Bridging the gap between functional and anatomical features of cortico-cerebellar circuits using Meta-Analytic Connectivity Modelling

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# Abstract

Theories positing that the cerebellum contributes to cognitive as well as motor control are driven by two sources of information: (1) studies highlighting connections between the cerebellum and prefrontal as well as motor regions, (2) functional neuroimaging studies demonstrating cerebellar activations evoked during the performance of cognitive and motor tasks. However, almost no studies to date have combined these two sources of information and investigated cortico-cerebellar connectivity during task performance. Through the use of a novel neuroimaging tool (Meta-Analytic Connectivity Modelling) we demonstrate for the first time that cortico-cerebellar connectivity patterns seen in anatomical studies and resting fMRI are also present during task performance. Consistent with human and non-human primate anatomical studies cerebellar lobules Crus I and II were significantly co-activated with prefrontal and parietal cortices during task performance, whilst lobules HV, HVI, HVIIb, and HVIII were significantly co-activated with regions around the pre- and postcentral gyrus. An analysis of the behavioural domains showed that these circuits were driven by distinct tasks. Prefrontal-parietal-cerebellar circuits were more active during cognitive and emotion tasks whilst motor-cerebellar circuits were more active during action execution tasks. These results highlight the separation of prefrontal and motor cortico-cerebellar loops during task performance, and further demonstrate that activity within these circuits relates to distinct functions.

# Introduction

A number of authors have suggested that in order to understand the functional properties of a brain region one must understand its anatomical features and connections ([Crick and Koch, 2005](#_ENREF_14); [Eickhoff and Grefkes, 2011](#_ENREF_21); [Passingham et al., 2002](#_ENREF_50)). A great deal is known about the intrinsic microstructure of the cerebellum ([Eccles et al., 1967](#_ENREF_18)), and a large number of studies have mapped cortico-pontine and cortico-cerebellar connections in humans and non-human primates (see [Ramnani, 2011](#_ENREF_55); [Strick et al., 2009 for review](#_ENREF_68)). Theories of cortico-cerebellar information processing have been in a large part driven by our understanding of cortico-cerebellar connectivity. Studies in both humans ([Buckner et al., 2011](#_ENREF_9); [Habas et al., 2009](#_ENREF_30); [Krienen and Buckner, 2009](#_ENREF_36); [O'Reilly et al., 2010](#_ENREF_49); [Ramnani et al., 2006](#_ENREF_56)) and non-human primates ([Kelly and Strick, 2003](#_ENREF_35); [Middleton and Strick, 2000](#_ENREF_43); [Middleton and Strick, 2001](#_ENREF_44); [Schmahmann and Pandya, 1997](#_ENREF_64)) have repeatedly demonstrated that the cerebellum receives inputs from a wide range of cortical territories including (but not restricted to) the premotor and primary motor cortices, medial and dorsal prefrontal cortex, and parietal cortex. Studies in nonhuman primates have also suggested that prefrontal and motor cortico-cerebellar circuits are completely independent of one another and do not exchange information at any point within the loop except for within the frontal lobe. Kelly and Strick ([2003](#_ENREF_35)) showed in non-human primates that the arm area of the primary motor cortex projected to cerebellar lobules HV, HVI, HVIIb, and HVIII, whilst tracer label injected into the dorsal bank of the sulcus principalis (putatively Walker’s Area 46) terminated in cerebellar lobules Crus I and Crus II. These same connections have been shown in humans using resting state fMRI ([Buckner et al., 2011](#_ENREF_9); [Habas et al., 2009](#_ENREF_30); [Krienen and Buckner, 2009](#_ENREF_36); [O'Reilly et al., 2010](#_ENREF_49)). Given that the cerebellum receives inputs from prefrontal and parietal regions that are known to process abstract information ([Badre and D'Esposito, 2009](#_ENREF_3)), and that this information does not integrate with motor cortico-cerebellar circuits, it would suggest that the cerebellum is not solely processing motor information. However, in order to further develop theories of cortico-cerebellar connectivity it is necessary to corroborate these findings with task-based information.

Along with studies of anatomical and functional connectivity, task-based functional neuroimaging studies have provided a wealth of evidence suggesting that the cerebellum is involved in processing both motor and non-motor information ([see Stoodley, 2012 for review](#_ENREF_65)). Petacchi et al., ([2005](#_ENREF_52)), Moulton et al., ([2010](#_ENREF_45)), and Stoodley and Schmahmann ([2009](#_ENREF_66)) have all conducted meta-analyses investigating task-dependent cerebellar processing. Whilst Petacchi et al., (2005) and Moulton et al., (2010) focussed on auditory and pain processing respectively, Stoodley and Schmahmann ([2009](#_ENREF_66)) investigated cerebellar processing during a variety of tasks ranging from cognitive to motor to emotion. They found that cerebellar lobules Crus I and II were active in studies investigating executive function, working memory, and language tasks, whilst motor control tasks consistently activated cerebellar lobules HV, HVI, and HVIII. This work thus provides further evidence that distinct regions of the cerebellum process distinct forms of information, both motor and associative. Although these findings are in keeping with cortico-cerebellar anatomy (i.e. cerebellar lobules interconnected with prefrontal cortex are active during associative tasks) it is essential to investigate cortico-cerebellar connectivity during task performance in order to ascertain the roles of cortico-cerebellar circuits in cognitive and motor control.

This study uses a novel neuroimaging tool (Meta-Analytic Connectivity Modelling (MACM)) to integrate connectivity information with behavioural information and as such extend our understanding of cortico-cerebellar information processing. MACM is a novel neuroanalytic tool that assesses brain-wise co-activation patterns of an anatomical region across a large number of databased neuroimaging results ([Eickhoff et al., 2011](#_ENREF_20); [Laird et al., 2009a](#_ENREF_38)). First, we identified for each voxel of the seed VOI those experiments in the BrainMap database that reported activation at that particular location. By performing an Activation Likelihood Estimation (ALE) meta-analysis over these experiments, we can generate a whole brain activation map showing all the brain regions that are active when voxels in the seed VOI are active. Differences in the co-activation patterns of the respective VOIs can be tested by directly contrasting the regional MACM patterns. Finally, in order to confirm a functional separation between the anatomical VOIs selected in this study we can assess the behavioural domain and paradigm class meta-data of experiments associated with the ensuing clusters. This manuscript describes the application of MACM to cortico-cerebellar connectivity and the ensuing behavioural differences.

# Methods

## Cerebellar VOIs

 Cerebellar lobules of interest were selected based on previous studies of primate cortico-cerebellar connectivity, specifically Kelly and Strick ([2003](#_ENREF_35)). Kelly and Strick ([2003](#_ENREF_35)) is the only study performed on non-human primates that traced anatomical connections from regions of the frontal lobe (dorsal bank of the sulcus principalis ([Walker’s Area 46; Walker, 1940](#_ENREF_71)) and the hand/arm region of the primary motor cortex) all the way to the cerebellar cortex. We decided to restrict our analyses to cerebellar lobules found in Kelly and Strick (2003), namely vermal and hemispheric lobules V, VI, Crus I, Crus II, VIIb, VIIIa and HVIIIb ([accounting for 86.34% of the cerebellar cortex; Diedrichsen et al., 2009](#_ENREF_16)). There are also additional practical reasons to restrict our analyses to these lobules. For example, many fMRI studies do not include the very posterior lobules of the cerebellum in the field of view, thus there are fewer studies reporting activations within lobules IX and X. Anterior lobules I-IV can also be contaminated by non-cerebellar signal originating from the occipital lobes directly above them, i.e., the ventral visual cortex ([Diedrichsen, 2006](#_ENREF_15)). Cerebellar lobular masks were extracted from the probabilistic cerebellar atlas of Diedrichsen et al., ([2009](#_ENREF_16)) and combined to create masks of interest (see Figure 1). For example, the seed mask for the analysis of cerebellar “motor’ lobules was created by combining masks of cerebellar lobules V, VI, VIIb, and VIII (red in fig 1). The atlas of Diedrichsen et al ([2009](#_ENREF_16)) conforms to the anatomical landmarks outlined by Larsell and Jansen ([1972](#_ENREF_42)). **Using these cerebellar lobules as seeds we will investigate differences in task-based connectivity between motor-projecting cerebellar lobules (V, VI, VIIb, VIII) and prefrontal-projecting cerebellar lobules (Crus I and II). We will additionally investigate differences in task-based connectivity between anterior motor-projecting cerebellar lobules (V, VI) and posterior motor-projecting cerebellar lobules (VIIb, VIII), given that posterior motor-projecting cerebellar lobules have selectively expanded in humans compared to non-human primates (**[**Balsters et al., 2010**](#_ENREF_4)**).**

## Meta-Analytic Connectivity Modelling

The BrainMap database (www.brainmap.org; [Fox and Lancaster, 2002](#_ENREF_28); [Laird et al., 2011](#_ENREF_37); [Laird et al., 2009a](#_ENREF_38); [Laird et al., 2005](#_ENREF_40)) was employed for the retrieval of relevant neuroimaging experiments. At the time of assessment, the database contained coordinates of reported activation foci and associated meta-data of over 11,000 neuroimaging experiments. For our analysis, only whole brain studies of healthy subjects reporting activation in standard stereotaxic space were considered, while all experiments that investigated age, gender, handedness or training effects or involved a clinical population were excluded. As the first step of the analysis we identified (separately for each seed region) all experiments that featured at least one focus of activation within the respective seed (MNI space). In order to facilitate such filtering, coordinates from Talairach space were converted into MNI coordinates by using Lancaster transformation ([Lancaster et al., 2007](#_ENREF_41)). Then, all experiments activating the currently considered seed were identified. The retrieval was solely based on reported activation coordinates, not on any anatomical or functional label.

Functional connectivity of the different seeds was evaluated using meta-analytic connectivity modelling (MACM; [Robinson et al., 2012](#_ENREF_59); [Robinson et al., 2010](#_ENREF_60)). The key idea behind MACM is to assess which brain regions are co-activated above chance with a particular seed region in functional neuroimaging experiments ([Eickhoff et al., 2010](#_ENREF_22); [Laird et al., 2009b](#_ENREF_39)). MACM entails to first identify all experiments in a database that activate a particular brain region as described above and then test for convergence across (all) foci reported in these experiments. Obviously, as experiments were selected by activation in the seed, highest convergence will be observed in the seed region. Significant convergence of the reported foci in other brain regions, however, indicates consistent co-activation, i.e., functional connectivity with the seed. The whole brain peak coordinates of the identified experiments were downloaded from BrainMap database for each seed region. Coordinates were analysed with the modified activation likelihood estimation (ALE) algorithm ([Eickhoff et al., 2012](#_ENREF_19); [Eickhoff et al., 2009](#_ENREF_23)) to detect areas of convergence. This approach models each focus as a Gaussian distribution reflecting empirical estimates of the uncertainty of different spatial normalization techniques and intersubject variability as a function of the number of subjects. Modelled activation (MA) maps are calculated for each experiment by combining the Gaussian distributions of the reported foci ([Turkeltaub et al., 2012](#_ENREF_69)). Taking the union across these yielded voxel-wise ALE scores that describe the convergence of results at each particular location of the brain. To distinguish ‘true’ convergence between studies from random convergence, i.e., noise, in the proposed revision of the ALE algorithm ([Eickhoff et al., 2012](#_ENREF_19)), ALE scores are compared to an empirical null-distribution reflecting a random spatial association between experiments ([Eickhoff et al., 2012](#_ENREF_19); [Turkeltaub et al., 2012](#_ENREF_69)). The p-value of an observed ALE is then given by the proportion of this null-distribution (precisely, its cumulative density function) corresponding equal or higher ALE values. The ALE maps reflecting the convergence of co-activations with any particular seed region were subsequently thresholded at p<0.05 cluster-level corrected (cluster-forming threshold: p<0.001 at voxel-level) and converted into Z-scores for display.

For further investigation of commonalities and distinctions between the functional connectivity of different seeds, conjunction and difference analyses were performed. For conjunction analysis the minimum statistic ([Nichols et al., 2005](#_ENREF_46)) was used, yielding voxels that showed significant values in both co-activation maps. The result corresponds to the intersection of the (cluster-level corrected) MACM maps ([Caspers et al., 2010](#_ENREF_10)). Difference maps were established by calculating the voxel-wise differences of the Z-scores obtained from the ALE maps of the two MACM analyses. When calculating difference maps, activation foci common to both conditions were removed. The difference maps were then tested against an ALE difference map assuming the null-distribution, which was generated from a random bipartition of the pooled experiments underlying either of the two inspected maps, at p < 0.001 ([Eickhoff et al., 2011](#_ENREF_20); [Rottschy et al., 2012](#_ENREF_61)). To avoid obtaining significant co-activation in voxels of the difference map that do not show significant co-activation on the underlying ALE map, the resulting maps were masked with the main effect of the respective ALE map. Furthermore, only regions with at least 20 cohesive voxels were considered in the resulting difference maps. Finally, anatomical allocation of all results was performed using the SPM Anatomy Toolbox (http://www.fz-juelich.de/inm/inm-1/spm\_anatomy\_toolbox, [Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

## Functional characterization

The functional characterization of the cerebellar regions was based on the ‘Behavioural Domain’ and ‘Paradigm Class’ meta-data categories available for each neuroimaging experiment included in the BrainMap database. Behavioural domains include the main categories cognition, action, perception, emotion, and interoception, as well as their related sub-categories. Paradigm classes categorize the specific task employed ([see http://brainmap.org/scribe/ for the complete BrainMap taxonomy; Fox et al., 2005](#_ENREF_27)).

In a first step, we determined the individual functional profile of each region of interest by using the probability of a psychological process being present given knowledge of activation in a particular brain region. This likelihood P(Task|Activation) can be derived from P(Activation|Task) as well as P(Task) and P(Activation) using Bayes rule. Significance (at p < 0.05, corrected for multiple comparisons using Bonferroni’s method) was then assessed by means of a chi-squared test ([Eickhoff et al., 2011](#_ENREF_20); [Laird et al., 2009b](#_ENREF_39); [Nickl-Jockschat et al., 2011](#_ENREF_47)). Secondly, we contrasted the functional profiles of the different regions of interest with each other. For these comparisons, the analysis was constrained to all BrainMap experiments activating either region. From this pool of experiments, the baserate is the apriori probability of any focus to lie in either of the two compared regions ([Cieslik et al., 2012](#_ENREF_13)). We then compared the occurrence probabilities of the tasks given activation in the one region (rather than in the other cluster) and assessed them by means of a chi-squared test (p < .05, corrected for multiple comparisons using Bonferroni’s method).

# Results

Studies in humans ([Buckner et al., 2011](#_ENREF_9); [Krienen and Buckner, 2009](#_ENREF_36); [O'Reilly et al., 2010](#_ENREF_49)) and non-human primates ([Kelly and Strick, 2003](#_ENREF_35)) have shown that cerebellar lobules HV, HVI, HVIIb, and HVIII receive inputs from primary motor cortex, whilst cerebellar lobules Crus I and Crus II receive inputs from prefrontal and parietal cortices. We begin by establishing whether these connectivity patterns also exist in task-dependent data. The results below are created using masks that are the combination of these cerebellar lobules, however MACM results for individual cerebellar lobules are available in supplemental materials. Results were calculated from the BrainMap database 24th May 2013.

### Connectivity of “motor” lobules

Table 1 lists regions co-activated with cerebellar lobules HV, HVI, HVIIb, HVIII. The BrainMap database contained 1359 experiments (17778 subjects and 19988 foci) which fell within any of the above mentioned cerebellar lobules. The MACM analysis found that regions that covaried significantly with cerebellar “motor” lobules included bilateral precentral and postcentral gyrus (areas 4 and 6), bilateral inferior frontal gyrus (pars opercularis; area 44), Supplementary Motor Area (SMA), bilateral inferior parietal lobule (hIP3), and subcortical structures including the left putamen, the right pallidum, and bilateral thalamus (see Figure 2a).

### Connectivity of “prefrontal” lobules

Table 2 lists regions co-activated with cerebellar lobules Crus I and Crus II. The BrainMap database contained 809 experiments (10683 subjects and 13109 foci) which fell within any of the above mentioned cerebellar lobules. A number of regions within the prefrontal cortex were co-activated with activity in these cerebellar lobules. This included activity in the middle and inferior frontal gyrus, precentral gyrus (area 6), superior medial gyrus (Pre-SMA) and bilateral insula, bilateral inferior parietal lobule, bilateral pallidum, and bilateral prefrontal-projecting regions of the thalamus (see Figure 2c).

### Common connectivity between “motor” and “prefrontal” lobules

Table 3 lists regions co-activated for both “motor” lobules (HV, HVI, HVIIb, HVIII) and “prefrontal” lobules (Crus I and Crus II) as inferred from the conjunction analyses of the two respective MACMs. This analysis revealed a number of regions in the frontal lobe including inferior, middle and superior frontal gyrus, precentral gyrus (Areas 44 and 6) and SMA. Bilateral inferior parietal lobule and right superior parietal lobule and left superior temporal gyrus were also activated. Right pallidum and left putamen, along with bilateral thalamus (Prefrontal projecting) were also active (see Figure 2e).

### Connectivity of “motor” vs. “prefrontal” lobules

Table 4 lists co-activation differences between cerebellar lobules Crus I and Crus II and cerebellar lobules HV, HVI, HVIIb, HVIII. These differences are also illustrated in figure 3. Motor lobules showed greater co-activation with motor regions within the frontal lobe (precentral gyrus and SMA; area 6), along with premotor-projecting regions of the thalamus. There was also greater connectivity with somatosensory regions (areas 1, 2, 3a, 3b), bilateral superior and medial parietal regions, bilateral superior temporal gyrus, and bilateral putamen and pallidum. Prefrontal lobules showed greater co-activation with anterior regions of the frontal lobe (bilateral inferior and middle frontal gyrus (areas 44, and 45)), Pre-SMA, inferior and superior parietal lobule, and angular gyrus.

### Connectivity of Anterior vs. Posterior “motor” lobules

Balsters et al ([2010](#_ENREF_4)) previously demonstrated differences in the evolutionary expansion of posterior cerebellar “motor” lobules (HVIIb and HVIII) compared to anterior cerebellar “motor” lobules (HV and HVI). We therefore used MACM to investigate task-dependent connectivity differences between these sets of cerebellar lobules. The BrainMap database contained 1337 experiments (17414 subjects and 19752 foci) which fell within anterior cerebellar “motor” lobules and 202 experiments (2477 subjects and 3932 foci) which fell within posterior cerebellar “motor” lobules. Table 5 lists co-activation differences between cerebellar lobules HV, HVI and HVIIb, HVIII. These differences are also illustrated in figure 4. Lobules HV and HVI showed greater co-activation with bilateral precentral gyrus (Area 6) and SMA, bilateral postcentral gyrus (areas 3a,b), left superior temporal gyrus, right supramarginal gyrus, bilateral thalamus (prefrontal, premotor and motor regions), left putamen and right palidum. Lobules HVIIb and HVIII showed greater co-activation with anterior regions of the superior medial gyrus (putatively pre-SMA), bilateral inferior frontal gyrus, left thalamus (prefrontal and parietal projecting), and right pallidum.

## Behavioural domains and paradigm classes for cerebellar lobules.

Figure 5 shows the behavioural domains and paradigm classes associated with activations that fell within cerebellar lobules HV, HVI, HVIIb, and HVIII (figure 5a) or Crus I and II (figure 5b) compared to base rate (i.e. the general probability of finding BrainMap activation in the seed), and the differences between these sources (figure 5c). As expected, studies activating cerebellar lobules HV, HVI, HVIIb, and HVIII were typically motor tasks, specifically action execution (see figure 5a). Studies where participants performed overt reading, flexion and extension, drawing and finger tapping activated cerebellar motor lobules greater than chance (Figure 5a). In contrast, studies involving working memory and pain perception activated cerebellar lobules Crus I and II (figure 5b green). Drawing and the Stroop task activated these lobules greater than chance. When comparing these two masks (“motor” vs “prefrontal” cerebellar lobules) we see that motor lobules were active during action execution compared to prefrontal lobules (figure 5c red) whereas attention, working memory and emotion activated “prefrontal” lobules compared to “motor” lobules (figure 5c green). Reading and finger tapping paradigms significantly activated “motor” lobules compared to “prefrontal” lobules whereas the Simon task, Stroop task and passive listening all significantly activated “prefrontal” lobules compares to “motor” lobules (figure 5c green).

Figure 6 illustrates the behavioural domains and paradigm classes that activated cerebellar lobules HV, HVI (figure 6a) and HVIIb, HVIII (figure 6b) compared to base rate, and differences between these sources (figure 6c). Activations within both VOIs were present for action, and action execution studies. However, cerebellar lobules HVIIb and HVIII showed significant greater activation for tasks involved action inhibition and action observation (figure 6c green) compared to anterior motor lobules (figure 6c red). The paradigms that drove these differences between anterior and posterior lobules were Go/No-Go tasks and action observation (figure 6c green).

# Discussion

 Studies investigating the anatomy of the cortico-cerebellar system have greatly contributed to the debate surrounding cerebellar contributions to cognition. Connectivity studies in both humans and non-human primates suggest that functionally distinct cortico-cerebellar loops exist; one concerned with ‘sensorimotor’ information the other with ‘associative/non-motor’ information ([Stoodley, 2012](#_ENREF_65)). This distinction is further supported by functional neuroimaging studies, perhaps most clearly and concisely shown through the use of meta-analytic tools ([E et al., 2012](#_ENREF_17); [Moulton et al., 2010](#_ENREF_45); [Petacchi et al., 2005](#_ENREF_52); [Stoodley and Schmahmann, 2009](#_ENREF_66)). However, these aforementioned studies focussed solely on activity within the cerebellum and did not investigate cortico-cerebellar connectivity. The present study uses MACM to bridge the large gap in the cortico-cerebellar literature between task-independent studies of connectivity and task-dependent functional neuroimaging studies. Our results show that cerebellar lobules HV, HVI, HVIIb and HVIII had greater co-activation with motor and somatosensory regions compared to lobules Crus I and II which showed greater co-activation with prefrontal and parietal regions. These separate co-activation profiles were driven by distinct behavioural domains as well. Regions that co-activated with Crus I and II were primarily driven by emotion and cognitive tasks, whilst regions that co-activated with HV, HVI, HVIIb and HVIII were driven by motor tasks.

## Distinct “associative” and “motor” cortico-cerebellar circuits

One key feature of this study is that connectivity patterns established using task-independent methods such as tracer studies, diffusion tractography, or resting fMRI, were replicated when using task-dependent data. As repeatedly seen in connectivity studies using humans ([Buckner et al., 2011](#_ENREF_9); [Krienen and Buckner, 2009](#_ENREF_36); [O'Reilly et al., 2010](#_ENREF_49)) and non-human primates ([Kelly and Strick, 2003](#_ENREF_35)) we found that lobules Crus I and II were co-activated with prefrontal and parietal cortices, whilst lobules HV, HVI, HVIIb, and HVIII were co-activated with pre- and postcentral gyrus (see figure 3). It is possible that by collapsing across lobules Crus I and II or HV and HVI we are introducing additional heterogeneity into the analyses and that lobules within each mask might have distinct roles to play in either motor or cognitive processes. For this reason we have provided additional analyses of individual lobules in supplemental materials. However, we would argue that analyses combining these cerebellar lobules are relevant given that they 1) conform with previous anatomical and functional connectivity studies ([Kelly and Strick, 2003](#_ENREF_35); [O'Reilly et al., 2010](#_ENREF_49)), 2) conform with studies showing distinct lobular specific evolutionary expansion ([Balsters et al., 2010](#_ENREF_4)) and most importantly, 3) the paradigm class information extracted from these masks shows a clear distinction between cognitive paradigms (Crus I and II) and motor paradigms (HV, HVI, HVIIb, and HVIII) which were found to evoke activations in these masks. Figure 2 shows a large degree of overlap between co-activation patterns from Crus I and II VOIs, and co-activation patterns from HV, HVI, HVIIb, HVIII VOIs (see figure 2e). However, we believe this is because the majority of cognitive paradigms also include a motor response to establish whether the participant has performed the task correctly. This is a particularly important issue for cerebellar studies where it is important to disambiguate cognitive processes from subsequent motor processes (see [Balsters and Ramnani, 2008](#_ENREF_5); [2011](#_ENREF_6); [Balsters et al., 2013 for examples using temporal jittering](#_ENREF_7)). FMRI studies of cognitive control typically include a motor response directly after a cue and the ‘cognitive subtraction’ approach is then used to remove common motor processes and isolate distinct cognitive processes. Given the large number of studies included in the generation of these MACMs (~52,000 foci), it is not possible to assess how many of these studies have used a control condition or quality of the control condition used. Rather than constrain the analyses to particular types of contrasts we performed the analyses in a purely data-driven fashion. By contrasting the maps generated using MACM we can clearly highlight the unique connectivity patterns of these functionally distinct (as confirmed by the paradigm class information) sets of cerebellar lobules. Similar to a standard fMRI study, comparing Crus I and II co-activation patterns with respect to HV, HVI, HVIIb and HVIII co-activations patterns clearly highlights the distinction between prefrontal-parietal-cerebellar circuits and motor-cerebellar circuits. This distinction was also apparent when analysing behavioural domain and paradigm class metadata. Studies using cognitive and emotional tasks activated Crus I and II, whilst studies using motor tasks, specifically action execution, activated HV, HVI, HVIIb and HVIII. Given differences in the MACM co-activation patterns, and differences in the tasks driving these cortico-cerebellar circuits, these results further suggest that independent cortico-cerebellar circuits contribute to both cognitive and motor control.

Middleton and Strick ([2000](#_ENREF_43); [2001](#_ENREF_44)) originally proposed that the cortico-cerebellar system was arranged as a collection of independent loops. The results of this study are in concert with this idea; however, it is important to state that even though separate cerebellar lobules were activated by different tasks, this does not mean that distinct regions of the cerebellum are performing different computations. Passingham et al ([2002](#_ENREF_50)) states that in order to understand the functions of a cortical region we must investigate its extrinsic connectivity *and* its intrinsic anatomical features. One of the most distinctive features of the cerebellar cortex is its uniform cellular structure ([Eccles et al., 1967](#_ENREF_18)). This uniformity conveys an important functional feature, namely that the cerebellar cortex performs the same process, or series of processes, regardless of whether the cortical input arrives from highly abstract/cognitive regions in the prefrontal cortex, or regions of the primary motor cortex concerned with the specific dynamics of movement. In the present study we find activations in the cerebellar cortex were significantly evoked by Action (execution, motor learning, observation), Cognition (language, music, working memory, attention), and Perception. This is consistent with previous meta-analyses that have also shown the cerebellum is active during a wide array of sensory, motor and higher cognitive processes ([E et al., 2012](#_ENREF_17); [Moulton et al., 2010](#_ENREF_45); [Petacchi et al., 2005](#_ENREF_52); [Stoodley and Schmahmann, 2009](#_ENREF_66)). Consequently, we would like to emphasise that even though the current study highlights that distinct regions of the cerebellum are involved in processing different behavioural domains, we do not suggest that the role of the cerebellum within these independent cortico-cerebellar circuits differs. Rather, we would agree with the theories proposed by Kawato and Wolpert ([Kawato and Wolpert, 1998](#_ENREF_34); [Wolpert et al., 1998](#_ENREF_72)) as well as Ramnani ([2006](#_ENREF_54)), i.e., that the role of the cerebellar cortex is to automate information processes within cortical territories, regardless of whether that involves automating motor control processes in the primary motor cortex or working memory processes within the prefrontal cortex. For example, Imamizu et al ([2003](#_ENREF_32); [2000](#_ENREF_33)) have demonstrated using fMRI that cerebellar lobules HV and HVI reduce in BOLD activity in a manner that conforms to control theoretic models of cerebellar function during the acquisition of a motor skill. Recently, Balsters and Ramnani ([2011](#_ENREF_6)) extended these ideas to investigate more abstract information processing. Whilst Imamizu et al ([2003](#_ENREF_32); [2000](#_ENREF_33)) showed that the acquisition of motor skills lead to cerebellar plastic changes within cerebellar lobules HV and HVI, Balsters and Ramnani ([2011](#_ENREF_6)) found that the automation of first-order rules lead to similar cerebellar plastic changes within Crus I, a region of the cerebellum repeatedly shown to be interconnected with the prefrontal cortex. Although the present study demonstrates that cortico-cerebellar circuits contribute to distinct behavioural domains, we would maintain that the role of the cerebellum within these circuits is constant, i.e. aiding the automation of cortical processing.

## Anatomical and functional differences between anterior (HV, HVI) and posterior (HVIIb, HVIII) cerebellar “motor” lobules

Studies of both anatomy and function have led to the proposal that dual routes exist within the cortical motor system ([Hoshi and Tanji, 2007](#_ENREF_31); [Passingham and Toni, 2001](#_ENREF_51); [Rathelot and Strick, 2009](#_ENREF_57)). Studies of the cytoarchitectonic properties of primary motor cortex (BA 4) show a separation between anterior and posterior regions ([areas 4a and 4p respectively; Geyer et al., 1996](#_ENREF_29)). This dichotomy was further supported by Rathelot and Strick ([2009](#_ENREF_57)) who subdivided the precentral gyrus into “old” and “new” M1 based on the presence of cortico-motoneuronal (CM) cells. CM cells within the caudal aspect of the precentral gyrus (putatively area 4p) allow signals from “new” M1 to bypass spinal cord mechanisms and output more complex motor behaviours. Phylo- and optogenetic studies suggest that this region has been “added” over the course of evolution, and is not present in all mammals ([Nudo and Masterton, 1988](#_ENREF_48)). Balsters et al ([2010](#_ENREF_4)) also demonstrated differences in the evolution of cerebellar lobules by showing that cerebellar lobules HVIIb and HVIIIa had increased in proportional volume in humans compared to non-human primates (capuchins and chimpanzees), whilst cerebellar lobules HV and HVI showed a significant decrease in proportional volume in humans compared to non-human primates. If evolutionary pressures act on complete functional systems rather than on individual brain areas ([Streidter, 2005](#_ENREF_67)) then one might predict that posterior cerebellar lobules would show greater connectivity with “new” M1, whilst anterior cerebellar motor lobules would show greater connectivity with “old” M1. This hypothesis was not supported by our results, which showed that cerebellar lobules HV and HVI had greater connectivity with the precentral gyrus overlapping with both areas 4a and 4p compared to cerebellar lobules HVIIb and HVIII. This would suggest that the evolutionary expansion of cerebellar lobules HVIIb and HVIII in humans is not likely to be related to the presence of CM cells and the differentiation between 4a and 4p. **Based on the anatomical tracing studies of Kelly and Strick (2003), we have assigned lobules HVIIB and HVIII as “motor” lobules. However, these lobules may in fact contribute to prefrontal/cognitive processes. Cerebellar lobules HVIIb and HVIII showed greater connectivity with the superior medial gyrus (putatively Pre-SMA), bilateral inferior frontal gyrus, and the left inferior parietal lobule. The paradigms found to evoke these connectivity differences were action observation and inhibition. Studies of both action inhibition and third person learning have often reported activations within the superior medial gyrus and cingulate cortex (**[**Apps et al., 2012**](#_ENREF_1)**;** [**Apps et al., 2013**](#_ENREF_2)**;** [**Chambers et al., 2009**](#_ENREF_12)**). It may thus be argued that cerebellar lobules HV and HVI have greater connectivity with the primary motor cortex and play a greater role in motor learning, whilst cerebellar lobules HVIIb and HVIII have increased connectivity with the superior medial gyrus a thus may have an increased role in observational learning, possibly related to the presence of mirror neurons (**[**Cattaneo and Rizzolatti, 2009**](#_ENREF_11)**).** One caveat of this analysis is that the number of experiments and foci contributing to anterior motor lobules is much higher than the number contributing to the posterior cerebellar lobules. Restrictions of the field of view in fMRI and default preprocessing settings in some neuroimaging packages mean that the posterior lobules of the cerebellum are often excluded from analysis and as such may be under-represented in these analyses. Although the exact functional distinction between these cerebellar lobules remains unclear, the use of MACM has helped us to refute potential hypotheses and develop novel hypotheses that will require further exploration, i.e., the possible distinction between action execution and observational learning within anterior and posterior cerebellar “motor” lobules.

## Functional vs. anatomical cerebellar parcellation

This study, like many others, used anatomical VOIs to investigate connectivity. There are two main reasons for this; 1) this approach is in keeping with the majority of cerebellar connectivity studies (both non-human primate tracer studies and resting state fMRI studies) which have discussed their results in terms of lobular cerebellar anatomy, and 2) a probabilistic atlas based on the lobular anatomy of the cerebellar cortex is available to facilitate this type of analysis ([Diedrichsen et al., 2009](#_ENREF_16)). However, the cerebellum can also be categorised based on climbing fibre inputs originating from the inferior olive ([Pijpers et al., 2005](#_ENREF_53); [Ruigrok, 2011](#_ENREF_62); [Voogd, 2012](#_ENREF_70)). Studies investigating cortico-ponto-cerebellar-thalamic loops have described an anterior-posterior cerebellar functional topography, but studies of olivo-cerebellar connectivity have demonstrated a medial-lateral functional topography within the cerebellum. Unfortunately it is not currently possible to investigate this olivo-cerebellar functional organisation using MRI, but resting state connectivity studies have begun using hierarchical clustering as an alternative to anatomical VOIs. Both Buckner et al ([2011](#_ENREF_9)) and Bernard et al ([2012](#_ENREF_8)) recently investigated cortico-cerebellar connectivity using a hierarchical clustering approach. The results of both analyses suggest that anatomical parcellations of the cerebellar cortex may be a rather crude approach that does not pick up functional sub-regions within cerebellar lobules. For example, both Buckner et al ([2011](#_ENREF_9)) and Bernard et al ([2012](#_ENREF_8)) show that Crus I contains 2-4 functional subdivisions. However, one broad criticism of hierarchical clustering approaches is that there is no gold-standard in choosing the right or even just the optimal number of clusters. This can be seen when one compares Buckner et al ([2011](#_ENREF_9)) (either 7 or 17 clusters) with Bernard et al ([2012](#_ENREF_8)) (20 clusters). The clustering algorithm of Bernard et al ([2012](#_ENREF_8)) separated lobules HV and HVI from lobules HVIIb and HVIII as functionally distinct units whilst neither of the solutions provided by Buckner et al ([2011](#_ENREF_9)) does. Although it is likely that these studies are more sensitive to functional subdivisions within the cerebellum there is still a great deal of uncertainty regarding this approach. An important extension of the present study would be to apply hierarchical clustering approaches to this task-dependent dataset. It is likely that the clustering achieved using task-dependent information compared to task-free fluctuations will be more informative and could help to refine our understanding of functional cortico-cerebellar differences. It would also be of interest to investigate MACM differences between cerebellar vermis and hemisphere. The cerebellar vermis has been linked to a wide array of behaviours such as posture and gait, eye movement, and emotional processing ([Schmahmann, 1997](#_ENREF_63)). Unfortunately, the size of the cerebellar vermis is very small ([<5% of the total cerebellar grey matter; Diedrichsen et al., 2009](#_ENREF_16)), and the relative sizes of vermal lobules range from 1.67% (lobule VI) to 0.05% (Crus I) total grey matter. Given the limited size of the cerebellar vermis as a whole, as well as the vermal components of specific lobules, it was not possible to extract enough activation foci within these regions to perform a reliable MACM analysis.

# Conclusions and outlook

 This study provides the first evidence that cortico-cerebellar circuits established using task-independent methods are also present using task-dependent data. MACM also provided behavioural meta-data demonstrating that these independent cortico-cerebellar circuits are driven by distinct tasks. Whilst this is important for developing our understanding of cerebellar information processing it is also important for understanding the consequences of cerebellar damage in different disease states. Reetz et al ([2012](#_ENREF_58)) used VBM to identify specific regions of cerebellar damage in a population with spinocerebellar ataxia 17 (SCA 17) compared to matched controls. Using these as VOIs it was then possible to investigate task-independent connectivity using resting state fMRI and task-dependent connectivity using MACM in a much larger sample of healthy controls. This approach highlights the behavioural and connectivity profiles of these affected regions in healthy individuals and then allows one to infer the likely consequences of damage to these regions. The results of Reetz et al (2012) showed that both cognitive and motor cortico-cerebellar circuits were damaged, explaining the brunt of motor deficits but also the broad spectrum of neuropsychiatric deficits seen in SCA17. The present study and the study of Reetz et al (2012) highlight the potential of MACM both as a method for probing the functions of neuroanatomical circuits in healthy individuals, but also as a tool to investigate the clinical relevance of cerebellar damage.

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**Table 1: MACM functional connectivity for lobules HV, HVI, HVIIb, and HVIII.** Cluster size indicates the number of voxels. Cytoarchitectonic and anatomical probabilities were established where possible using the Anatomy toolbox ([Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |  |   |  |   |   |
| Right Cerebellum | 7690 | 9.14 | 22 | -56 | -22 |  Lobule VI (95%) |
| Left Cerebellum | same cluster | 8.92 | -28 | -60 | -26 |  Lobule VI (96%) |
| Cerebellar Vermis | same cluster | 8.82 | 6 | -64 | -18 |  Lobule VI (59%) |
|   |   |  |   |  |   |   |
| ***Frontal Lobe*** |   |  |   |  |   |   |
| Left Insula Lobe | 7716 | 8.86 | -34 | 20 | 2 |  Area 6 (60%) |
| Left Precentral Gyrus | same cluster | 8.77 | -36 | -18 | 58 |  Area 6 (70%) |
| Left Precentral Gyrus | same cluster | 8.77 | -50 | -6 | 44 |  Area 44 (40%) |
| Left Precentral Gyrus | same cluster | 8.75 | -48 | 6 | 32 |   |
| Left Superior Frontal Gyrus | same cluster | 8.75 | -26 | -4 | 60 |   |
| Left Inferior Frontal Gyrus (p. Opercularis) | same cluster | 8.59 | -52 | 12 | 0 |   |
| Right Insula Lobe | 2873 | 8.83 | 34 | 20 | 2 |   |
| Right Middle Frontal Gyrus | same cluster | 8.64 | 28 | -4 | 56 |   |
| Right Inferior Frontal Gyrus (p. Opercularis) | same cluster | 8.61 | 52 | 12 | 26 |  Area 44 (40%) |
| RightPrecentral Gyrus | same cluster | 8.61 | 52 | -2 | 40 |  Area 6 (70%) |
| Left SMA | 2752 | 9.12 | -2 | 6 | 54 | Area 6 (60%) |
| Right Middle Frontal Gyrus | 163 | 8.01 | 40 | 40 | 26 |   |
| Right Precentral Gyrus | 78 | 7.57 | 38 | -18 | 60 |  Area 6 (80%) |
|   |   |   |   |  |   |   |
| ***Parietal Lobe*** |   |   |   |  |   |   |
| Left Inferior Parietal Lobule  | 7716 (previous cluster) | 8.72 | -30 | -56 | 52 |  SPL (7A) (40%) |
| Left SupraMarginal Gyrus | same cluster | 8.63 | -54 | -24 | 18 |  OP 1 (80%) |
| Left Inferior Parietal Lobule  | same cluster | 8.58 | -42 | -40 | 42 |  hIP3 (20%) |
| Right Inferior Parietal Lobule  | 595 | 8.59 | 42 | -44 | 46 |  hIP2 (50%) |
| Right Superior Parietal Lobule  | same cluster | 8.57 | 32 | -56 | 48 |  hIP3 (50%) |
|   |   |  |   |  |   |   |
| ***Temporal Lobe*** |   |   |   |  |   |   |
| Right Superior Temporal Gyrus | 76 | 6.03 | 56 | -24 | 4 |   |
| Right Middle Temporal Gyrus | same cluster | 5.82 | 56 | -36 | 6 |   |
| Right Superior Temporal Gyrus | 62 | 6.2 | 60 | -32 | 22 |  IPC (PF) (50%) |
|   |   |  |   |  |   |   |
| ***Occipital Lobe*** |   |   |   |  |   |   |
| Left Middle Occipital Gyrus | 96 | 7.86 | -28 | -92 | -2 |   |
| Right Inferior Occipital Gyrus | 62 | 6.26 | 32 | -88 | -8 |  hOC3v (V3v) (30%) |
| Left Calcarine Gyrus | 38 | 6.13 | -12 | -92 | -2 |  Area 17 (60%) |
|   |   |  |   |  |   |   |
| ***Subcortical*** |   |   |   |  |   |   |
| Left Putamen | 7716 (previous cluster) | 8.8 | -24 | -4 | 4 | n/a |
| Left Pallidum | same cluster | 8.6 | -18 | -2 | 0 | n/a |
| Right Pallidum | 2873 (previous cluster) | 8.73 | 24 | 2 | 2 | n/a |
| Left Thalamus | 1590 | 9.05 | -12 | -18 | 6 |  Th-Prefrontal (82%) |
| Right Thalamus | same cluster | 8.87 | 12 | -16 | 6 |  Th-Prefrontal (84%) |
| Left Thalamus | same cluster | 8.08 | -20 | -16 | 0 |  Th-Premotor (32%) |

**Table 2: MACM functional connectivity for lobules Crus I and II.** Cluster size indicates the number of voxels. Cytoarchitectonic and anatomical probabilities were established where possible using the Anatomy toolbox ([Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |  |   |  |   |   |
| Left Cerebellum | 3128 | 8.74 | -32 | -62 | -28 |  Lobule VIIa Crus I (62%) |
| Right Cerebellum | 2928 | 8.79 | 34 | -64 | -28 |  Lobule VIIa Crus I (62%) |
| Right Cerebellum | same cluster | 8.56 | 26 | -58 | -20 |  Lobule HVI (78%) |
|   |   |  |   |  |   |   |
| ***Frontal Lobe*** |   |  |   |  |   |   |
| Left SMA | 2100 | 8.82 | -2 | 14 | 48 |  Area 6 (30%) |
| Left Precentral Gyrus | 1589 | 8.61 | -48 | 8 | 30 |  Area 44 (30%)  |
| Left Precentral Gyrus | same cluster | 7.73 | -50 | -4 | 44 |  Area 6 (60%) |
| Left Insula Lobe | 1395 | 8.78 | -32 | 22 | 0 |   |
| Left Inferior Frontal Gyrus (p. Orbitalis) | same cluster | 8.49 | -48 | 16 | -6 |   |
| Right Insula Lobe | 861 | 8.73 | 38 | 22 | -4 |   |
| Right Inferior Frontal Gyrus (p. Opercularis) | 646 | 8.57 | 50 | 10 | 28 |  Area 44 (40%) |
| RightPrecentral Gyrus | same cluster | 6.55 | 52 | 2 | 44 |  Area 6 (50%) |
| Left Superior Frontal Gyrus | 341 | 8.6 | -26 | -4 | 62 |   |
| Left Precentral Gyrus | same cluster | 6.03 | -34 | -16 | 60 |  Area 6 (90%) |
| Right Inferior Frontal Gyrus (p. Triangularis) | 253 | 8.49 | 44 | 36 | 26 |   |
| Right Middle Frontal Gyrus | 217 | 8.53 | 28 | -4 | 56 |   |
|   |   |  |   |  |   |   |
| ***Parietal Lobe*** |   |   |   |  |   |   |
| Left Inferior Parietal Lobule  | 970 | 8.57 | -30 | -56 | 50 |  SPL (7A) (50%) |
| Left Inferior Parietal Lobule  | same cluster | 8.52 | -40 | -48 | 44 |  hIP1 (50%) |
| Right Angular Gyrus | 615 | 8.51 | 32 | -60 | 50 |  hIP3 (40%) |
| Right Inferior Parietal Lobule  | same cluster | 8.47 | 42 | -44 | 48 |  hIP2 (50%) |
|   |   |  |   |  |   |   |
| ***Temporal Lobe*** |   |   |   |  |   |   |
| Left Superior Temporal Gyrus | 16 | 5.78 | -58 | -38 | 12 |   |
|   |   |  |   |  |   |   |
| ***Occipital Lobe*** |   |   |   |  |   |   |
| Left Inferior Occipital Gyrus | 187 | 6.9 | -24 | -94 | -4 |  hOC3v (V3v)(40%) |
| Left Middle Occipital Gyrus | same cluster | 6.58 | -30 | -92 | 4 |   |
| Left Middle Occipital Gyrus | same cluster | 6.52 | -28 | -94 | 2 |   |
|   |   |  |   |  |   |   |
| ***Subcortical*** |   |   |   |  |   |   |
| Left Putamen | 1395 (previous cluster) | 8.51 | -22 | 0 | 4 | n/a |
| Left Pallidum | same cluster | 6.25 | -16 | 0 | 2 | n/a |
| Left Thalamus | 834 | 8.6 | -10 | -18 | 6 |  Th-Prefrontal (90%) |
| Right Thalamus | same cluster | 8.58 | 10 | -16 | 6 |  Th-Prefrontal (88%) |
| Right Pallidum | 233 | 8.5 | 20 | 4 | 4 |   |
| Right Caudate Nucleus | same cluster | 6.28 | 14 | 8 | 6 |   |

**Table 3: Conjunction between MACM functional connectivity maps for lobules HV, HVI, HVIIb, HVIII and Crus I, II.** Cluster size indicates the number of voxels. Cytoarchitectonic and anatomical probabilities were established where possible using the Anatomy toolbox ([Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |  |   |   |   |   |
| Right Cerebellum | 6992 | 8.79 | 34 | -64 | -28 |  Lobule VIIa Crus I (62%) |
| Left Cerebellum | same cluster | 8.74 | -32 | -62 | -28 |  Lobule VIIa Crus I (62%) |
| Right Cerebellum | same cluster | 8.56 | 26 | -58 | -20 |  Lobule HVI (78%) |
| Left Cerebellum | same cluster | 6.94 | -10 | -76 | -26 |  Lobule HVI (58%) |
|   |   |  |   |  |   |   |
| ***Frontal Lobe*** |   |  |   |  |   |   |
| Left Insula Lobe | 10904 | 8.78 | -32 | 22 | 0 |   |
| Right Insula Lobe | same cluster | 8.73 | 38 | 22 | -4 |   |
| Left Precentral Gyrus | same cluster | 8.61 | -48 | 8 | 30 |  Area 44 (40%) |
| Left Superior Frontal Gyrus | same cluster | 8.6 | -26 | -4 | 62 |   |
| Right Inferior Frontal Gyrus (p. Opercularis) | same cluster | 8.57 | 50 | 10 | 28 |  Area 44 (40%) |
| Right Middle Frontal Gyrus | same cluster | 8.53 | 28 | -4 | 56 |   |
| Left SMA | 2729 | 8.82 | -2 | 14 | 48 |   |
| Right Middle Frontal Gyrus | 379 | 7.99 | 42 | 38 | 26 |   |
|   |   |  |   |  |   |   |
| ***Parietal Lobe*** |   |   |   |  |   |   |
| Left Inferior Parietal Lobule  | 1444 | 8.57 | -30 | -56 | 50 |  SPL (7A)  |
| Left Inferior Parietal Lobule  | same cluster | 8.51 | -40 | -44 | 44 |  hIP2 (30%) |
| Right Angular Gyrus | 1087 | 8.5 | 32 | -58 | 50 |  hIP3(30%)  |
| Right Inferior Parietal Lobule  | same cluster | 8.47 | 42 | -44 | 48 |  hIP2 (50%)  |
| Right Superior Parietal Lobule  | same cluster | 4.98 | 18 | -62 | 62 |  SPL (7A) (30%) |
| Right Superior Parietal Lobule  | same cluster | 3.97 | 16 | -68 | 54 |  SPL (7P) (60%) |
|   |   |  |   |  |   |   |
| ***Temporal Lobe*** |   |   |   |  |   |   |
| Left Superior Temporal Gyrus | 231 | 5.66 | -58 | -36 | 12 |   |
| Left Superior Temporal Gyrus | same cluster | 3.91 | -58 | -20 | 2 |   |
|   |   |  |   |  |   |   |
| ***Subcortical*** |   |   |   |  |   |   |
| Left Thalamus | 10904 (previous cluster) | 8.6 | -10 | -18 | 6 |  Th-Prefrontal (88%) |
| Right Thalamus | same cluster | 8.58 | 10 | -16 | 6 |  Th-Prefrontal (90%) |
| Left Putamen | same cluster | 8.51 | -22 | 0 | 4 | n/a |
| Right Pallidum | same cluster | 8.5 | 20 | 4 | 4 | n/a |

**Table 4: Differences in MACM functional connectivity between lobules HV, HVI, HVIIb, HVIII and Crus I, II.** Cluster size indicates the number of voxels. Cytoarchitectonic and anatomical probabilities were established where possible using the Anatomy toolbox ([Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Motor > PFC** | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |  |   |  |   |   |
| Rigth Cerebellum | 7037 | 8.13 | 24 | -58 | -34 |  Lobule HVI (18%) |
|   |   |  |   |  |   |   |
| ***Frontal Lobe*** |   |  |   |  |   |   |
| Left Insula Lobe | 6841 | 5.11 | -40 | -2 | 2 |   |
| Right Insula Lobe | 2454 | 5.01 | 36 | 4 | 6 |   |
| Left Middle Cingulate Cortex | 1632 | 8.13 | -2 | 2 | 40 |   |
| Left SMA | same cluster | 3.94 | -8 | -4 | 64 | Area 6 (50%) |
| Right Precentral Gyrus | 289 | 7.57 | 38 | -18 | 60 | Area 6 (80%) |
| Right Middle Cingulate Cortex | 78 | 3.22 | 6 | 14 | 32 |   |
|   |   |  |   |  |   |   |
| ***Parietal Lobe*** |   |  |   |  |   |   |
| Left Rolandic Operculum | 6841 (previous cluster) | 7.18 | -48 | 0 | 6 |   |
| Left Postcentral Gyrus | same cluster | 5.08 | -34 | -36 | 46 |  SPL (7PC) (20%) |
| Left Inferior Parietal Lobule  | same cluster | 4.42 | -52 | -22 | 38 |  Area 2 (70%) |
| Left Inferior Parietal Lobule  | same cluster | 3.8 | -50 | -28 | 36 |  IPC (PFt) (60%) |
| Right Postcentral Gyrus | 2454 (previous cluster) | 7.28 | 56 | -4 | 34 |  Area 6 (50%)  |
| Right Postcentral Gyrus | same cluster | 4.28 | 58 | 0 | 18 |  Area 3b (30%) |
| Right Rolandic Operculum | same cluster | 4.01 | 56 | -14 | 10 |  OP 4 (50%) |
| Right Rolandic Operculum | same cluster | 3.95 | 60 | -4 | 16 |  Area 3a (30%) |
| Right Postcentral Gyrus | 124 | 3.11 | 44 | -30 | 48 | Area 2 (80%) |
| Right Postcentral Gyrus | same cluster | 2.51 | 40 | -40 | 60 | Area 1 (80%) |
| Right Superior Parietal Lobule  | 13 | 2.25 | 32 | -50 | 60 | Area 2 (40%) |
|   |   |  |   |  |   |   |
| ***Temporal Lobe*** |   |  |   |  |   |   |
| Left Superior Temporal Gyrus | 6841 (previous cluster) | 6.89 | -56 | -4 | -2 |   |
| Right Superior Temporal Gyrus | 2454 (previous cluster) | 5.69 | 58 | -32 | 22 |  IPC (PFcm) (50%) |
| Right Superior Temporal Gyrus | same cluster | 3.99 | 58 | -12 | 8 |  TE 1.0 (50%) |
| Left Middle Temporal Gyrus | 17 | 2.51 | -46 | -70 | 8 |   |
|   |   |  |   |  |   |   |
| ***Subcortical*** |   |  |   |  |   |   |
| Left Putamen | 6841 (previous cluster) | 8.13 | -24 | -2 | -6 |   |
| Left Thalamus | same cluster | 8.08 | -20 | -16 | 0 |  Th-Premotor (33%) |
| Left Pallidum | same cluster | 3.94 | -26 | -8 | -4 |   |
| Right Pallidum | 2454 (previous cluster) | 8.13 | 26 | -4 | -2 |   |
| Right Putamen | same cluster | 3.94 | 28 | 8 | 4 |   |
| Right Thalamus | 215 | 8.13 | 14 | -16 | 0 |  Th-Premotor (73%) |
| **PFC > Motor** | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |  |   |  |   |   |
| Left Cerebellum | 5842 | 8.13 | -34 | -62 | -40 |  Lobule VIIa Crus I (58%) |
|   |   |  |   |  |   |   |
| ***Frontal Lobe*** |   |  |   |  |   |   |
| Left Inferior Frontal Gyrus (p. Triangularis) | 1931 | 8.13 | -32 | 28 | 0 |   |
| Left Inferior Frontal Gyrus (p. Orbitalis) | same cluster | 3.96 | -44 | 26 | -14 |   |
| Left Insula Lobe | same cluster | 3.6 | -26 | 26 | -4 |   |
| Left Inferior Frontal Gyrus (p. Orbitalis) | same cluster | 3.35 | -54 | 24 | -8 |   |
| Left Inferior Frontal Gyrus (p. Triangularis) | same cluster | 3.2 | -54 | 28 | 16 |  Area 45 (80%) |
| Left Middle Frontal Gyrus | same cluster | 3.17 | -36 | 34 | 22 |   |
| Right Middle Frontal Gyrus | 739 | 6.53 | 46 | 34 | 30 |   |
| Right Inferior Frontal Gyrus (p. Triangularis) | same cluster | 3.67 | 52 | 26 | 22 |   |
| Right Inferior Frontal Gyrus (p. Opercularis) | same cluster | 3.66 | 52 | 18 | 34 |  Area 45 (60%) |
| Right Inferior Frontal Gyrus (p. Triangularis) | same cluster | 3.49 | 52 | 28 | 16 |  Area 45 (70%) |
| RightPrecentral Gyrus | same cluster | 3.06 | 50 | 10 | 32 |  Area 44 (40%) |
| Left Superior Medial Gyrus | 563 | 8.13 | 0 | 28 | 40 |   |
| Right Superior Medial Gyrus | same cluster | 6.96 | 6 | 26 | 44 |   |
| Right Middle Cingulate Cortex | same cluster | 3.94 | 10 | 28 | 38 |   |
| Right Insula Lobe | 558 | 8.13 | 42 | 22 | -10 |   |
| Right Inferior Frontal Gyrus (p. Orbitalis) | same cluster | 3.94 | 42 | 28 | -8 |   |
| Right Inferior Frontal Gyrus (p. Triangularis) | same cluster | 3.2 | 50 | 26 | 2 | Area 45 (50%) |
| Right Middle Frontal Gyrus | 111 | 3.54 | 32 | 48 | 18 |   |
| Left Precentral Gyrus | 109 | 3.28 | -38 | 2 | 58 |   |
| Left Middle Frontal Gyrus | same cluster | 2.92 | -46 | 6 | 54 |   |
| Right Middle Frontal Gyrus | 70 | 2.31 | 34 | 2 | 62 |   |
| Right SMA | 20 | 2.94 | 8 | 20 | 60 |   |
|   |   |  |   |  |   |   |
| ***Parietal Lobe*** |   |  |   |  |   |   |
| Left Inferior Parietal Lobule  | 715 | 8.13 | -38 | -50 | 42 |  hIP1 (50%) |
| Left Superior Parietal Lobule  | same cluster | 5.52 | -34 | -64 | 48 |  SPL (7A) (50%) |
| Left Inferior Parietal Lobule  | same cluster | 2.06 | -44 | -50 | 56 |  IPC (PFm) (40%) |
| Right Angular Gyrus | 569 | 6.31 | 38 | -62 | 50 |   |
| Right Inferior Parietal Lobule  | same cluster | 4.9 | 42 | -56 | 50 |  IPC (PGa) (50%) |
| Right Superior Parietal Lobule  | same cluster | 4.82 | 40 | -56 | 54 |  SPL (7A) (60%) |
| Right Inferior Parietal Lobule  | same cluster | 2.75 | 52 | -46 | 52 |  IPC (PFm) (90%) |
| Right Inferior Parietal Lobule  | same cluster | 1.99 | 56 | -40 | 46 |  IPC (PF) (50%) |
|   |   |  |   |  |   |   |
| ***Temporal Lobe*** |   |  |   |  |   |   |
| Left Middle Temporal Gyrus | 107 | 3.94 | -56 | -42 | 0 |   |
|   |   |  |   |  |   |   |
| ***Occipital Lobe*** |   |  |   |  |   |   |
| Right Middle Occipital Gyrus | 36 | 3.45 | 34 | -82 | 6 |   |
|   |   |  |   |  |   |   |
| ***Subcortical*** |   |  |   |  |   |   |
| Right Pallidum | 74 | 2.58 | 14 | 4 | 0 | n/a |

**Table 5: Differences in MACM functional connectivity between lobules HV, HVI and HVIIb, HVIII.** Cluster size indicates the number of voxels. Cytoarchitectonic and anatomical probabilities were established where possible using the Anatomy toolbox ([Eickhoff et al., 2007](#_ENREF_24); [Eickhoff et al., 2006](#_ENREF_25); [Eickhoff et al., 2005](#_ENREF_26)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ant motor > Post motor** | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |   |   |   |   |   |
| Left Cerebellum | 7119 | 8.13 | -22 | -56 | -32 | lobule HVI (14%) |
|   |   |   |   |  |   |   |
| ***Frontal Lobe*** |   |   |   |  |   |   |
| Left Postcentral Gyrus | 1031 | 3.9 | -52 | -10 | 26 |  Area 3b (40%) |
| Left Precentral Gyrus | same cluster | 3.3 | -38 | -8 | 60 |  Area 6 (50%) |
| Left Postcentral Gyrus | same cluster | 3.28 | -46 | -12 | 30 |  Area 3a (50%) |
| Left Postcentral Gyrus | same cluster | 2.49 | -52 | -18 | 20 |  OP 1 (40%)  |
| Right SMA | 679 | 3.78 | 2 | -6 | 56 | Area 6 (80%) |
| Right Postcentral Gyrus | 563 | 3.45 | 50 | -12 | 32 |  Area 3b (80%) |
| RightPrecentral Gyrus | 283 | 3.24 | 40 | -12 | 54 |  Area 6 (50%) |
| Right Postcentral Gyrus | same cluster | 2.94 | 42 | -20 | 50 |  Area 3b (90%) |
| Right Insula Lobe | 183 | 2.62 | 44 | 10 | 2 |   |
| Left Postcentral Gyrus | 14 | 2.16 | -38 | -26 | 46 | Area 3a (60%) |
|   |   |   |   |  |   |   |
| ***Parietal Lobe*** |   |   |   |  |   |   |
| Right SupraMarginal Gyrus | 358 | 2.63 | 62 | -26 | 26 |  IPC (PF) (40%) |
| Right SupraMarginal Gyrus | same cluster | 2.55 | 62 | -20 | 24 |  IPC (PFop) (30%) |
| Left Superior Parietal Lobule  | 58 | 2.23 | -18 | -68 | 46 |  SPL (7A) (30%) |
|   |   |   |   |  |   |   |
| ***Temporal Lobe*** |   |   |   |  |   |   |
| Left Superior Temporal Gyrus | 64 | 2.23 | -50 | -4 | -8 |   |
|   |   |   |   |  |   |   |
| ***Occipital Lobe*** |   |   |   |  |   |   |
| Left Middle Occipital Gyrus | 90 | 3.2 | -32 | -90 | -6 |  hOC4v (V4) (40%) |
|   |   |   |   |  |   |   |
| ***Subcortical*** |   |   |   |  |   |   |
| Left Thalamus | 355 | 3.49 | -8 | -10 | -2 |  Th-Prefrontal (90%) |
| Right Thalamus | 120 | 2.56 | 16 | -16 | 4 |  Th-Premotor (65%) |
| Right Thalamus | same cluster | 2.51 | 14 | -20 | 2 |  Th-Motor (34%) |
| Right Pallidum | 100 | 2.39 | 24 | -6 | 6 |   |
| Left Putamen | 92 | 2.88 | -28 | -14 | 0 |   |
| **Post motor > Ant motor** | **Cluster** |  | **Co-ordinate** | **Cytoarchitectonic BA** |
| **Label** | **Size** | **Z** | **(x y z)** |  **(Probability if available)** |
| ***Cerebellum*** |   |   |   |   |   |   |
| Left Cerebellum | 1721 | 8.13 | -24 | -64 | -50 |  Lobule HVIIIa (70%) |
| Right Cerebellum | same cluster | 4.86 | 6 | -74 | -36 |  Lobule VIIb (46%) |
| Left Cerebellum | same cluster | 3.58 | -16 | -54 | -58 |  Lobule HVIIIb (85%) |
| Right Cerebellum | 145 | 4.7 | 20 | -66 | -50 |  Lobule HVIIIa (60%) |
|   |   |   |   |  |   |   |
| ***Frontal Lobe*** |   |   |   |  |   |   |
| Left Superior Medial Gyrus | 370 | 6.27 | -2 | 20 | 42 |   |
| Left SMA | same cluster | 3.22 | -8 | 16 | 52 |   |
| Left Inferior Frontal Gyrus (p. Triangularis) | 140 | 3.45 | -38 | 28 | 24 |   |
| Right Inferior Frontal Gyrus (p. Orbitalis) | 87 | 3.19 | 36 | 28 | -6 |   |
| Left Insula Lobe | 41 | 2.73 | -32 | 20 | -6 |   |
| Right Middle Cingulate Cortex | 12 | 2.18 | 4 | 18 | 30 |   |
|   |   |   |   |  |   |   |
| ***Parietal Lobe*** |   |   |   |  |   |   |
| Left Inferior Parietal Lobule  | 131 | 3.09 | -44 | -44 | 46 | hIP2 (20%) |
|   |   |   |   |  |   |   |
| ***Subcortical*** |   |   |   |  |   |   |
| Right Pallidum | 46 | 2.11 | 14 | 6 | -2 | n/a |
| Left Thalamus | 37 | 2.5 | -16 | -22 | 14 |  Th-Parietal (36%) |
| Left Thalamus | same cluster | 2.14 | -12 | -24 | 8 |  Th-Prefrontal (56%) |

# Figures

Figure 1: Cerebellar lobular masks. Red lobules are classified as “motor” lobules (V, VI, VIIb and VIII), blue lobules are classified as “prefrontal” lobules (Crus I and Crus II). Masks are overlayed on the FSL standard template moving from anterior-> posterior.

Figure 2: MACM connectivity maps for lobules HV, HVI, HVIIb, HVIII (red, a-b), Crus I and II (blue, c-d) and overlap (purple, e-f). A, C, and E show left hemisphere, top view and right hemisphere activations rendered on ch2better.nii anatomical image. B, D, and F show coronal slices with cerebellar activations along with the same slice of the probabilistic cerebellar atlas ([Diedrichsen et al., 2009](#_ENREF_16)) for comparison.

Figure 3: MACM connectivity differences maps. Red activations show where lobules HV, HVI, HVIIb, HVIII had greater connectivity than lobules Crus I and II. Blue activations show where connectivity was greater for Crus I and II compared to lobules HV, HVI, HVIIb, HVIII. A) shows left hemisphere, top view and right hemisphere activations rendered on ch2better.nii anatomical image. B) shows coronal slices with cerebellar activations along with the same slice of the probabilistic cerebellar atlas ([Diedrichsen et al., 2009](#_ENREF_16)) for comparison.

Figure 4: MACM connectivity differences maps. Green activations show where lobules HV and HVI had greater connectivity than lobules HVIIb and HVIII. Yellow activations show where connectivity was greater for HVIIb and HVIII compared to lobules HV and HVI. A) shows left hemisphere, top view and right hemisphere activations rendered on ch2better.nii anatomical image. B) show coronal slices with cerebellar activations along with the same slice of the probabilistic cerebellar atlas ([Diedrichsen et al., 2009](#_ENREF_16)) for comparison.

Figure 5: Functional profiling of cerebellar “motor” (HV, HVI, HVIIb, HVIII) and “prefrontal” (Crus I and Crus II) lobules. **Bar plots show significant associations (FDR corrected, p<0.05)** of a psychological term (behavioral domains and paradigm classes) from BrainMap meta-data given observed brain activity. Functional profiling was performed as individual motor (A) and prefrontal (B) masks, and difference analyses (C). In all plots the x-axis indicates relative probability values, red refers to “motor” cerebellar lobules and green refers to “prefrontal” cerebellar lobules.

Figure 6: Functional profiling of cerebellar anterior (HV, HVI) and posterior (HVIIb, HVIII) “motor” lobules. **Bar plots show significant associations (FDR corrected, p<0.05)** of a psychological term (behavioral domains and paradigm classes) from BrainMap meta-data given observed brain activity. Functional profiling was performed as individual anterior (A) and posterior (B) masks, and difference analyses (C). In all plots the x-axis indicates relative probability values, red refers to anterior cerebellar “motor” lobules and green refers to posterior cerebellar “motor” lobules.