in coordination (Thach, 1998), balance (Morton and Bastian, 2004) and timing (Ivry and Keele, 1989). With the emergence of cognitive neuroscience in the 1980's, it was first suggested that the cerebellum could be functionally involved in non-motor processes (see Schmahmann 1991, 2010 for reviews). Leiner, Leiner, and Dow et al. (1986) formalised this idea, based on the finding that, in primates, the cerebellar cortex expanded in parallel with association regions of the cerebral cortex. Since this original paper, anatomical, clinical, and neuroimaging studies have substantiated this original hypothesis by demonstrating an involvement of the cerebellum in a wide range of cognitive, motor, and affective processes (for reviews, see Fiez, 1996; Schmahmann, 1996; Strick et al. 2009; Timmann et al. 2010).

1.2 Clinical Evidence

The cerebellum has been predominately associated with motor control, primarily for the reason that clinical manifestations following cerebellar damage relate most demonstrably to motor function impairments. For example, neurodegenerative diseases such as spinocerebellar ataxias (SCA's) often lead to clinical manifestations of ataxic gait, dysarthria, dysmetric, and dysdiadochokinesia (Manto, 2005) while cerebellar lesions can result in motor dysmetria and intention tremor (Holmes, 1939). However, cerebellar abnormalities have also been attributed to a host of social and cognitive impairments, and many neuropsychological studies have reported impairments on perceptual, executive, linguistic, emotional and cognitive tasks in patients with focal or degenerative disorders of the cerebellum (Botez-Marquard et al. 1994; Grafman et al. 1992; Levisohn et al. 2000; Molinari et al. 2004; Riva and Giorgi, 2000; Schmahmann et al. 2007). Indeed, there is strong evidence for a functional topography of the cerebellum based on structure-function relationships in sub-regions of this structure. Namely, the constellation of cognitive deficits, otherwise known as "cerebellar cognitive affective syndrome" (CCAS; Schmahmann and Sherman, 1998), occurs more often following posterior lobe damage (Schmahmann and Sherman, 1998) while sensorimotor impairments, such as ataxia, and dysmetria, are most often observed following anterior lobe damage (Schmahmann et al. 2009). Further, damage to the posterior midline vermal regions (Levisohn et al. 2000) has been linked to dysregulation of affective processing, predominately in children. The accumulation of this clinical work, although inconsistent, points towards a functional involvement of the cerebellum in different cognitive, motor, and affective processes.

1.3 Neuroimaging Evidence

The advent of functional neuroimaging, in particular functional magnetic resonance imaging (fMRI), provided a unique opportunity to corroborate previous clinical findings by observing cerebellar activity *in vivo* in human participants. This eventually lead to an explosion of papers demonstrating cerebellar activations in response to motor, cognitive, and affective processing. Classically, fMRI studies have substantiated the well-documented finding of motor specialisation in the cerebellum, revealing a distinct somatotopy for hand, foot, and even tongue representations. Specifically, there are two ipsilateral representations of hand movements, one in the anterior and the other in the posterior cerebellum (Wiestler et al. 2011), while saccadic eye movements are typically localised to the oculomotor vermis (Takagi et al. 1998). Extending beyond the motor domain, Petersen and colleagues published a pioneering positron emission tomography (PET) study, which revealed a prominent activation in right lateral cerebellum while participants performed a semantic retrieval task (Petersen et al. 1989). In the past 25 years, more than 15,000 fMRI studies have reported blood oxygen level dependent (BOLD) signal changes in the cerebellum during a wide range of mental and motor activities. Some examples are sensorimotor processing (Grodd et al. 2001), semantic discrimination (Xiang et al. 2003), sensory processing (Blakemore et al. 2001), mental imagery (Lotze et al. 1999), classical conditioning (Thurling et al. 2015), linguistic processing (Ackermann et al. 1998), attentional modulation (Allen et al. 1997), timing estimation (Ivry and Keele, 1989), and emotion perception (Schmahmann, 2000).

One important insight to be gained from this extensive neuroimaging literature is that, functionally, the cerebellum is highly heterogeneous (for meta-analyses, see Stoodley and Schmahmann, 2009; Van Overwalle et al. 2014; Stoodley, 2012). Across studies, different tasks reliably activate different locations on the cerebellar cortex. The classic nomenclature of the cerebellum has focused on its lobular structure, with the 10 lobules (numbered I – X) organised along the superior to inferior axis (Larsell, 1947). Each lobule includes a vermal (medial) and hemispheric (lateral) component. The largest lobule VII is further subdivided into VIIa (Crus I and Crus II) and VIIb. On a broad level, the anterior lobe of the cerebellum is thought to be specialised for motor function, while the posterior lobe activates predominately in response to non-motor or "higher-order" cognitive processes (Stoodley and Schmahmann, 2010; Timmann et al. 2008). Beyond a relatively crude motor/non-motor dichotomy of cerebellar specialisation, there are other findings of cerebellar function that have been extensively reported in the literature. First, much like the cerebral cortex, there are laterality effects in the cerebellum, namely, there appears to be a right-hemisphere lateralisation for language and verbal working memory tasks (Crus I and II) while spatial processing tasks are lateralised to the left hemisphere of Crus I and II. Second, based on clinical and neuroimaging work, there is a possible specialisation for affective and emotional processing in the vermis of the cerebellum (Schmahmann et al. 2007). Overall, cerebellar activity patterns are elicited in response to a plethora of tasks that span numerous cognitive, affective, social, and motor domains (for reviews, see Strick et al. 2009; Timmann et al. 2010 Buckner, 2013; Stoodley, 2012; Stoodley & Schmahmann, 2010; Fiez, 1996).

1.4 Cortical-Cerebellar Loops

Evidence for functional heterogeneity in the cerebellum, as established by clinical and functional neuroimaging studies, is largely supported by early observations from anatomical work. The cerebral cortex projects to the cerebellum via the pontine nuclei. This projection constitutes one of the largest fiber systems in the human brain. Importantly, the system is organised in a highly specific manner, with each functional module of the cerebellum receiving input from a different cortical area. This finding is perhaps explained by the fact that the cerebellum evolved in parallel with the frontal lobes (Rilling and Insel, 1998) and that cerebellar areas interconnected with the prefrontal cortex (PFC) underwent a greater expansion compared to the somatomotor regions of the cerebellum. This highly organised topography is not specific to the cerebellar cortex, indeed ventral portions of the cerebellar dentate nucleus, the major output station from the cerebellum to the PFC, expanded much more rapidly than the dorsal portion, which connects the cerebellum with motor regions of the cerebral cortex. This expansion of the prefrontal cortical-cerebellar loop (Balsters et al. 2010) likely endowed the human cerebellum with an involvement in higher-order cognitive processes, providing an anatomical substrate for cerebellar contribution to cognition (Schmahmann and Pandya, 1997). These insights from evolution have been supported by studies using polysynaptic tracing agents in non-human primates. Specifically, polysynaptic tracing studies in non-human primates have shown that each functional area of the cerebellum appears to receive input from a relatively small cerebral area. For example, tracers injected into Brodmann area 46 label restricted lateral parts of Crus II. Importantly, the combined use of anterograde and retrograde viruses has shown that Area 46 projects to, and receives input from the same cerebellar area. These insights have motivated a vertical, closed-loop conceptualisation of the cerebellum, where each cerebellar region tightly interacts with a restricted set of cerebral regions. These circuits, demonstrated using connectional data from non-human primates, have also been reported using resting state functional correlations, demonstrating functionally and anatomically distinct cerebrocerebellar circuits (Buckner et al. 2011; Habas et al. 2009; O'Reilly et al. 2010). While the majority of the cerebral cortex projects parasynptically to the cerebellum, there are no known anatomical connections between the cerebellar cortex and the inferior temporal gyrus and the primary visual cortex. Interestingly, in human brains, the dominant contribution to the cerebellum comes from the PFC and parietal lobe, with approximately 70% of all cortical-cerebellar projections originating from cerebral association areas. What this suggests is that PFC and parietal inputs to the cerebellum are at least, if not more, significant than inputs arising from the cerebral motor cortex. Overall, anatomical work promotes the idea that the cerebellum operates in a closed-loop circuitry with distinct regions of the cerebellum, both receiving projections from, and projecting back to these regions (Botez et al. 1985; Kelly & Strick, 2003; Middleton & Strick, 1994; Schmahmann, 1991, 1996; Voogd & Glickstein, 1998).

1.5 Gap in the Literature

The past two decades of neuroimaging, clinical, and anatomical work suggests an involvement of the cerebellum in tasks spanning motor, cognitive, affective, and social domains. Despite mounting evidence that the cerebellum is likely as functionally heterogeneous as the cerebral cortex, a comprehensive map detailing a clear functional organisation has yet to be established for this structure. Previous studies have been unable to accomplish this goal, because they used a highly restricted set of task conditions, often limited to a single functional domain. These studies

attempted to understand functional specialisation of the cerebellum by mapping task-evoked activations to different locations on the cerebellar cortex, which were particularly responsive to some, or all, aspects of the task. Using this approach, most studies concluded that because region X was significantly activated by task A, it must follow that region X is functionally specialised for task A processing. Of course, the obvious problem with this restricted task-mapping approach is that it fails to fully characterise the functional specialisation of region X. In order to build up a fully representative picture of specialisation within region X, it is necessary to demonstrate that this region also becomes active in response to tasks B, C, and D, but not to tasks, E, F, and G. By incorporating a broader task battery, we avoid making specious inferences based on restricted task-mappings, and instead achieve a more complete understanding of functional specialisation within a given brain region (i.e. the cerebellum).

To provide a complete map of the functional organisation of the cerebellum, it is far more powerful to summarise activation in terms of features rather than tasks. A feature can be thought of as a hypothetical tuning function, a model of what the activation profile of a single unit of measurement (i.e. voxel) could be. Feature-based approaches, which describe activity patterns using latent variables of the data (i.e. bottom-up), are a particularly powerful way of providing an overall characterisation of functional organisation. By abstracting from task labelling, feature-based approaches can characterise the functional specialisation of a particular region for bottom-up features that are encoded by task-evoked activity patterns. This way, a region is not in danger of becoming a "theory of mind" region. Rather, functional activation within this region is described in terms of an underlying feature that is inherent to some, if not all, aspects of a certain set of tasks.

1.6 Comprehensive Map of Functional Organisation: A Novel Approach

The primary aim of this work was to provide a comprehensive map of functional organisation in the cerebellum, using a bottom-up feature-based approach. We define functional topography as the spatially ordered projection of task-evoked activations to functionally specialised locations on the cerebellar surface. To do this, it was necessary to depart from traditional methods and procedures and adopt a novel and rather radical task design. Specifically, we acquired a condition-rich dataset (34 tasks; 61 task conditions) on seventeen participants across four separate fMRI scanning sessions, resulting in 8 hours of fMRI data per subject. This unique and exhaustive task battery was chosen for the express purpose of exploring the full breadth of the functional subspace spanned by the cerebellum, on the same set of subjects. The tasks included in the current design were chosen to reflect a broad range of motor, cognitive, and affective domains, far exceeding the scope of existing datasets (5-task maximum; Stoodley et al. 2012) that have been utilised to explore functional topography in the same set of subjects.

One might argue that rather than acquiring an expansive dataset, a more straight-forward solution to overcoming the restricted task-mapping problem would be to consolidate previously reported task-evoked activations. Indeed, this approach, which would be far less costly, challenging, and of course, time-consuming, could conceivably yield a comprehensive functional map of the cerebellum. We did not decide on this meta-analytic approach for a number of reasons. First, because whole-brain analysis is not always the standard, the cerebellum has often been omitted from neuroimaging studies. Indeed, the cerebellum was excluded from the original Talairach

stereotaxic atlas, which partly explains its absence from many early fMRI studies. Of course, not only does this reduce the power of a meta-analytic approach but it also misrepresents the existing literature, which would introduce a bias into a meta-analysis. Second, the majority of studies report group-level, cluster activations in favour of individual-subject, unthresholded activity patterns. Group-level reporting is a problem because it obviates any existing inter-subject variability, while thresholded clustering fails to capture the full functional profile of activation. There are other problems with the meta-analytic approach, namely that imaging acquisition and analysis steps (i.e. field strength, sequence type, preprocessing pipelines etc) are inconsistent across studies, introducing variability into the results. Similarly, studies often include drastically different sample sizes, which impact the reliability of the findings. While a meta-analytic approach is useful for providing a summary of the literature, it is not amenable to bottom-up feature modelling. For this reason, we decided to collect a condition-rich dataset on the same set of subjects, which allowed us to derive a comprehensive map of functional organisation using bottom-up feature modelling.

1.7 Summary of Results

Using this condition-rich dataset, we leveraged the known functional heterogeneity of the cerebellum to derive a comprehensive bottom-up map of functional organisation. Further, we demonstrated that functional boundaries within the cerebellum do not align with an anatomical lobular folding, compared to randomly simulated borders. This finding challenges the common use of the lobular nomenclature for localising functional activations in the cerebellum. This work offers two major contributions to the field. First, to our knowledge, this task battery is the most expansive in the literature, making this work the veritable "look-up table" for functional topography in the cerebellum. Second, we show that functional boundaries in the cerebellum, derived from task-evoked activations, do not align with lobular demarcations. Based on this finding, we challenge the field to adopt a functional, rather than a lobular nomenclature, to better understand the functional topography of this structure.

2. Methods

2.1 Participants and Ethics Statement

All experimental procedures were approved by the nonmedical research ethics committee at Western University. All subjects gave their informed consent prior to study commencement. There were 21 subjects in study 1 and 17 of this original cohort returned approximately one year later (mean=11 months, s.d.=12 weeks) to participate in study 2. The 4 subjects (mean age=24.19, s.d.=2.26) who did not return for study 2 were not included in the study 1 analysis. Therefore, in total, 17 healthy, right-handed individuals (10 females, 7 males; mean age=26.34, s.d.=4.25) with no self-reported history of neurological or psychiatric illness were included in both study 1 and study 2 analyses. Right-handedness was confirmed by a score greater than 40 on the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2 Behavioural Training

All 17 participants underwent three days of training on the study 1 and study 2 task batteries respectively. All tasks except for rest and the three movie tasks (landscape, nature, and romance) were trained. For each study, all three behavioural sessions took place over the course of 5-7 days. Tasks were tested in short blocks of 35 s. An instruction screen was presented for the first 5 s of each block, specifying the upcoming task and instructions (e.g., 'Theory of Mind Task!' Use your LEFT hand. 1 = false belief. 2 = true belief), followed by 30 s for the designated task. On-line feedback was provided for response-dependent tasks (green or red squares to indicate correct or incorrect responses, respectively), and an overall accuracy score was provided at the end of the run for tasks requiring a button response. The first day was used to familiarise the participants with the requirements for each of the 17 tasks. On the second day, 11 of the 17 tasks, those requiring button-press responses, were grouped together into 7-minute runs so that participants could learn to alternate between tasks, and on the third day, participants practiced all 17 tasks in 10-minute runs. On training days 1 and 2, participants could read through the instructions at their own pace while the instructions were automatically paced on the third training day, to prepare participants for testing in the scanner. The training program ensured that participants were familiar with task requirements and that they were experienced at switching between tasks. On the third behavioural training day, all participants reached asymptotic performance (>85% correct on all tasks) with this amount of training. In this manner, we reduced the impact of learning during the scanning sessions.

2.3 Scanning Sessions

For both study 1 and study 2, all 17 participants completed the first scanning session within the first week of the final behavioural training session (mean=3.67 days, s.d.=5.7 days) and the second scanning session was completed no more than 7 days after the first scanning session (mean=2.89 days, s.d.=3.89 days). Each scanning session consisted of eight imaging runs (10 min total duration/run). Each task was presented once in an imaging run, producing a final scanning data set in which each task was tested 16 times. The task order was balanced from run-to-run to reduce order effects. All participants performed the same task paradigm (same order of

tasks and runs) to allow for cross-subject analyses on the time series level (results not presented here). Participants were well-trained on the tasks at the time of scanning, therefore, to reduce the recall of specific stimulus-response associations, novel sets of stimuli were used, where possible, across all imaging runs (see Tables 1 and 2 for full description).

2.4 Image Acquisition

All fMRI data were acquired at the Centre for Functional and Metabolic Mapping (CFMM) at Western University on a 3T Siemens scanner. Whole-brain functional images were acquired using an EPI sequence with multi-band acceleration (factor 3, interleaved) with an in-plane acceleration (factor 2), developed at the Centre for Magnetic Resonance Research at the University of Minnesota. Imaging parameters were: TR=1 sec, FOV=20.8cm, phase encoding direction=P>>A, acquiring 48 slices with in-plane resolution of 2.5 mm x 2.5 mm and 3 mm thickness. GRE field maps were also acquired in order to apply distortion correction in case EPI images were distorted due to B0 inhomogeneities (TR=.5 s, FOV=24 cm, 46 slices with in-plane resolution of 3 mm x 3 mm x 3 mm. We also acquired online physiological recordings of both heart and respiration during each functional run given that task-related changes in heart rate can impact the estimation of the hemodynamic response and first-level general linear model fit (Hillenbrand, Ivry, & Schlerf, 2016). No participants had to be excluded from either study 1 or study 2 due to excessive motion. For anatomical localisation and normalisation, a 5 min high-resolution scan of the whole brain was acquired (MPRAGE, FOV=15.6cm x 24 cm x 24 cm, at 1x1x1 mm voxel size).

2.5 General Procedural Details

We tested 17 tasks in study 1 and 17 tasks in study 2. Participants performed each of the 17 tasks for 35 s, once per scanning run. Each 35 s task was divided into a 5 s instruction period followed by a 30 s execution period. The motivation for testing all tasks in a run (rather than assigning one task per run) was to ensure a common baseline for all tasks, enabling optimal between-task comparison. Many of the tasks in both study 1 and study 2 were divided into more than one condition (e.g. simple finger movements and finger sequences in the motor task) resulting in a total of 29 task conditions for study 1 and 32 task conditions for study 2. Where possible, novel stimuli were introduced across imaging runs to reduce stimulus-response learning. For a full description of the tasks, along with the accompanying references, see Tables 1 and 2.

Shared Tasks
To assess the test-retest reliability of cerebellar activity patterns, 8 tasks from study 1 were repeated in study 2 (tasks flagged by an asterisk in Tables 1 & 2). Three of the 8 tasks (object N-Back, visual search, semantic retrieval) had a discrete trial structure, whereby each unique stimulus (e.g. picture, letter, noun) was presented 15 times for 1.6 s at a time, and the response was completed within this window, followed by an inter-trial interval (ITI) of 400 ms. Exceptions were the motor task (trials=8; stim/resp duration=4.6 s; ITI=400 ms), theory of mind (trials=2; stim/resp = 9.6/4.6 s; ITI=400 ms) and action observation (trials=2; stim duration=14 s; ITI=1 s) while spatial navigation and rest did not have a discrete trial structure (trials=1; duration=30 s; ITI=0 s).

Unique Tasks
There were 9 tasks unique to study 1 (i.e. tasks not shared with study 2). Six tasks had the same discrete trial structure, whereby a unique stimulus was presented 15 times for 1.6 s and the response was completed within this window, followed by an ITI of 400 ms. Exceptions were Go-No Go (trials=30; stim/resp duration=800 ms; ITI=200 ms) and motor imagery (trials=1; duration=30 s; ITI=0 s). Similar to study 1, there were 9 unique tasks in study 2. The movie tasks (landscape, romance, and nature) did not have a discrete trial structure (trials=1; duration=30 s; ITI=0) while the prediction, spatial map, and response alternatives tasks had the same trial structure (trials=6; stim/resp=4.8 s; ITI=200 ms). The other 3 tasks had a different trial structure: mental rotation (trials=9; stim/resp duration=3 s; ITI=300 ms), body motion processing (trials=10; stim/resp duration=3; ITI=0), rules task (trials=4; stim/resp duration=7.3s; ITI=200 ms).

Hand Assignment Across Tasks
To reliably elicit ipsilateral- and contralateral activation in the "hand knob" regions of the cerebellum, tasks requiring a motor response were assigned to either the left or right hands. The hand assignment was consistent across study 1 and 2 for the shared tasks to ensure test-retest reliability. For tasks requiring 2-choice discrimination, responses were made with the index or middle finger of the designated hand. All finger-press responses were recorded on a four-key button box.

Eye-Tracking
Eye-tracking data were recorded on the third behavioural training day (study 1: n=15; study 2: n=17) to obtain an estimate of saccadic eye movements for each of the tasks. Eye-tracking data from 2 participants in study 1 were not collected and eye-tracking data were excluded from 3 participants in study 2 as the pupil could not be reliably tracked. Cerebellar function has been theorised to be strongly associated with eye movements (Glickstein, 2006), therefore, eye-tracking was done as a precautionary measure to ensure that cerebellar activation is really attributable to task-related changes rather than saccadic eye movements.

Table 1. fMRI Study 1 Task Design

Study 1 Tasks	Task Description	Task Conditions	Novel Stimuli
Checkerboard (Krasnow et al. 2003)	Passive viewing, pictures of objects and a checkerboard pattern. Pictures were obtained from IAPS		No
Motor (Wiestler et al. 2013)	6-element sequence , either requiring one key press with each of six fingers (bimanual) or repetition of a single key press with one finger (unimanual left or right)	Single finger / Sequence	No
Action Observation (Cross et al. 2012)	Passive viewing of videos of knots being tied by two hands, learning the name of the knot (presented at the top of screen) and viewing of videos of the same knot rotating on a turn-table. Video were obtained from Cross et al. (2012)	Rotating knots / Knot tying	Yes
Motor Imagery (Boly et al. 2007)	Imagine playing an energetic game of tennis		No
Spatial Navigation (Boly et al. 2007)	Imagine walking from room to room in childhood home, with a cue specifying the path to be taken (e.g., "Imagine walking from the kitchen to the bedroom, stopping to look around at different rooms")		Yes
Interval Timing (Schubotz et al. 2001)	2AFC, indicating if a tone is short (100ms) or long (175ms)		No
Arithmetic (Rickard et al. 2000)	2AFC, indicating if simple multiplication equations (e.g. 2x7=14) are correct or incorrect. For control task, participants viewed a series of four numbers (5,2,4,2) and indicated presence/absence of target number (e.g., 1)	Number identification / Arithmetic Verification	Yes
Visual Search (Donner et al. 2002)	2AFC, indicating if target stimulus ("L") is present among distractors ("T"), with varying set size (4, 8, 12)	4 letters / 8 letters / 12 letters	No
Stroop (Egner et al. 2005)	3AFC, indicating color of stimulus word (red, blue, green, or yellow), comparing conditions in which colour-word mapping is congruent or incongruent	Congruent / Incongruent	No
Verbal Working Memory (Owen et al. 2005)	2AFC, indicating if current stimulus in stream of letters (a, b, or c) matches letter displayed two items previously (2-back)	0-Back / 2-Back	No
Object Working Memory (Owen et al. 2005)	As above, with pictures (fire hydrant, lamp, or zip) instead of letters (2-back)	0-Back / 2-Back	No
Semantic Retrieval (Fiez et al. 1996)	Verb generation task requiring covert responses to visually-presented nouns, either repeating the stimulus (Read) or generating a verb associated with the noun (Generate). Example nouns were obtained from Kurland et al. (2014)	Read nouns / Generate verbs	Yes
Affective Processing (Moulton et al. 2011)	2AFC, indicating if picture (scenes, animals, foods) is pleasant or unpleasant. Pictures were obtained from IAPS	Pleasant / Unpleasant	No
Facial Emotions (Baumann et al. 2012)	2AFC, indicating if picture depicts sad or happy face. Pictures were obtained from IAPS	Happy / Sad	No
Go No-Go (Elliott et al. 2000)	Go-No Go task with positive (Go) or negative (No Go) words. Stimuli were obtained from Elliott et al. (2000)	Go / No-Go	No
Theory of Mind (Dodell-Feder et al. 2011)	2AFC to indicate if short story contains true or false belief. Example stories obtained from Dodell-Feder et al. (2011)		Yes
Rest (Yeo et al. 2011)	Passive viewing of fixation cross with eyes open		No

In total, there were 17 tasks in study 1 that were divided into 29 task conditions. Novel stimuli were introduced where possible (fourth column). Abbreviations: AFC – Alternative Forced Choice; IAPS – International Affective Picture System

Table 2. fMRI Study 2 Tasks

Study 2 Tasks	Task Description	Task Conditions	Novel Stimuli
Spatial Map	Memorise a spatial mapping of numbers (either, 1, 4, or 7) for subsequent recall	1 number 4 numbers 7 numbers	No
Mental Rotation (Shepard and Metzler, 1971)	Mentally rotate target object to determine whether it can be brought into alignment with baseline object. Difficulty is measured by angular disparity between target and baseline image. Stimuli were obtained from Ganis and Kievit (2015)	0 degree 50 degree 100 degree	Yes
Motion Processing (Troje et al. 2002)	2AFC to identify intact point-light walkers (either happy or sad) or scrambled walkers (fast or slow). Stimuli obtained from Troje et al. (2002)	Intact Scrambled	Yes
Concrete Permuted Rules Operations (CPRO) (Ito et al. 2017)	Apply task-rule set (logic, sensory, & motor rules) to two consecutively presented stimuli (rectangles: either red or blue, vertical or horizontal)		Yes
Prediction (Moberget et al. 2014)	2AFC task to indicate if five sequentially-presented words comprise a semantically meaningful sentence. Stimuli obtained from D'Mello et al. (2017)	True Violated Scrambled	Yes
Response Alternatives (Casini and Ivry, 1999)	Execute a fast motor response to an imperative signal (white cross) that appears in one of 1, 2, or 4 primed positions	1 option 2 alternatives 4 alternatives	No
Nature Movie	Passive viewing of a nature clip of kickboxing kangaroos, taken from "Planet Earth II: Islands"		Yes
Romance Movie	Passive viewing of an emotional love story between two characters from the Pixar movie "Up"		Yes
Landscape Movie	Passive viewing of an aesthetically-pleasing clip that depicts a diverse scenery, taken from Vimeo		Yes
Action Observation* (Cross et al. 2012)	Passive viewing of videos of knots being tied by two hands, learning the name of the knot (presented at the top of screen) and viewing of videos of the same knot rotating on a turn-table. Video were obtained from Cross et al. (2012)	Knot tying Rotating knots	Yes
Motor * (Wiestler et al. 2013)	6-element sequence, either requiring one key press with each of six fingers (bimanual) or repetition of a single key press with one finger (unimanual left or right)	Simple finger Sequence	No
Spatial Navigation* (Boly et al. 2007)	Imagine walking from room to room in a familiar childhood home, with a cue specifying the path to be taken (e.g., "Imagine walking from the kitchen to the bedroom, stopping to look around at different rooms")		Yes
Visual Search*	2AFC, indicating if target stimulus ("L") is present among distractors ("T"), with varying set size (4, 8, 12)	4 letters 8 letters 12 letters	No
Object Working Memory* (Owen et al. 2005)	2AFC, indicating if current stimulus in stream of pictures (whistle, plate, or fork) matches picture displayed two items previously (2-back)	0-Back 2-Back	No
Semantic Retrieval* (Fiez et al. 1996)	Verb generation task requiring covert responses to visually-presented nouns, either repeating the stimulus (Read) or generating a verb associated with the noun (Generate). Nouns were selected by the experimenter	Read nouns Generate verbs	Yes
Theory of Mind* (Dodell-Feder et al. 2011)	2AFC to indicate if short story contains true or false belief (Theory of Mind task). New stories were written by the experimenter using the same structure as those published by Dodell-Feder et al. (2011)		Yes
Rest* (Yeo et al. 2011)	Passive viewing of fixation cross with eyes open		No

In total, there were 32 task conditions in study 1. Shared tasks (i.e. tasks common to both study 1 and study 2) are highlighted here with an asterisk. The task design for these shared tasks remained the same across both studies. Novel stimuli were introduced where possible (indicated by 'yes' or 'no' in the fourth column). Abbreviations: AFC – Alternative Forced Choice.

2.6 Imaging analysis

Image Preprocessing
Data preprocessing was carried out using tools from SPM 12 (Friston et al. 1994), Caret (Van Essen, 2012), Freesurfer (Fischl, 2012) and SUIT (Diedrichsen, 2006; Diedrichsen et al. 2009), as well as custom-written scripts written in MATLAB 2015b. The same processing pipeline was used for both study 1 and study 2. For all participants, the anatomical image was acquired in the first scanning session and it was then resliced into the Left-Inferior-Posterior (LPI) coordinate frames and the location of the anterior commissure was set to the origin of the image (xyz coordinate [0 0 0]). Functional data from sessions 1 and 2 were aligned using the 6-parameter rigid body transformation and the anatomical image was co-registered with the mean functional image. The aligned functional images were then realigned to the co-registered mean functional image. Smoothing was not applied to the functional images.

General Linear Model
A general linear model (GLM) was used to fit whole-brain data for study 1 and study 2 separately, using 29 and 32 task regressors respectively. The success of the GLM in estimating true neural signal from the data was determined by a measure of pattern consistency (i.e. signal-to-noise) yielded by the model fit. The high-dimensional autocorrelation model (FAST option in SPM), which determines the optimal temporal autocorrelation yielded the best signal-to-noise (SNR). Traditional high-pass filtering (HPF), as implemented in SPM was not applied. Instead, the FAST option was used as a filter in the GLM. The betas from the first-level GLM were univariately prewhitened: the betas were divided by the square root of the residual mean square image. Rather than using rest as a common reference, we used the mean of all task conditions during this session. This resulted in a more stable estimate of activation as we do not consider rest to yield zero activation, rather it involves specific activations of the so-called default mode network (Yeo et al. 2011).

SUIT
The spatially unbiased infratentorial template (SUIT) toolbox (v3.2) in SPM 12 was used to isolate the cerebellum from the rest of the brain and to provide a normalisation to the spatially unbiased template of the cerebellum. The segmentation implemented in the SUIT toolbox in SPM 12 was used to create tissue probability maps of cerebellar grey and white matter, and a cerebellar grey-matter isolation mask. The cerebellar isolation mask was modified to ensure that there were no shared voxels between the superior cerebellum and the directly abutting cortical regions of the inferior temporal and occipital cortex. A buffer zone was created by isolating the shared voxels between the occipital cortex and the superior cerebellum. This buffer zone was then removed from the cerebellar and cortical masks and visualised in the MRIcron tool (http://people.cas.sc.edu/rorden/mricron/index.html) to ensure that there were no shared voxels across masks. The corrected grey matter probabilistic mask of the cerebellum was then normalised into SUIT space using the diffeomorphic anatomical registration (DARTEL) algorithm (Ashburner, 2007). This algorithm deforms the cerebellum to simultaneously fit the probability maps of cerebellar grey and white matter into the SUIT atlas template. This non-linear deformation was then applied to the anatomical and functional data. The activation estimates (i.e. betas), contrasts, and residual mean-square images from the first-level GLM were resliced into SUIT space. Finally, all volume-averaged task-evoked activations were visualised

on a surface-based, flat-map representation of the cerebellar cortex, freely available in the SUIT toolbox (see Diedrichsen & Zotow, 2015 for more details).

2.7 Evaluation of Task-Evoked Activity Patterns

Motor Feature Model
We wanted to visualise task-evoked activity patterns in the cerebellum that extended beyond the domain of motor function. However, many of the 61 task conditions, although not designed to test motor function, were likely to evoke motor-related function (i.e. saccadic eye movements for a visual search task). Therefore, to account for motor-related activations across all 61 task conditions, we built a motor feature model, which included three classical motor features: left and right hand movements (i.e. number of button presses), and saccades (i.e. number of eye movements). All motor features were normalised by the duration of each task condition. A velocity-based algorithm, implemented in the Eyelink toolbox (Cornelissen et al. 2002) identified saccadic eye movements as periods in which the rate of change of the position of gaze surpassed a fixed velocity threshold of 30 deg/s. To provide an estimate of saccadic eye movements, a group-averaged measure of saccades was computed per task condition. For example, tasks that required sentence-reading (i.e. social cognition task), elicited, on average, a larger number of saccades relative to tasks with little-to-no visual stimuli (i.e. rest).

We computed a design matrix for each individual subject that comprised the three motor features plus the 29 (study 1) and 32 (study 2) task conditions (identity matrix with 1 on the diagonal for each task condition). Then, to remove the influence of the motor features from the activation maps, we calculated an L2-norm regression (i.e. ridge regression) on the activation estimates of each individual subject. The "cleaned-up" activation estimates were then averaged across subjects and mapped onto the surface of the cerebellar cortex.

Reliability of Activity Patterns
To determine the within-subject reliability (across scanning sessions) and the true functional variability of the activity maps across subjects, we conducted a correlational analysis of activity patterns (across voxels). All correlations were calculated on all task conditions and on all voxels in SUIT space. To determine the within-subject reliability, we correlated the estimates from the 1st and 2nd session within each subject and session. These correlations could be directly compared to the between-session, between-subject correlations. The difference in these two correlations were then taken as a measure of the true inter-subject variability of the functional organisation of the cerebellum.

2.8 Evaluation of Representational Structure

Distance Measure
Representational similarity analysis (RSA) was used to investigate the representational structure of the cerebellum (see Diedrichsen and Kriegeskorte, 2017). Dissimilarity between activity patterns was measured for each pair of task conditions using the cross-validated Mahalanobis distance (Walther et al. 2016). The distances were calculated using imaging runs as independent partitions. The advantage of cross-validation is that it ensures that the distance between two activity patterns is zero if they are not statistically different from each other. Task conditions

differed from study 1 to 2, introducing a different baseline, therefore, dissimilarity estimates had to be estimated and predicted separately for both study datasets.

Reliability and Visualisation of Distance Measures
Between-subject reliability of the representational dissimilarity matrix (RDM) was computed by taking the average correlation of distances, across all possible participant pairs for study 1 and study 2 separately. Within-subject reliability was similarly computed by taking all possible session pairs, within each subject. The diagonal of the RDM was excluded from this correlational analysis. To quantify the heterogeneity of task-evoked activity patterns, one-sample t-tests against zero (corrected for multiple comparisons) were calculated for all possible pairwise distances for the study 1 and study 2 representational matrices respectively.

Classical multidimensional scaling (MDS) was employed to visualise the distances between all possible pairs of task conditions for study 1 and study 2 separately. MDS is an effective visualisation technique that projects the *N*-dimensional RDM into a lower-dimensional space so that distances from the higher space are preserved with as much integrity as possible. MDS was performed on the group-averaged RDM and the first three dimensions were visualised in a 3-dimensional space. Although the coordinates corresponding to the task conditions can be rotated in the multi-dimensional space, we just show one example projection for the purposes of visualisation. An agglomerative hierarchical clustering function was implemented in MATLAB and it was used to assign each task condition to a cluster. This clustering approach, which used a Euclidean distance as a measure of dissimilarity between pairs of tasks, allowed for optimal visualisation of task similarity in a 3-dimensional space.

2.9 Estimating a Comprehensive Map of Functional Organisation

We used spatial independent component analysis (ICA) to derive a functional feature map of the cerebellar cortex. ICA (Calhoun, 2009) attempts to describe the activity profile at each location on a map as a linear combination of a number of latent features. Each feature is characterised by an activation profile across tasks along with a map demonstrating how it is distributed across the cerebellar cortex. Spatial ICA attempts to make the spatial maps as independent as possible.

ICA was performed on the univariately prewhitened and group-averaged activity estimates, without first accounting for the motor features. The Fast ICA pipeline (Hyvarinen, 1999) started with a Principal Component Analysis (PCA) to reduce the group-averaged activity estimates from an *N*-dimensional space to a lower dimensional projection, retaining the first 11 components (or "features") best capturing >95% of the variance of the data. ICA then rotated these 11 axes non-orthogonally to maximize the non-Gaussianity of the task-evoked activity patterns. Each feature was assigned either a negative or positive sign by the fastICA algorithm. To capture the full spectrum, the feature matrix (11 features x P voxels) was modified to include both the positive and negative signs of each source (22 features x P voxels). A "winner-take-all" approach was then performed so that each vertex of the cerebellar surface was assigned to the feature (either positive or negative) that explained the largest amount of variance. From this "winner-take-all" approach, each feature was then assigned a colour, creating a map that detailed a bottom-up, functional organisation of the cerebellum.

The functional map derived using ICA was dictated by the latent structure of the task-evoked data, which meant that inferences had to be based on post-hoc labelling of features. Each

of the features comprised a different weighting of task-evoked activity patterns. To determine which task conditions loaded most strongly onto each feature, the feature matrix was projected into task space. As a further visualisation, the task weights for two given features (e.g. feature 1 & 2) were plotted against each other to determine differences in task loadings.

Lobular versus Random Tessellation
We wanted to assess whether the functional boundaries, defined in the bottom-up feature map, coincided with the lobular nomenclature. The first step was to randomly tessellate the surface of the cerebellum 1000 times to test a null model of functional/lobular boundary correspondence. Random tessellations were calculated by computing a Voronoi tessellation, which partitioned the cerebellar surface into regions based on a distance measure between sampled points. As these tessellations were randomly constructed, the boundaries were not expected to overlap with meaningful functional or lobular demarcations. Then a G-test was calculated, first between each random tessellation and the latent feature map, and then between the lobular tessellation and the latent feature map. A G-test is a test that assesses the likelihood-ratio between observed and expected values. For example, the null model of the G-test states that a vertex in region X of the randomly tessellated map does not have any bearing on the same vertex being present in region Y of the latent feature map. By computing one likelihood-ratio estimate for each random tessellation (with the latent feature map), we built a null model that described the mutual information shared between maps. Similarly, we also calculated a likelihood-ratio estimate for the lobular tessellation (with the latent feature map) to determine whether the expected overlap between these two maps differed from the null distribution. This analysis allowed us to statistically quantify the observed overlap between functional boundaries of our latent feature map and the lobular boundaries of the standard lobular nomenclature.

3. Results

3.1 Summary of Methods

We implemented a novel approach, one that offers a dramatic departure from existing studies, in order to derive a comprehensive map of functional organisation in the cerebellum. To this end, we have developed an extensive task battery, comprising 34 tasks (or 61 task conditions) that leverages known functional heterogeneity, thereby allowing us to explore the full breadth of activity patterns in this structure. While conventional approaches typically describe a cerebellar region as being activated by a given task (task-mapping approach), we were interested in describing cerebellar activation in terms of its latent structure. To do this, we used a bottom-up approach to obtain the latent features that accounted for variance of the cerebellar activity patterns. Then, using a "winner-take-all" approach, these features were mapped onto the surface of the cerebellum, yielding a comprehensive, bottom-up map of functional organisation.

3.2 Activity Maps

To visualise the activity patterns of the 61 task conditions, we first corrected the activity maps for the three shared low-level motor features (see methods). Task-evoked activity patterns were then averaged across subjects, which were then presented as unthresholded maps on a flat representation of the cerebellar cortex (Diedrichsen and Zotow, 2015). We chose a flat-map representation for data visualisation so that the full spatial extent of task-evoked activity patterns could be visualised all at once. The disadvantage of the traditional volume-based displays is that they only provide one particular view of the data, and it is often the case that alternative visualisations of neighbouring slices tell different visual stories.

Motor Feature Maps
There was a distinct and stable somatotopy in the human cerebellum for left and right hand function (Figure 1A & 1B) and saccadic eye movements (Figure 1C). These results serve to validate the functional specialisation of the cerebellar motor cortex (V/VI lobular boundary and lobule VIIIb) for the representation of finger movements, and the oculomotor vermis as the region activated for saccadic eye movements. Left and right hand activity patterns closely corresponded to previously reported finger-specific representations in the "hand knob" regions of the human cerebellum (Wiestler et al. 2011). The localisation of saccadic activation to the oculomotor vermis (vermal lobules VI and VIIa) was in line with previously reported lesion work in primates (Takagi et al. 1998) as well as task-evoked fMRI studies (Nitschke et al. 2004).
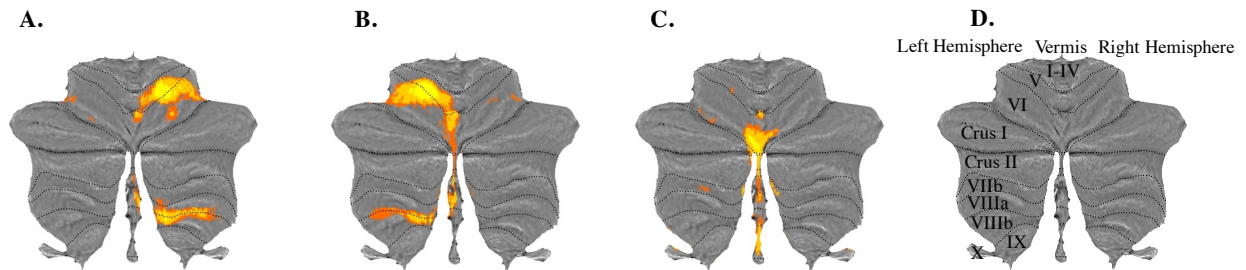
Figure 1. Motor Feature Maps. Group-averaged activation estimates for right hand presses (A), left hand presses (B), and saccadic eye movements (C) presented on a flat-map representation of the cerebellar surface where lobules (I-X) are demarcated by dashed black lines across the left and right hemispheres and the vermis (D).

Task-Evoked Activations

Even after accounting for motor requirements, the task conditions elicited distinct activity patterns in the cerebellum (Figure 2). Many tasks elicited a distributed spatial profile of activation that spanned many lobules, both in the anterior-to-posterior and medial-to-lateral directions.

Motor

In particular, complex finger sequences (shared: E) and the visual search task (shared: K-M) elicited strong activity in "hand knob" regions of the cerebellum (lobules V, VI) as well as the saccadic regions (oculomotor vermis) while the action video (shared: B), activated somatomotor regions surrounding the primary motor areas (VI, VIIb, VIIIa & VIIIb).

Social Cognition

In contrast to the motor-related tasks, medial hemispheric regions of Crus I and II were strongly activated by social cognitive tasks: the theory of mind task (shared: A) and the romance movie (unique: R2). Further, abstract mentalising tasks such as spatial navigation (shared: H) and motor imagery (unique: K1), elicited weak activations in lobule IX.

Working Memory

Tasks with high memory load: verbal N-Back (unique: N1-O1), picture N-Back (shared: F-G) and the spatial map task (unique: F2-H2) elicited bilateral activity in the most lateral aspects of Crus I.

Dynamic Viewing

Natural viewing tasks: nature and landscape movies (unique: A2-B2), and the romance and knot-viewing movies (unique: R2; shared: C) bilaterally activated medial Crus I and II and lobule IX.

Laterality Effects

Laterality effects were also observed for both the right and left cerebellar hemispheres. Tasks that required semantic and/or logical reasoning such as the permuted-rules and prediction tasks (unique: L2-O2) were right lateralised to Crus I hemisphere and lobule VIIb. Similarly, verb generation (shared: I), but not noun reading (shared: J), was strongly right lateralised to Crus I and II, while biological motion processing tasks (unique: P2-Q2) were left lateralised to Crus I and II.

Remaining Tasks
Affective and emotional processing of pleasant/unpleasant and happy/sad pictures did not elicit distinct activation patterns compared to the passive viewing of checkerboards (unique: D1-H1). Similarly, executive function tasks such as the Go/No-Go (unique: A1-B1) and stroop tasks (unique: L1-M1) did not elicit very strong or distinct activity patterns, much beyond motor-related activations. Highly automatised tasks such as noun reading (shared: J) and simple finger movements (shared: D) showed activity similar to rest (shared: N), with relatively high activity across the full extent of Crus I and II, the equivalent of a default-mode network within the cerebellum (Habas et al. 2009; Buckner et al. 2011).

Overall, these group-averaged activity patterns, for both classical motor features and task conditions, demonstrated that the cerebellum is activated for a diverse number of processes spanning multiple cognitive and motor domains. In particular, we demonstrated cerebellar involvement in motor, social, emotional, language, mentalising, natural viewing, and working memory processes.
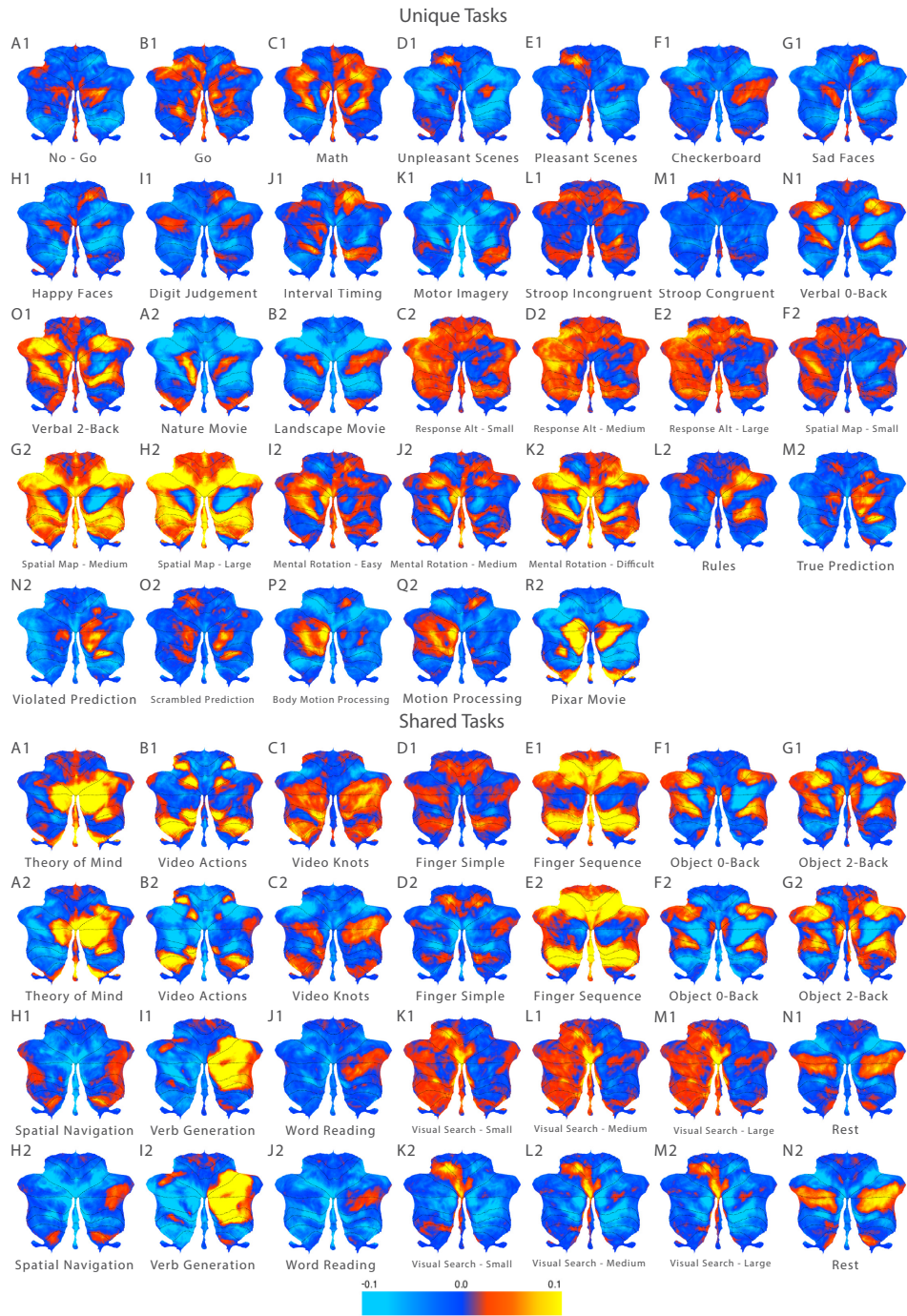
Figure 2. *Task Activity Maps. Unthresholded, group-averaged activity patterns for 61 task conditions (after the removal of activity patterns related to basic motor output). Upper panel: tasks unique to study 1 (denoted by 1) and tasks unique to study 2 (denoted by 2). Lower panel: tasks shared across study 1 (denoted by 1) and study 2 (denoted by 2). Brighter colours indicate increased activation and darker colours indicate decreased activations (both relative to baseline).*

Reliability of Activity Patterns

In our paradigm we chose to study the functional organisation of the cerebellum in a small set of participants across a broad range of tasks. This contrasts with a meta-analytical approach that compares activation patterns both across tasks and subjects. The advantage of the former approach is that we can account for the inter-subject variability of the functional organisation. To measure the extent to which the functional organisation is shared or idiosyncratic, we computed the correlation of the activity patterns of all tasks between every possible pair of subjects and sessions.

Within- and between-subject values were calculated for the average betas (Figure 3), and separately for tasks unique to study 1, tasks unique to study 2, and shared tasks. Average task-evoked activity patterns were reliable within the same subjects (i.e. across independent scanning sessions) and these correlations were consistent across datasets; R=.45 for unique study 1 tasks, R=.48 for unique study 2 tasks, and R=.51 for shared tasks. Similarly, average task-evoked activity patterns were reliable across subjects and again, these correlations were consistent across datasets; R=.17 for unique study 1 tasks, R=.19 for unique study 2 tasks, and R=.22 for shared tasks.

Thus, we found that the task activity patterns were reliable, even on a voxel-by-voxel basis without any applied spatial smoothing. Further, we found that there was considerable and true inter-subject variability, accounting for approximately 60% of the systematic variance of these functional maps. This stresses the importance of a "deep phenotyping" approach (Poldrack et al. 2015) in trying to understand functional organisation in the brain.
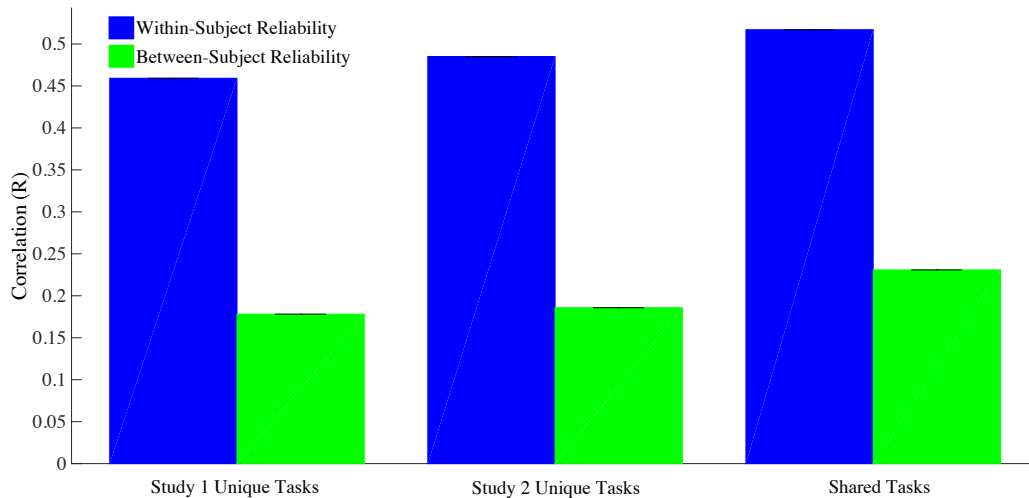
Figure 3. *Reliability of mean, task-evoked activity patterns. These reliability measures were calculated within-subject (blue) and between-subject (green), separately for tasks unique to study 1, tasks unique to study 2, and shared tasks.*

3.3 Understanding Task Structure in the Cerebellum

Univariate contrast analysis, computed from the first-level general linear model (GLM), was useful for visualising the task-evoked activity patterns (Figure 2). The insights that can be gained

from investigating individual task maps, however, is limited. Specific regions do not activate for one set of tasks only, but usually are co-activated to a certain degree by many different task paradigms. Rather than labelling a specific cerebellar region as being the "theory-of-mind region", our approach allows us to determine the underlying processes or features that best describe task-evoked cerebellar activation.

Here, we take a purely "bottom-up" approach to this question, trying to infer the latent task activations from the cerebellar activity patterns. As a first step, we visualised the arrangement of the different tasks in functional space. Multivariate analysis, specifically representational similarity analysis (RSA), achieves this goal by quantifying pairwise similarity measures of task-evoked activity patterns, on the same set of subjects. This approach complements a univariate analysis by providing a quantitative measure of similarity between all pairs of task-evoked activity patterns. By compiling these distance measures into a representational dissimilarity matrix (RDM), we were able to provide a quantitative measure of task similarity. Further, to visualise the relative similarity of task conditions in a representational space, we projected the data into a lower dimensional space and visualised a 3-dimensional projection using multi-dimensional scaling (MDS). Overall, representational similarity analysis proved exceptionally useful for both quantifying and visualising the "uniqueness" of task-evoked activity patterns in the cerebellum.

Representational Dissimilarity Matrix (RDM)
A representational dissimilarity matrix (RDM) was computed for the pairwise dissimilarities for study 1 (29 task conditions) and study 2 (32 task conditions) separately. Dissimilarity was given in terms of the cross validated squared Mahalonbis distance between the true activity patterns for pairwise task conditions, normalised by the number of voxels. Of all the possible pairwise distances, only 3.45% (study 1) and 3.43% (study 2) did not evoke significantly different activity patterns. In study 1 (Figure 4A), making up this small percentage were picture-based tasks (1-4), visual search conditions (5-7), stroop conditions (8 & 9), verbal N-Back conditions (10 & 11) and abstract thinking tasks (12 & 13). In study 2 (Figure 4B), the prediction conditions (1-3), biological motion task condition (4 & 5), response alternatives (6-8), and visual search conditions (9-11) were not distinguishable from one another. In addition, the medium-level difficulty of the spatial mapping task was not significantly different from any of the mental rotation conditions while simple noun reading was not statistically different from the violated prediction task condition. Tasks that were not dissimilar from one another were mostly conditions arising from the same task (i.e. visual search, stroop task, and picture-based tasks). Overall, the vast majority of task conditions for both study 1 and study 2 exhibited unique activity patterns in the cerebellum.

A.

1. Unpleasant Scenes
2. Pleasant Scenes
3. Sad Faces
4. Happy Faces
5. Visual Search – small
6. Visual Search – medium
7. Visual Search – difficult
8. Stroop – Incongruent
9. Stroop – Congruent
10. Verbal 0-Back
11. Verbal 2-Back
12. Motor Imagery
13. Spatial Navigation
14. Object 0-Back
15. Object 2-Back
16. No-Go
17. Go
18. Math
19. Digit Judgment
20. Checkerboard
21. Interval Timing
22. Finger Simple
23. Word Reading
24. Theory of Mind
25. Video Actions
26. Finger Sequence
27. Verb Generation
28. Video Knots
29. Rest

B.

1. True Prediction
2. Violated Prediction
3. Scrambled Prediction
4. Biological Processing
5. Motion Processing
6. Response Alt – easy
7. Response Alt – medium
8. Response Alt – difficult
9. Visual Search – small
10. Visual Search – medium
11. Visual Search – difficult
12. Mental Rotation – easy
13. Mental Rotation – medium
14. Mental Rotation – difficult
15. Spatial Map – medium
16. Spatial Map – difficult
17. Object 2-Back
18. Object 0-Back
19. Romance Movie
20. Theory of Mind
21. Verb Generation
22. Finger Sequence
23. Rules
24. Word Reading
25. Spatial Navigation
26. Spatial Map – easy
27. Nature Movie
28. Landscape Movie
29. Finger Simple
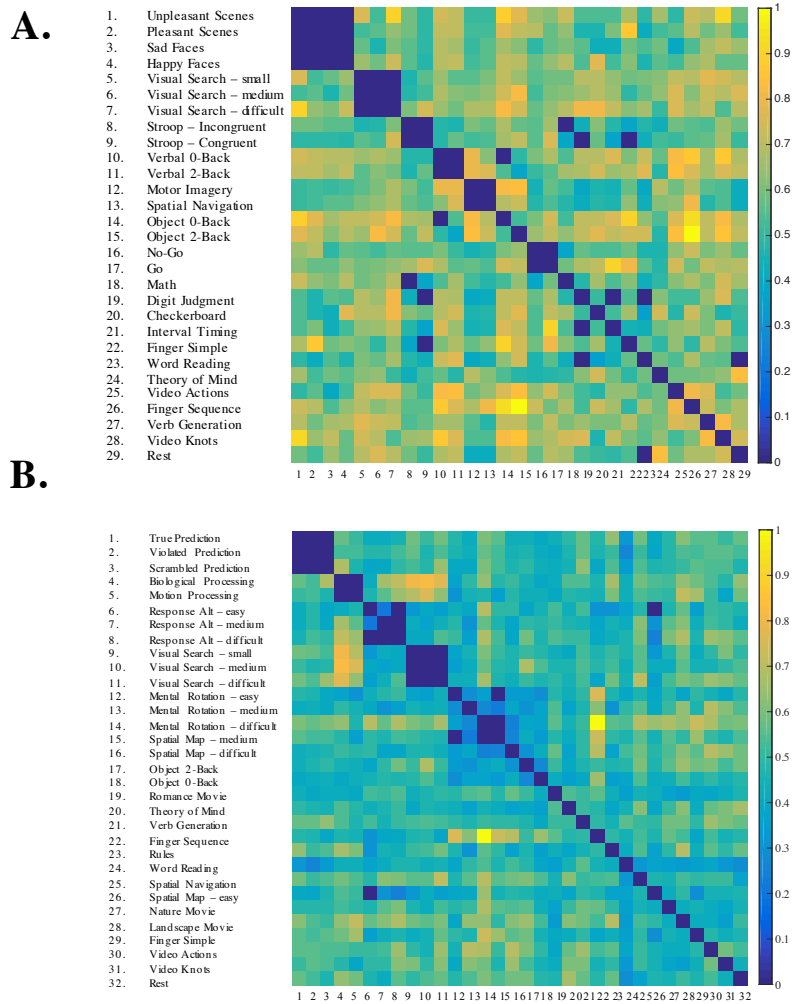30. Video Actions
31. Video Knots
32. Rest

Figure 4. Representational dissimilarity matrix (RDM) of pairwise distances calculated on univariately prewhitened, and cross-validated task-evoked activity patterns (A: study 1; B: study 2). Distances that were not significantly different from zero (i.e. no dissimilarity between activity patterns) were coloured in dark blue

Multi-Dimensional Scaling (MDS)
In order to visualise the relative similarity of task conditions in representational space, the distance measures were projected into a lower dimensional space. While the MDS plot can be rotated to project different 3-dimensional views, one example projection was chosen for visualisation purposes for both study 1 (Figure 5A) and study 2 (Figure 5B). Task conditions were organised into 9 (study 1) and 8 (study 2) distinct clusters, characterised by high similarity of task-evoked activations. For example, in both study 1 and 2, simple finger movements and word reading were very similar to the rest condition while the complex finger sequence task was very distinct from most other task conditions. Again in both studies, working memory tasks (study 1: verbal and object N-Back; study 2: object N-Back and spatial map) clustered together. In study 1, picture-based tasks, such as happy/sad faces, checkerboard, and pleasant/unpleasant scenes were clustered together while movie-based tasks in study 2 (landscape, nature, and action observation movies) were highly similar. In both study 1 and study 2, there were certain tasks,

namely, verb generation, theory of mind, finger sequence, and video actions and knots that elicited the most dissimilar activity patterns in the cerebellum.

Overall, The MDS plots for study 1 and study 2 indicate a rich representational structure in the cerebellum for task conditions spanning multiple motor, cognitive, and affective domains. In particular, tasks that engage working memory processes as well as social cognitive processes seem to be particularly successful in differentially activating specialised regions of the cerebellum while tasks that rely on heavy visual input (picture-based tasks) do not elicit strong or distinct differences.
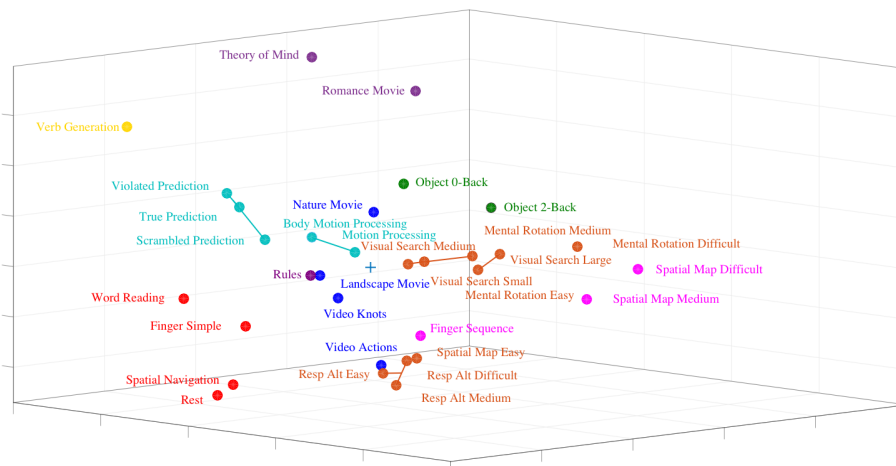
A.
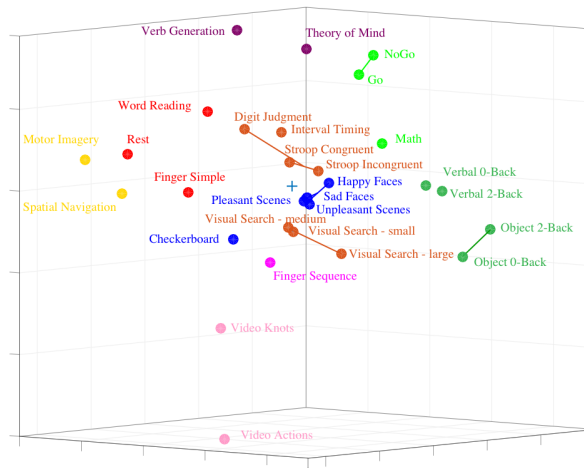
B.

Figure 5. Multi-dimensional scaling (MDS) plots in three dimensions depicting the relative similarity of the activity patterns for study 1 (A) and study 2 (B) task conditions. Hierarchical clustering was applied to the tasks, with lines connecting patterns of higher similarity. Colours indicate cluster membership.

The RDM and MDS results were presented on the group-level. Therefore, to ensure both between- and within subject consistency of distance measures, we computed 1) between-subject correlations for each individual subject RDM, and 2) within-subject correlations for the 14 task conditions common to study 1 and study 2 (across 4 scanning sessions). The average between-subject correlation was .54 for the study 1 RDM and .61 for the study 2 RDM while the within-subject correlation for shared tasks was .88. We can report good between- and within-subject reliability of distance measures, which indicates 1) that on average, similar patterns of activation were elicited across subjects, and 2) that robust activity patterns for shared tasks were elicited within individual subjects across four independent scanning sessions spanning 12 months.
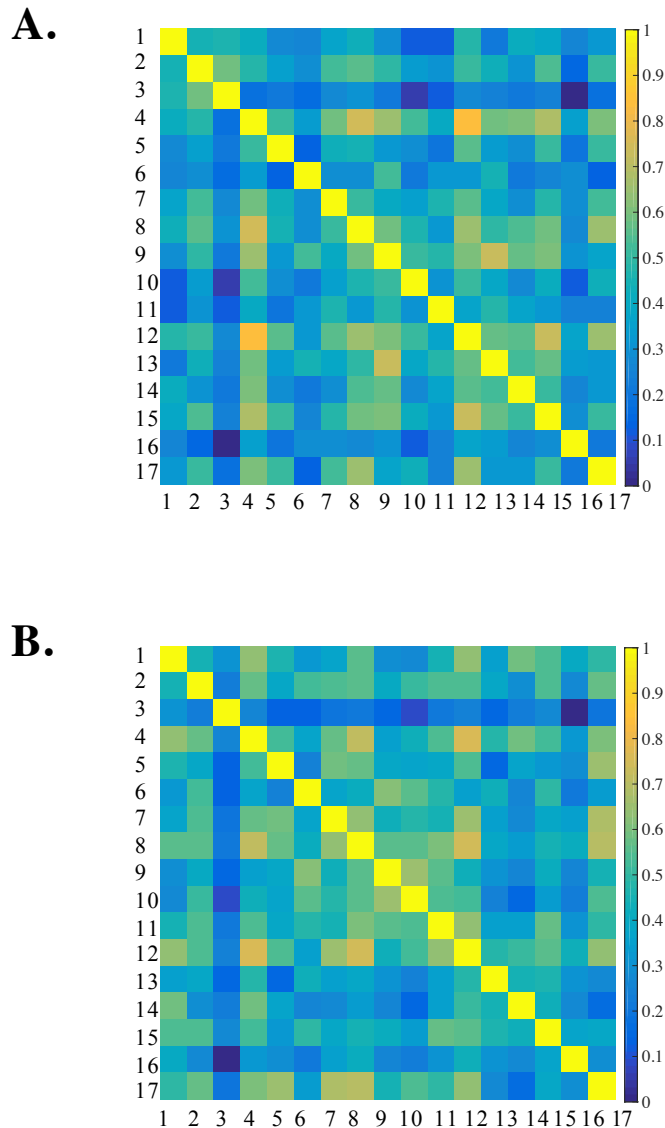

A.

B.

Figure 6. Reliability of Distances. Reliability matrix of between-subject correlations of distances for study 1 (A) and study 2 (B) for all 17 subjects. The diagonal includes a correlation of 1 (each subject correlated with themselves) while the off-diagonal reveals between-subject variability.

Overall, by leveraging insights from multivariate methods, namely representational similarity analysis, we were able to show that our chosen task battery was successful in exploring a heterogeneous subspace of the cerebellum. This is good news, as the success of determining latent features describing task-evoked activations is dependent on the far-reaching exploration of a rich functional subspace.

3.4 Comprehensive Map of Functional Organisation

The aim of this study was to explore the entire breadth of cerebellar functional activations in order to provide a comprehensive map of functional organisation within this structure. Unlike previous studies which have used restricted task-sets to investigate functional topography (e.g. Stoodley et al. 2012), our rich and comprehensive task-set (61 task conditions) allowed us to characterise the functional organisation of the cerebellum in terms of latent bottom-up features. By employing an extensive task battery spanning multiple cognitive, motor, and affective domains, we were able to leverage the known functional heterogeneity of this structure and simultaneously activate all functional subdivisions within the same set of subjects.

Independent component analysis (ICA) yielded 11 dominant features that largely accounted for the variance of cerebellar activity patterns. A "winner-take-all" approach was then used to assign each cerebellar voxel to the features that had the most similar profile of functional activation, producing a map that revealed a structured, bottom-up organisation of the cerebellum (Figure 8A). Of the 11 features, three were spatially aligned with regions of the cerebellum that typically activate in response to classical motor features; these were left hand presses, right hand presses, and saccadic eye movements. Specifically, two of the three features were localised to the left and right "hand knob" regions of the anterior and posterior cerebellum (Figure 7A) while the third feature was localised to the oculomotor vermis. Tasks that elicited a large number of saccadic eye movements (i.e. visual search, spatial map, theory of mind, and mental rotation) loaded most strongly onto the feature in the oculomotor vermis, while tasks that had been assigned to the left and right hands were most strongly weighted by the left and right lateralised features that were spatially localised to lobules V, VI, and VIIIb (Figure 7B).

Beyond these motor features, there appeared to be medial-to-lateral subdivisions, most dominant in Crus I and II and lobule VIIb, regions that are typically associated with higher-level cognitive functions. A task loading matrix (Figure 8B) characterises the loadings of each task condition onto the 11 features. Working memory tasks (i.e. verbal and object N-Back, spatial map) loaded most strongly onto the left lateralised feature in hemispheric Crus I and II; dynamic viewing tasks (i.e. romance, landscape, nature movie tasks and the biological motion processing task) were strongly weighted by the left lateralised feature in medial Crus I and II; word-dominant tasks (i.e. theory-of-mind, verb generation) loaded most strongly onto the right lateralised feature in medial-to-lateral Crus I and lobule VIIb and medial Crus II; social cognitive tasks (i.e. theory-of-mind, romance movie) were heavily weighted by the right lateralised feature in medial-to-lateral Crus I and II; mentalising tasks (i.e. spatial navigation, motor imagery) were strongly weighted by the right lateralised feature in hemispheric Crus I and II and lobule VIIb and action tasks (i.e. action observation, motor sequence) loaded strongly onto a distributed set of somatomotor regions in medial lobule VI and bilaterally in medial lobule VIIIa and medial-to-lateral lobule VIIIb.

A.
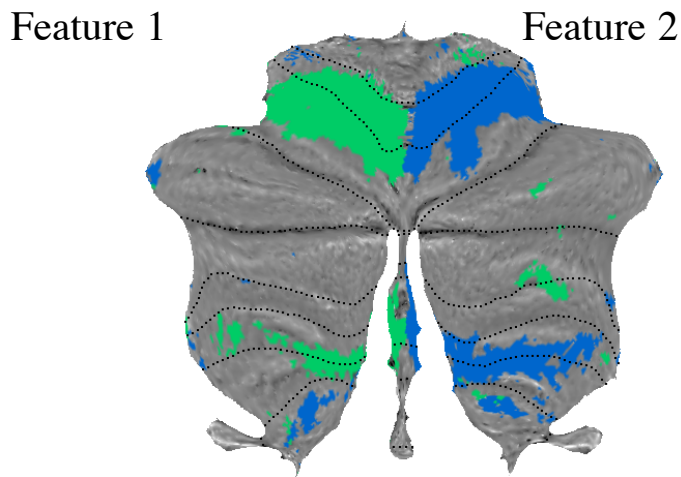
Feature 1   Feature 2

B.
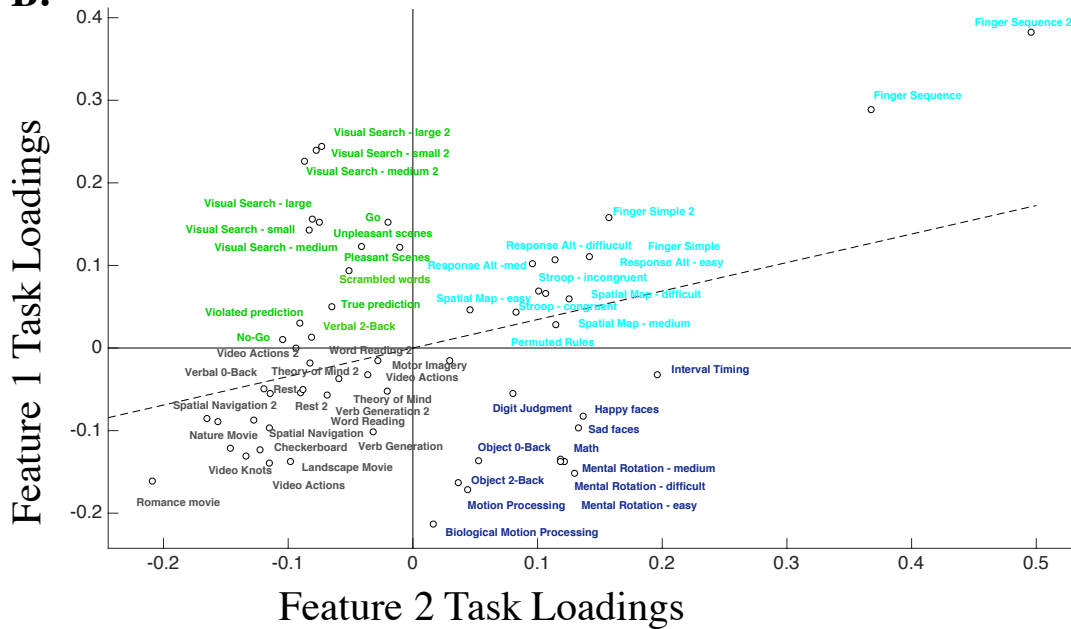
Figure 7. (A) Task loadings onto motor features, derived using a bottom-approach. Features 1 and 2 were localised to the left and right motor regions of the cerebellum. Dashed lines represent lobular boundaries (I-X). (B) Tasks assigned to the left hand (green) loaded onto feature 1, tasks assigned to the right hand (blue) loaded onto feature 2, bimanual tasks (cyan) loaded strongly on both features while non-response dependent tasks (black) did not load strongly onto either feature 1 or 2.

25

A.

Left Hand Responses
Motor Sequence
Visual Search
Affective Processing
Prediction
Go-No-Go

Oculomotor
Visual Search
Spatial Map
Mental Rotation
Theory of Mind

Right Hand Responses
Motor Sequence
Object N-Back
Mental Rotation
Emotional Processing
Arithmetic
Biological Motion Processing

Working Memory
Spatial Map
Object N-Back
Verbal N-Back
Mental Rotation

Verbal Fluency
Theory of Mind
Verb Generation

Dynamic Viewing
Romance Movie
Nature Movie
Biological Motion
Processing

Social Cognition
Theory of Mind
Romance Movie

Mentalising
Spatial Navigation
Motor Imagery

Salience
Romance Movie
Nature Movie
Affective Processing
Emotional Processing

Action
Action Observation
Motor Sequence

B.

Row labels (top to bottom): No-Go, Go, Theory of Mind, Video Actions, Video Knots, Unpleasant Scenes, Pleasant Scenes, Math, Digit Judgment, Checkerboard, Sad Faces, Happy Faces, Interval Timing, Motor Imagery, Finger Simple, Finger Sequence, Verbal 0-Back, Verbal 2-Back, Object 0-Back, Object 2-Back, Spatial Navigation, Stroop – Incongruent, Stroop – Congruent, Verb Generation, Word Reading, Visual Search – Small, Visual Search – Medium, Visual Search – Large, Rest, Rules, True Prediction, Violated Prediction, Scrambled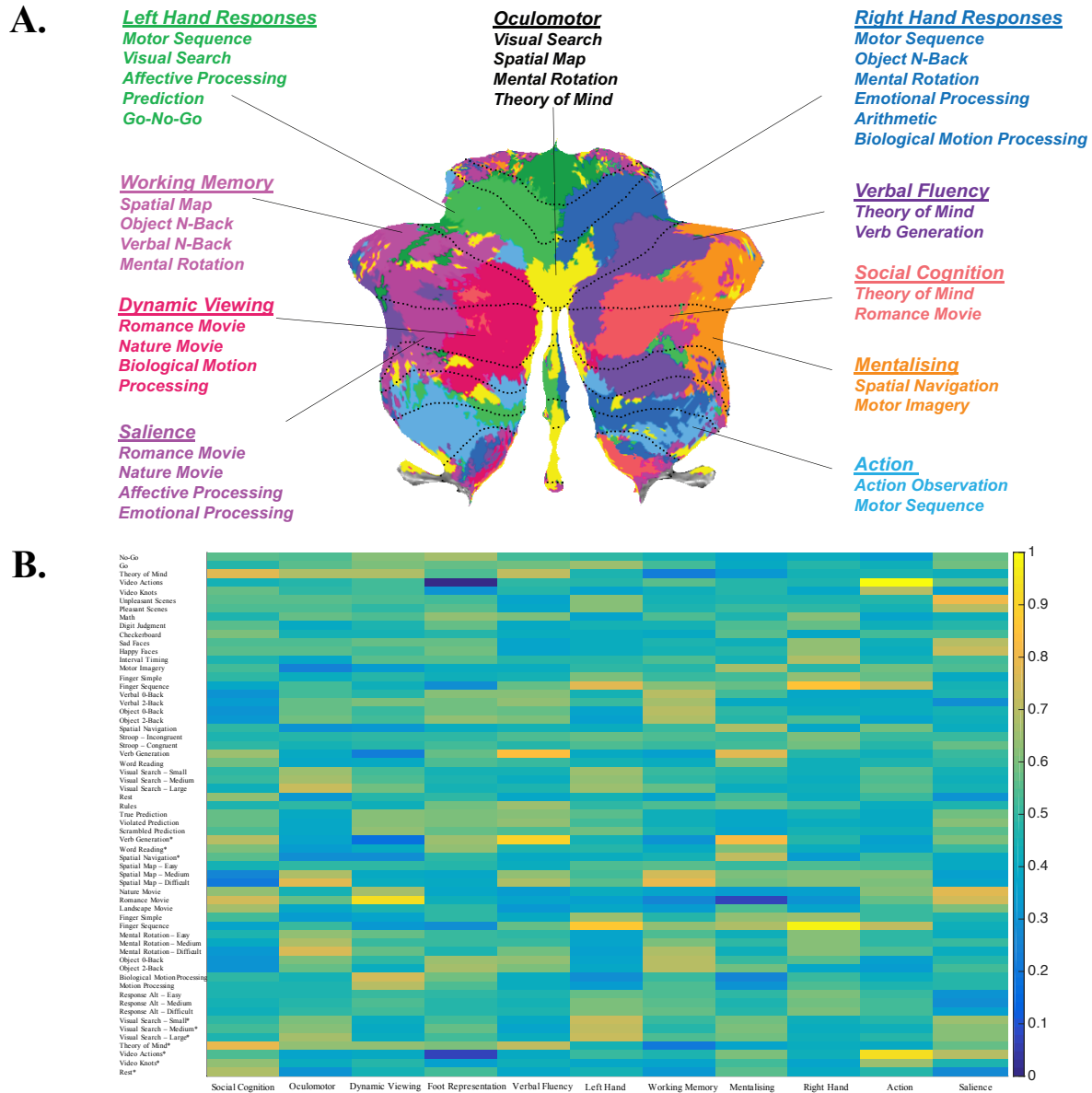 Prediction, Verb Generation*, Word Reading*, Spatial Navigation*, Spatial Map – Easy, Spatial Map – Medium, Spatial Map – Difficult, Nature Movie, Romance Movie, Landscape Movie, Finger Simple, Finger Sequence, Mental Rotation – Easy, Mental Rotation – Medium, Mental Rotation – Difficult, Object 0-Back, Object 2-Back, Biological Motion Processing, Motion Processing, Response Alt – Easy, Response Alt – Medium, Response Alt – Difficult, Visual Search – Small*, Visual Search – Medium*, Visual Search – Large*, Theory of Mind*, Video Actions*, Video Knots*, Rest*

Column labels: Social Cognition, Oculomotor, Dynamic Viewing, Foot Representation, Verbal Fluency, Left Hand, Working Memory, Mentalising, Right Hand, Action, Salience

Figure 8. Comprehensive Map of Functional Organisation (A) and Task Loading Matrix (B). A bottom-up approach (using ICA) identified 11 features that characterised cerebellar organisation in a maximally independent fashion (A). A "winner-take-all" approach was used to assign different parts of the cerebellum to specific features. The features were tentatively semantically labelled based on their task-activity profiles (see B). Task conditions that strongly loaded onto these features are listed below each semantic label and are coloured in brighter colours in the task loading matrix. Dashed black lines represent lobular boundaries (I-X).

3.5 Functional Boundaries Do Not Coincide with Lobular Assignment

It is the current standard in the literature to assign functional activation in the cerebellum to lobular compartments (Figure 9A). However, it is not entirely clear that the functional boundaries (Figure 8A; coloured regions) coincide with the lobular compartments (Figure 9A). Therefore, to determine whether the functional borders closely corresponded to the widely adopted lobular nomenclature, we generated 1000 random tessellations of the cerebellar surface (Figure 9B; example voronoi map) and then used a G-test to quantify the overlap between each of the random tessellations and the bottom-up functional map. Similarly, we performed a G-test between the lobular tessellation and the bottom-up functional map to determine the extent to which the borders overlapped. Using the overlap estimates of the random tessellations as a null model, we found that the lobular assignment did no better than chance at estimating the functional borders of the bottom-up functional map (Figure 9C).

This result indicates that a lobular assignment, which is the current nomenclature for localising functional activation, is not entirely valid for studying functional topography of the cerebellum. Rather, a functional parcellation would appear to be a more favourable alternative.
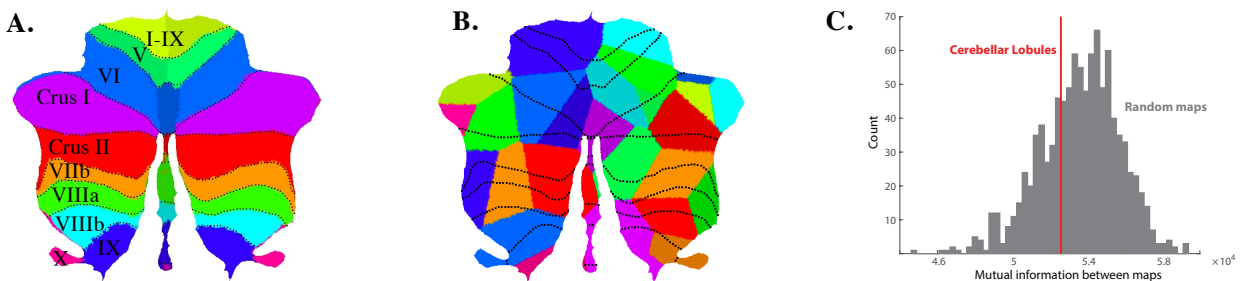

Figure 9. *Lobular versus Functional Parcellation. Functional boundaries within the comprehensive bottom-up map do not align with either a lobular compartmentation (A) or a random tessellation (B) of the cerebellar surface (C).*

4. Discussion

4.1 Summary of Approach and Results

The aim of this study was to provide a comprehensive map of functional organisation of the cerebellum, using a bottom-up feature modelling approach. We employed an extensive task battery (61 task conditions) on the same set of subjects, across 4 independent scanning sessions to leverage the known functional heterogeneity of this structure. In determining a functional organisation of the cerebellum, we demonstrated that a rich assortment of task conditions, spanning multiple cognitive, motor, and affective domains, elicited a functional topography in the cerebellum that was reliable across subjects and sessions. To our knowledge, this is the most exhaustive task battery to be tested on the same set of subjects, making this work the veritable "look-up table" for functional topography in the cerebellum. Furthermore, we also showed that there is a latent structure in the cerebellum that is demarcated by clear functional boundaries. We also demonstrated that these functional boundaries, as defined by a bottom-up feature model, do not respect lobular boundaries, the nomenclature widely adopted in the literature. The latter result has important implications for future studies, namely it motivates the field to adopt a nomenclature that corresponds to a functional rather than a lobular assignment.

4.2 Functional Topography Relative to Previous Investigations

Our results substantiate many previous investigations, which have reported cerebellar involvement during motor, cognitive, and affective tasks (see Stoodley, 2012 for a review). Namely, we confirmed, using univariate contrast analysis and bottom-up feature modelling, that there is a spatially ordered projection of functional activation to specific locations on the cerebellar cortex. These activations extended far beyond a basic motor organisation to the following domains: language, working memory, action, social cognition, and natural viewing.

Basic Motor Organisation
Both the motor feature maps and the latent feature map confirmed a basic motor organisation in the cerebellum. Left and right hand movements activated "hand knob" regions (lobules V/VI and VIIIb) of the human cerebellum (Wiestler et al. 2011) while saccadic eye movements were localised to the oculomotor vermis (vermal lobules VI and VIIa). These results are in line with previous primate lesion work (Takagi et al. 1998) and task-evoked fMRI work (Nitschke et al. 2004). Furthermore, these somatotopic maps were also consistent with connectivity studies, which have shown strong co-activation between motor "hand knob" regions of the cerebral cortex and the cerebellum as well as the occipital lobe (specifically the lingual gyrus) and the oculomotor vermis of the cerebellum (Buckner et al. 2011). We know from polysynaptic tracing data from non-human primates that the cerebral and cerebellar motor cortices are connected in the form of a closed-loop circuit, supporting the orderly functional mapping between the cerebral cortex and the cerebellum. These results serve to validate the functional specialisation of the cerebellar motor cortex (V/VI lobular boundary) for finger movements, and the oculomotor vermis as the region activated for saccadic eye movements.

Language
We observed a lateralisation of activation to the right posterolateral cerebellum evoked by the verb generation task, a finding that has been supported by both clinical (Ackermann et al., 1992) and neuroimaging literatures (Fiez and Raichle, 1997; Lurito et al. 2000) as well as a meta-analysis (Stoodley and Schmahmann, 2009). In addition, the bottom-up modelling approach also identified a right-lateralised "verbal fluency" feature for which verb generation and theory of mind were most strongly weighted. Indeed, this latent variable is concordant with earlier studies reporting right-lateralised activation in response to verbal fluency tasks (Petersen et al. 1988, Raichle et al. 1994). Finally, semantic predictability and prediction violations were associated with increased bilateral activation in Crus I and II consistent with the results reported by Moberget et al. (2014) and D'Mello et al. (2017).

Working Memory
Verbal and picture N-Back paradigms, along with a newly devised spatial map task, bilaterally activated the hemispheres of Crus I and II. This rather stereotyped pattern of activation has been reliably evoked by previous working memory studies (see Desmond et al. 1997; Diedrichsen and Zotow, 2015; Fiez et al. 1996; Honey et al. 2000; LaBar et al. 1999; Tomasi et al. 2005; Valera et al. 2005). Further, the bottom-up modelling approach identified a "working memory" feature, left lateralised to Crus I and II. All working memory tasks (i.e. spatial map, verbal and object N-Back) were most strongly weighted by this feature, perhaps suggesting a functional specialisation of this reason for working memory processes.

Executive Function
Many studies have reported cerebellar activation in response to executive function tasks (Blackwood et al. 2004; Harrington et al. 2004; Rao et al 1997). However, as executive function is a relatively high-level concept, it is difficult to pinpoint sub-regions of the cerebellum that activate in response to "pure" measures of executive function. Cerebellar regions recruited by executive functioning also subsume regions involved in processing task-specific information. For example, the spatial map task, here considered a working memory task, may also be regarded as an executive function task. A meta-analysis by Stoodley and Schmahmann (2009) reported a distributed pattern of activation in response to executive function tasks, that included bilateral activations in lobule VI, Crus I, and VIIb. In the current work, classical executive function tasks such as the stroop task did not show strong activations much beyond the motor domain while the go condition of the go/no-go task showed some bilateral activation of the Crus I and II hemispheres. Another executive function task, the permuted rules task, which leverages logical reasoning as well as sensory discrimination, was right lateralised to Crus I and II in a medial-to-lateral fashion. Executive function tasks were not weighted strongly by any of the non-motor features of the latent feature map, indicating that the processes underlying these tasks are not heavily weighted by the cerebellum.

Social Cognition
A plethora of neuroimaging studies and meta-analyses have implicated the cerebellum in social cognitive processing (see Kober et al. 2008; Molenberghs et al. 2012; Svoboda et al. 2006). A meta-analysis by Van Overwalle et al. (2014) reported that of all social cognitive tasks (i.e. theory of mind, morality, mentalising, mirroring/observation), it was abstraction in mentalising that elicited the most robust cerebellar activity, as reported by 67%-100% of all analysed studies.

Abstract mentalising, for the purposes of the meta-analysis, was defined as the act of thinking introspectively about the future as well as reflecting on the autobiographical past. In the current work, the spatial navigation task, along with rest elicited activity patterns similar to the ALE analysis points reported by Van Overwalle et al. (2014). Rest activated medial portions of Crus I and II, while spatial navigation activated lobule IX, regions of the cerebellum that functionally correlate with activity in the default mode network (Buckner et al. 2011; Habas et al. 2009; Nguyen et al. 2016).

Natural Viewing
Dynamic and ecologically valid contexts provide a powerful approach to studying the neural basis of social cognition, emotion, and perception (see Hasson et al. 2008a; Hasson and Honey, 2012). Indeed, to our knowledge, there is only one such study that has demonstrated reliable cerebellar activation in response to an engaging and salient movie (Nguyen et al. 2016). We found that movie tasks (landscape, romance, and nature movies) bilaterally activated medial Crus I and II, as well as inferior HVIIIb/HIX, substantiating the findings reported by Nguyen et al. (2016). In the latent feature map of functional organisation, movie tasks are heavily weighted by the "dynamic viewing" feature, which is left-lateralised to medial Crus I and II.

Low-Level Features
Low-level auditory and visual tasks failed to activate the cerebellum. However, this finding is unsurprising, largely due to the fact that there are no anatomical connections between either the inferior temporal cortex or the primary visual cortex, and the cerebellum.

Which findings were not supported by the current work?
There were some findings that have been consistently reported in the literature that were not supported by the current work. First, the theory of mind task, tested in both studies, was very successful in eliciting reliable activity patterns in medial Crus I and II. However, this finding diverges rather drastically from the Van Overwalle et al. (2014) meta-analysis, which did not find robust cerebellar activity during theory of mind tasks. Second, there was little to no evidence for the lateralisation of spatial processing tasks to the left hemisphere of Crus I and II and lobule VIIb, as revealed in the meta-analysis conducted by Stoodley and Schmahmann (2009). Similarly, emotional and affective processing tasks elicited marginal activations in vermal Crus I and II, despite strong evidence from clinical and neuroimaging studies for a "limbic" cerebellum. These discrepancies are likely due to a whole host of factors, namely differences in task design, use of novel stimuli, and extensive task training.

We demonstrated using univariate contrast analysis, representational similarity analysis, and a data-driven, bottom-up approach that the cerebellum is functionally heterogeneous for a wide range of cognitive, motor, and affective processes. Further, we corroborated existing evidence for a motor/non-motor dichotomy in the cerebellum, by demonstrating that the anterior lobe is functionally specialised to process motor-related function, while the posterior lobe (Crus I and II in particular) is strongly engaged in higher-order cognitive processes. This gross functional subdivision of motor/non-motor function in the cerebellum is supported by anatomical findings in non-human primates, which indicates that there are separate closed-loop circuits between distinct regions of the cerebral cortex and sub-regions of the cerebellum (i.e. cortical-ponto-cerebellar and cerebellar-thalamic-cortical tracts) that are likely functionally specialised for

motor and non-motor function alike. Functional neuroimaging work also corroborates these anatomical findings by demonstrating that hemispheric lobules Crus I and II are functionally connected with prefrontal and parietal regions, while lobules V and VIIIb share a similar functional profile with primary motor and somatomotor regions of the cerebral cortex (Buckner et al. 2011; Habas et al. 2009; Krienen and Buckner, 2009; O'Reilly et al. 2010). Overall, our results not only showed evidence for a clear alignment of motor and non-motor function to anterior and posterior lobes respectively, but they extended beyond this dichotomy to demonstrate a rich mosaic of cerebellar functional specialisation.

4.3 Functional Boundaries of the Cerebellum

However, it is the current standard in the literature to assign functional activation not only to anterior and posterior lobes, but also to lobular compartments (I-X). While many previous investigations have shown alignment of motor and non-motor function to the anterior and posterior lobes of the cerebellum, further functional subdivisions, based on lobular boundaries, are more opaque. Indeed, recent studies have observed that there are prominent functional differences along the medial-to-lateral extent of a single lobule for many task-evoked activations (Diedrichsen & Zotow, 2015), while another study recently showed that functional topography often spans multiple lobules (Buckner et al. 2011). By leveraging the latent structure of the cerebellar activity patterns to derive a bottom-up map of functional organisation, we were able to determine that functional boundaries follow a medial-to-lateral pattern that does not coincide with lobular boundaries. This functional organisation, which drastically diverges from lobular compartmentation, calls into question the validity of the current nomenclature for understanding functional topography in the cerebellum.

Given that a plethora of neuroimaging studies have reported cerebellar activation in response to numerous cognitive, motor, and affective tasks, it is perhaps surprising that functional boundaries within this structure have not yet been established. There are two main reasons for this. The first is likely related to the task paradigms employed by previous studies. A primary aim of many cerebellar neuroimaging studies is to test for a cerebellar function and this is usually done by examining the activity patterns elicited by a controlled set of task conditions. However, this restricted task-mapping approach, while useful for testing specific hypotheses about cerebellar function, cannot explore the full breadth of functional activation in the cerebellum. Therefore, unless a condition-rich dataset is employed, the success of using a bottom-up approach to derive a comprehensive functional map is severely compromised. Second, by analysing functional activation on the volume, an entire visual story is missed. A strength of the current work is that all feature and task-evoked activations were presented on a continuous cerebellar surface. By adopting these surface-based visualisation approaches, it is easy to appreciate the full functional diversity of activation elicited in the cerebellar cortex.

4.5 Limitations of the Current Work

While this work took many leaps, there were also a few limitations to our approach. First, the latent feature map that we present was derived on group-averaged activation estimates, rather than on an individual subject level. Our results showed that there was considerable and true inter-subject variability, accounting for approximately 60% of the systematic variance of the task-

evoked activity maps. Therefore, by calculating a bottom-up feature model on group-averaged activation estimates, we miss a vast proportion of the variance that is idiosyncratic to each individual subject. The aim of this work was not to provide individual-subject functional maps. However, ultimately, it will be very important to understand whether inter-subject differences yield vastly different latent feature maps, especially if we are to propose an overhaul of the lobular existing nomenclature.

Second, we omitted a top-down approach of feature-based modelling in deriving a comprehensive functional map. Unlike the bottom-up approach, which leverages latent variables, the top-down approach adopts known mental concepts as features. The advantage of the top-down approach is that features always have known labels, while the bottom-up approach provides features that do not easily translate into meaningful psychological constructs. We chose a bottom-up approach based on preliminary findings (not shown here) that it outperformed a top-down approach in predicting the largest proportion of cerebellar variance. However, it would be interesting to further explore the top-down approach in future analyses to determine whether top-down and bottom-up feature-based approaches yield equivalent functional maps of the cerebellum.

4.4 Understanding the "What" and "Why" of Cerebellar Heterogeneity

Like most previous studies, the current results depict "how" the cerebellum activates for a diverse range of tasks. However, the spatial mapping of activity patterns does not inform us on "what" the cerebellum contributes to the performance of these tasks, nor does it demonstrate "why" the cerebellum is organised along functional rather than lobular boundaries. Ultimately, the holy grail of cerebellar research is to determine the "what" and "why" of cerebellar functioning, above and beyond the "how".

Molecular work provides some key insights into "why" the cerebellum is organised along functional boundaries that do not coincide with lobular compartments. While the cerebellum can be grossly divided into lobes and lobules, it can also be subdivided mediolaterally into zones or stripes (Hawkes & Mascher, 1994; Hawkes, 1997, Herrup & Kuemerle, 1997; Voogd & Glickstein, 1998). Specifically, it is thought that there are seven pairs of sagitally organised bands located on either side of the cerebellar midline that have characteristic afferent and efferent projections. The boundaries of these bands, which are demarcated by different patterns of gene expression, are not only independent of lobulation but are also thought to be functionally significant, given the heterogeneity of Purkinje cell afferents. Many studies have demonstrated that the compartmentation of the cerebellar cortex, evident from gene expression, aligns with an afferent topography of cerebellar function (Oscarsson, 1979; Voogd and Ruigrok, 1997). For example, there is a close correspondence between Purkinje cell projections in the anterior lobe and different response latencies (Oscarsson, 1979), while boundaries of tactile receptive fields in the cerebellum closely align with the expression of the zebrin II molecular marker in parasagittal stripes. Although it is unknown how functional heterogeneity in the cerebellum relates to the processing of afferent information, it is possible that the mosaic anatomical organisation of the cerebellar cortex is the scaffold on which cerebellar function is organised. A medial-to-lateral organisation of functional boundaries, as indicated by the current work, may be supported by the diverse phenotypes of individual cell types in the cerebellar cortex.

Diverse theories have been proposed in an attempt to explain "what" the cerebellum contributes to cognitive, motor, and affective processing. One dominant theory postulates that the cerebellum executes one universal computation on heterogeneous afferent input arriving from the cerebral cortex (universal cerebellar transform, see Schmahmann, 1991, 2000; internal model theory, see Ito, 2006). This theory of a universal computation arises from clinical findings of domain-specific impairments in language, spatial processing, and executive functioning following localised cerebellar lesions (Schmahmann and Sherman, 1998). Additional theories posit a cerebellar role for error detection (Andreasen and Pierson, 2008), timing (Ivry et al. 2002), sequencing (Molinari et al. 2008), and task difficulty (Salmi et al. 2010; Xiang et al. 2003), mechanisms that are relevant to a host of cognitive processes (i.e. working memory, language, and spatial processing).

We now have a comprehensive map of functional organisation in the cerebellum which lends itself nicely to answering these "why" and "what" questions. However, at present, it is unlikely that we will be able to answer the "why" question, given the considerable challenges that would accompany the mapping of functional topography to differential gene expression in the human cerebellar cortex. However, we are now in a favourable position to better understand "what" the cerebellum contributes to cognitive processes.

4.6 An Outlook to the Future of Cerebellar Neuroimaging

To date, the utility in understanding "what" the cerebellum contributes to cognitive processes has been compromised for two major reasons. First, many studies of the cerebellum concentrate on a single functional domain in testing for a cerebellar contribution to cognitive processing. By focusing on a single task domain, this approach fails to explore the entire breadth of functional activation, making it very difficult to make strong inferences about more general principles of cerebellar function. Second, function is often attributed to cerebellar activation without simultaneously considering activity in the cerebral cortex. Given that each cerebellar region is tightly interconnected with specific regions of the cerebral cortex, it is unlikely that we can understand the importance of activation in sub-regions of the cerebellum without simultaneously considering corresponding cerebral activation. For example, consider the observation that a cerebellar region shows increased activity during the violation of a linguistic prediction task. One might infer that this part of the cerebellum is involved in predictive processes, perhaps in generating the prediction or in detecting the violation of a prediction. However, if one observed the same difference in the cortical region projecting to that cerebellar region, this hypothesis would be drastically weakened. Rather, the function (linguistic prediction or linguistic error detection) might occur upstream of the cerebellum or emerge from interactions across the cortical-cerebellar loop, but not the cerebellum per se. Therefore, to gain insights into the specific functional contributions of this structure, future studies should build cortical-cerebellar connectivity models to determine whether cerebellar activity can be predicted on the basis of activity patterns in the cerebral cortex. Fortunately, the current work offers the perfect condition-rich dataset on which these cortical-cerebellar models can be trained and tested, paving the way for novel insights into unique cerebellar computations.

5. Conclusion

5.1 Two Main Contributions to the Field

The sum of this work contributes two major insights to the field. First, we have created the most expansive task battery in the literature (61 task conditions) and used it to show that the cerebellum is uniquely and reliably activated for a plethora of cognitive, motor, and affective tasks. We propose this work as the veritable "look-up table" for functional topography of the cerebellum. Second, by using a rich task battery to bring the cerebellar cortex into as many diverse activation states as possible, we can use a bottom-up approach to establish a comprehensive map of functional organisation. By exploiting the latent structure of cerebellar activation, we show that functional boundaries do not coincide with lobular boundaries. This is an important insight as classically; fMRI activations are reported as being localised to specific lobules. Going forward, we suggest a revision of the lobular nomenclature to include functional subdivisions. In addition, we also recommend that future neuroimaging studies use a spatial normalisation method, along with a surface-based visualisation approach (see Diedrichsen and Zotow, 2015), to allow for full appreciation of the functional heterogeneity of the cerebellar cortex. Finally, by devising a condition-rich task battery, this work has laid the foundation for discovering conclusive principles of cerebellar function. Future work should leverage insights from this dataset to build cortical-cerebellar connectivity models in order to test domain-general hypotheses about the function of the cerebellum.

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Trinity College Dublin
First-Class Honours Degress (B.A), Psychology and French
Advisor: Redmond O'Connell, Ph.D.

Western University, Canada
M.Sc. Neuroscience
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Scholarships

Postgraduate Scholarship of Ireland ($141,000) awarded by the Irish
Research Council (declined)

Ussher Fellowship ($84,000), awarded annually by Trinity College
Dublin (declined)

Shortlisted for a Fulbright Student Award

Wellcome Trust Biomedical Vacation Scholarship ($2,500)

Junior Freshman Prize ($100) awarded by Trinity College Dublin
For first-class honours in Freshman examinations

Entrance Scholarship ($450) awarded by Trinity College Dublin

Irish Scholarship ($60,000), awarded by the Department of Education and Skills

Research Experience

Professor Orla Hardiman's Laboratory, School of Medicine at Trinity College Dublin

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