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Dysfunctional Activation of the Cerebellum in Schizophrenia: A Functional Neuroimaging Meta-Analysis

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Abstract

The cognitive dysmetria framework postulates that the deficits seen in schizophrenia are due to underlying cerebello-thalamo-cortical dysfunction. The cerebellum is thought to be crucial in the formation of internal models for both motor and cognitive behaviors. In healthy individuals there is a functional topography within the cerebellum. Alterations in the functional topography and activation of the cerebellum in schizophrenia patients may be indicative of altered internal models, providing support for this framework. Using state-of-the-art neuroimaging meta-analysis, we investigated cerebellar activation across a variety of task domains affected in schizophrenia and in comparison to healthy controls. Our results indicate an altered functional topography in patients. This was especially apparent for emotion and working memory tasks, and may be related to deficits in these domains. Results suggest that an altered cerebellar functional topography in schizophrenia may be contributing to the many deficits associated with the disease, perhaps due to dysfunctional internal models.

Keywords

schizophrenia; meta-analysis; cerebellum; cognitive dysmetria; functional neuroimaging; internal models

Introduction

Schizophrenia is a debilitating disorder, characterized by a wide array of deficits involving executive function, emotion, working memory, language, and motor functioning (Andreasen & Olsen, 1982; Gold & Harvey, 1993; Pantelis et al., 1997). Because of the broad presentation and accompanying debilitating effects, there is great interest in understanding the neural substrates of these characteristics. One prominent model, cognitive dysmetria

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Authorship

Both authors developed the study concept, and J.A.B. implemented the literature search and meta-analysis under the supervision of V.A.M. J.A.B. and V.A.M. interpreted the data. J.A.B. wrote the manuscript and V.A.M. provided critical revisions. Both authors approved the final version of the manuscript for submission.

Conflict of Interest Declaration

There are no potential conflicts of interest to report.

(Andreasen et al., 1996; Andreasen, Paradiso, & O'Leary, 1998), implicates the cerebellum and its networks with both the prefrontal and parietal cortices (via the cerebello-thalamo-cortical circuit) in cognitive and affective deficits and symptoms (Andreasen et al., 1996, 1998). Cognitive dysmetria refers to the constellation of cognitive deficits seen in patients with schizophrenia. This framework, modeled off from the notion of motor dysmetria where individuals have uncoordinated movements, suggests that uncoordinated thought may be occurring in schizophrenia (Andreasen et al., 1996). Patients have marked cognitive and affective deficits, and the cerebellum, which is important for coordinating motor behavior, and its thalamo-cortical networks are implicated and may contribute to cognitive deficits as well.

While the cerebellum is most often conceptualized as a motor structure, its connections with both motor and non-motor cortical regions indicate that it plays a role across domains (Ramnani, 2006), and the functional topography of this structure (regionally specific activations for different task domains) also supports this notion (Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012). Recent theories postulate that the cerebellum forms internal models (both forward and inverse) for both motor and higher level cognitive tasks, allowing for ongoing feedback resulting in well-timed and coordinated behaviors (Ito, 2008; Ramnani, 2006). Relying on similar cellular mechanisms and architecture, the cerebellum may also coordinate higher level thought related to cognition and affective processing. Indeed there is now an extensive body of literature indicating cerebellar involvement in the cognitive and affective domains (for a review see Strick, Dum, & Fiez, 2009).

As noted above, a growing body of evidence indicates that the cerebellum has a distinct functional topography. At the most basic level, distinct regions associated with motor and cognitive function characterize this topography. Dissociated closed-loop motor and cognitive circuits have been mapped in non-human primates (Dum & Strick, 2003; Kelly & Strick, 2003; Strick et al., 2009), and recent neuroimaging work has indicated comparable circuits in the human brain as well (Bernard et al., In Press; Bernard et al., 2012; Habas et al., 2009; Krienen & Buckner, 2009; O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010; Salmi et al., 2010). The dissociated motor and cognitive circuits result in segregated inputs and outputs of the cerebellum based on the regions with which it is connected. Recently, both meta-analysis and functional neuroimaging methodologies have further supported these distinct motor and cognitive dissociations within the cerebellum, and provided evidence for a more fine-grained functional topography across a variety of task domains with remarkable consistency across studies and methods (E, Chen, Ho, & Desmond, 2012; Stoodley & Schmahmann, 2009a, 2010; Stoodley et al., 2012). The anterior cerebellum (lobules I-V) as well as lobules VIIa and VIIb in the posterior cerebellum are implicated in motor function (Grodd, Hülsmann, Lotze, Wildgruber, & Erb, 2001; Stoodley & Schmahmann, 2009, 2010; Stoodley et al., 2012). The more lateral posterior regions of the cerebellum, particularly, lobule VI, Crus I, Crus II, and lobule VIIb are associated with a variety of cognitive functions (working memory, language, executive function) as well as affect, and verbal and spatial processing are differentially lateralized (Stoodley & Schmahmann, 2009, 2010; Stoodley et al., 2012). However, it is of note that lobule VI has resting state connections with both motor and prefrontal cortical regions, and has also been

implicated in motor learning (Bernard & Seidler, 2013; Bernard et al., 2012). Thus, evidence indicates that the cerebellum is involved in motor, cognitive, and affective processing, but its topography indicates somewhat distinct processing regions across the structure. Importantly, the MODular Selection And Identification Controller (MOSAIC) computational model (Hiroshi Imamizu, Kuroda, Miyauchi, Yoshioka, & Kawato, 2003; Wolpert & Ghahramani, 2000) suggests that there is a modular organization to the cerebellum with distinct representations for internal models of differing behaviors. The functional topography and closed-loop circuitry of the cerebellum support this notion.

As such, the cerebellum in schizophrenia has been a topic of great recent interest (reviewed in Andreasen & Pierson, 2008; Picard, Amado, Mouchet-Mages, Olié, & Krebs, 2008) and there is now quite a bit of evidence indicating differences in cerebellar morphology in patients with schizophrenia and those at risk for psychosis (e.g., Bottmer et al., 2005; Dean et al., 2014; Jacobsen et al., 1997; Levitt et al., 1999), and both structural and functional connectivity between the cerebellum and cortex are altered (Liu, Fan, Xu, & Wang, 2011). Understanding differences in cerebellar activation across task domains in patients with schizophrenia is therefore of particular interest, and would provide important insight into the potential role of the cerebellum in cognitive and affective function, as well as its role in symptoms.

Given that there now exists a large body of functional neuroimaging data in patients with schizophrenia, meta-analysis allows us to investigate patterns across these data sets and patient groups to better understand cerebellar dysfunction in this population. Indeed, meta-analyses of functional neuroimaging data have already provided important insight across multiple behavioral domains, including emotion, executive function, and memory (e.g. Achim & Lepage, 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Taylor et al., 2012). Recently, Lungu and colleagues investigated the cerebellum in schizophrenia (Lungu et al., 2012) by noting whether or not there was hypo- or hyper-activation in patients with schizophrenia relative to controls. Additionally, they provided a graphical representation of the location of cerebellar foci for each study. While this was a timely study that provided general information about cerebellar activation, inference is relatively limited, particularly given the advances in neuroimaging methodology that allow for sophisticated quantitative comparison of activation across groups (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Thus while the work of Lungu and colleagues provided interesting descriptive information and some evidence of abnormal cerebellar activation in individuals with schizophrenia (based on chi-squared tests), the appropriate quantitative comparisons optimized for neuroimaging data across groups can provide an important perspective for understanding both cerebellar activation differences in these patients, as well as differences in the functional topography of cerebellar activation across groups.

The goal of this review was to use activation-likelihood estimation (ALE) meta-analysis (Laird et al., 2005; Turkeltaub et al., 2012, 2002), which is specifically designed to compare neuroimaging results across studies, to investigate differences in activation across a variety of task domains affected in schizophrenia (i.e., emotion, executive function/attention, language, motor function, and working memory) between patients with schizophrenia and controls, and to investigate differences in cerebellar functional topography across these

groups. Thus, this allowed for a quantitative review of cerebellar dysfunction in patients with schizophrenia. We hypothesized that the schizophrenia group would show decreases in cerebellar activation across task domains, consistent with previous work, but that there would be differences in the functional topography of the cerebellum in these patients.

Methods

Literature Search

Papers were identified through two PubMed searches (<http://www.ncbi.nlm.nih.gov/pubmed>). In both searches, we used the limits “Adult 19–44”, “English”, and “Humans”. We limited our meta-analysis to this age group for two reasons. First, prior meta-analyses and work investigating the functional topography of the cerebellum has focused on healthy young adult populations (E, Chen, Ho, & Desmond, 2012; Stoodley & Schmahmann, 2009; Stoodley et al., 2012), and such a limit is necessary for comparisons with the extant literature. Second, there is significant evidence to indicate that cortical activation during motor and cognitive tasks differs in older adulthood (Cabeza, 2002; Seidler et al., 2011), and this is also appears to be the case in the cerebellum (reviewed in Bernard & Seidler, In Press; Carp, Park, Hebrank, Park, & Polk, 2011). Here, we were most interested in the effect of disease on cerebellar activation, and therefore wanted to exclude aging populations where there may be additional interactions between advanced age and disease that we would be unable to account for. The tasks included in our analyses were limited to the following categories in order to investigate cerebellar topography with respect to prior work in healthy adults (E et al., 2012; Stoodley & Schmahmann, 2009): emotion, executive function/attention, language, motor, and working memory (see Supplementary Table 1 for task inclusions by category). Additional exclusion criteria were consistent with prior cerebellar meta-analyses (Bernard & Seidler, 2013; Stoodley & Schmahmann, 2009). That is, we excluded papers that did not use functional neuroimaging methods, did not report coordinates in the cerebellum, did not report coordinates in standard space, studies using only region of interest analyses, and those that did not use standard contrasts analyses (e.g. independent components analysis). The search terms were defined in a way that paralleled terms recently used in meta-analyses of the cerebellum in healthy adults (Bernard & Seidler, 2013; E et al., 2012; Stoodley & Schmahmann, 2009) to allow for comparisons across investigations. The first search used the search term “cerebell* AND imaging AND schizophrenia”. This search resulted in 345 possible papers, and this was narrowed down to 14 papers for inclusion (Table 2). Because of the low number of papers, and given that the cerebellum is at times not discussed in manuscripts where such foci are found, we conducted a second broader search using the search term “schizophrenia AND neuroimaging”. Furthermore, this additional search eliminated any bias that existed in our initial search due to the inclusion of the term “cerebellum”. This search resulted in 1932 possible papers, and these were ultimately narrowed down to 28 additional papers (Table 1). In total, 42 papers were included in our analyses. In both cases, numerous papers were excluded. We first removed papers that were focused on structural imaging and did not include functional conditions. From there, functional analyses were further examined to determine whether or not they used standard GLM analyses, and included cerebellar foci presented in standard space (MNI or Talairach). Foci from both patients and control subjects were included in our

analyses to allow for comparison across groups. Table 1 provides details regarding the imaging modality, task, contrasts, and number of foci for both the patient and control groups. The number of studies included in each task domain are comparable to prior meta-analyses of the cerebellum in healthy adults (Bernard & Seidler, 2013; E et al., 2012; Stoodley & Schmahmann, 2009).

ALE Meta-Analysis

All analyses were conducted using GingerALE 2.3 (<http://www.brainmap.org/ale/>; Eickhoff et al., 2009; Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Laird et al., 2005; Turkeltaub et al., 2012), using the most recent algorithm designed to minimize the impact of individual experiments (Turkeltaub et al., 2012). Foci were first organized by task domain and further divided into those associated with patients and those associated with healthy controls. Because of the need to have all foci in the same standardized space, Talairach coordinates were converted to MNI space. All papers where data were normalized directly into Talairach space, along with those papers that specified the use of the Lancaster (icbm2tal) transform (Lancaster et al., 2007) were transformed to MNI space also using the Lancaster transform. This approach was also taken for papers published after the Lancaster transform was available, but for which no transform was specified in the article text. For papers where MNI data were transformed to Talairach space using the Brett (mni2tal) transform, and any paper prior to 2007 where coordinates were transformed but the transform was not specified, we used the inverse of the Brett transform to bring the foci into MNI space.

The text files were then entered into GingerALE for analysis. The algorithm computes activation likelihood estimation (ALE) values for every voxel in the brain, resulting in estimations of the likelihood that a particular voxel is activated during a given task (Eickhoff et al., 2009). During analysis, a full-width half half-maximum (FWHM) Gaussian blur is used on each set of foci, but the FWHM value is adjusted automatically based on the number of subjects associated with each set of foci (Eickhoff et al., 2009). In our analyses, the output indicated that the FWHM was between 8 and 11 mm. We used the smaller more conservative mask option available in GingerALE. For the within-group analyses for each task category cluster level correction was used, as suggested by Eickhoff and colleagues (Eickhoff et al., 2012). All ALE maps were thresholded using an uncorrected $p < .001$ as the cluster-forming threshold, and FDR $p < .05$ for cluster-level inference, with 5000 threshold permutations. Because GingerALE is not very robust when small numbers of studies are included for group contrasts (less than 15 per group), we were unable to use a similar correction for our group contrasts. We therefore evaluated all group contrasts and conjunctions using an uncorrected $p < .05$ with 10,000 p-value permutations and a minimum cluster size of 50 mm^3 . This cluster size minimum was imposed to help account, at least in part, for this lack of additional statistical correction. It is also of note that all results presented from these analyses well exceed this size minimum (please see Table 3). Contrasts were computed using the foci from each group, as opposed to using group contrasts from the original manuscripts included in this study. Not all included studies included both a patient and control group. For example, several studies consisted of investigating patients with schizophrenia before and after a treatment intervention, and did evaluate healthy controls. Therefore, in order to include all of the possible foci and have more power, we contrasted

the foci from each group on all of the behavioral domains for the individual contrasts. Cluster locations were identified using the Schmahmann atlas (Schmahmann et al., 1999), as the vast majority of studies in these analyses used standard normalization procedures, due to the unavailability of the SUIT template (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009; Diedrichsen, 2006) and normalization procedure (for further discussion of this issue, please see our limitations section).

Results

Within Group Task Activation

We first evaluated activation overlap for each task domain in the patient and control data separately (Figure 1). Table 2 provides the peak coordinates, weighted centers, cluster sizes, and cerebellar lobules for each task separately for the controls and the patients.

Emotion tasks activated Crus I bilaterally in control individuals, in addition to Crus II and Lobule VI. This pattern is consistent with previous meta-analyses investigating cerebellar function (E et al., 2012; Stoodley & Schmahmann, 2009). In patients with schizophrenia, activation was shifted slightly medially to primarily include lobule VI, though activations were also seen in the brainstem and ventral regions of the cortex bordering the cerebellum. This latter finding is likely the effect of the normalization parameters and smoothing that result in the bleeding of activation on the regions near the cerebellar-cortical boundary.

Activation during executive function and attention tasks was also bilateral and predominantly activated Crus I and lobule VI in control individuals. In patients, there was again bilateral activation in Crus I and lobule VI, but regions previously associated with motor function and networks with the motor cortex (lobule V and VIIIb) (Bernard et al., 2012; Stoodley & Schmahmann, 2009) were also activated.

Unlike Stoodley and colleagues (Stoodley & Schmahmann, 2009) we found activation for language related tasks in the left lateral cerebellum in healthy control populations, whereas we found the activation in patients in the expected right hemisphere (primarily Crus I). With respect to motor tasks, control activation was largely focused on the bilateral secondary motor representation in lobules VIIIa and VIIIb (Grodd et al., 2001), with some more anterior activation in left lobule VI. In patients, activation was localized primarily to left lobule V.

Finally, we investigated the activation patterns associated with working memory in both patients with schizophrenia and control subjects. The bilateral clusters of activation in Crus I and Crus II are consistent with extant meta-analyses (Bernard & Seidler, 2013; E et al., 2012; Stoodley & Schmahmann, 2009), though there appears to be less activation in the patients (for a quantitative comparison, please see below).

Group Differences in Task Activation

Visual examination of our initial analyses indicated that cerebellar activation across a variety of task domains was altered in patients with schizophrenia, consistent with our hypothesis. To quantitatively test our hypothesis, we use statistical contrasts of the ALE

maps for patients with schizophrenia and controls within each task domain to investigate group differences, as well as overlap between the two groups. Broadly speaking, our results support the notion that task-related cerebellar activity is altered in schizophrenia, which is perhaps indicative of dysfunctional internal models of complex behavior. We discuss the specific patterns for each task domain in turn (Table 3, Figure 2).

Across multiple studies of emotion, the most striking finding was that of greater left Crus I and II activation in healthy controls compared to patients. There was a small area of overlap in right Lobule VI, as well as a small region of greater activation in patients, though this was located in the ventral visual cortex (please see our limitations section for a specific discussion of this). Overall, it appears as though patients with schizophrenia are not engaging the cerebellum to the same degree as control individuals during emotion tasks, and this may potentially contribute to symptomatology and affective deficits in this population (Kring & Moran, 2008; Taylor et al., 2012).

Executive function and attention tasks resulted in greater activation in lobule VI of patients with schizophrenia. There are also substantial regions of overlap in bilateral lobule VI. There are some regions of overlap, but also differences in the topography of activation. Within the cognitive task domain, it is interesting to note that the effects for working memory were quite the opposite, though the impact with respect to functional topography and internal models is similar. For these tasks, there were several small clusters of overlap in bilateral Crus I, but there was also a large cluster of significantly greater activation in left Crus I, and a small cluster in right Crus I. Together, this indicates that although some similar cerebellar resources are engaged during working memory in both groups, the topography of this activation differs to some degree and the degree of activation is somewhat decreased in patients.

The group contrasts during a variety of language tasks revealed that there were small regions of significantly higher activation for each group. Controls showed significantly greater activation in medial regions of the secondary motor representation (lobules VIIa/VIIIb), while the patient group had significantly higher activation in right Crus I. The greater control activation may have to do with tasks requiring speech production, which may be influenced by anti-psychotic medications due to its motor components.

Motor activation, like language, also showed distinct regions of activation in both the control and schizophrenia groups. In the controls relative to patients with schizophrenia, activation during motor tasks was increased in left Crus I, secondary motor lobules VIIa and VIIIb, along with left lobule VI. The increased engagement of Crus I is of interest given its role in cognitive function and associations with prefrontal cortical regions (Bernard et al., 2012; Stoodley & Schmahmann, 2009), and this may be important for understanding behavioral differences between patients and controls. Conversely, the patient group engaged left lobules V and VI more than control individuals.

Finally, in addition to several task domains where the patient group showed decreased functional activation relative to controls, it is worth noting that there were several studies included in our meta-analysis that did not show any statistically significant cerebellar

activation foci in individuals with schizophrenia (Table 1). This further supports the argument that there is a general decrease in cerebellar involvement in motor and cognitive performance in schizophrenia, and is consistent with the findings of Lungu and colleagues (Lungu et al., 2012).

Discussion

Using ALE meta-analysis we quantitatively demonstrated that patients with schizophrenia have altered cerebellar activation relative to control subjects. Regions of decreased activation were seen across all of the investigated task domains except for executive function/attention, though there were also areas of increased activation for language, motor, and executive function/attention tasks. In particular, regardless of task domain, activation decreases were particularly common in the lateral lobules VI and Crus I. Together, this is indicative of an altered functional topography within the cerebellum for this patient group, and provides additional support for cerebellar involvement in cognitive dysmetria. Furthermore, we speculate that this altered functional topography may result in altered and dysfunctional internal models, particularly forward models, in patients with schizophrenia.

Cerebellar Functional Topography in Controls and Patients with Schizophrenia

Across all task domains investigated here, we found that the functional topography in control individuals was generally consistent with the topography described in previous investigations using meta-analysis (E et al., 2012; Stoodley & Schmahmann, 2009) and task-based functional neuroimaging (Stoodley et al., 2012). However, we did see some slight differences in language and motor activation. For language tasks, we found activation in the left hemisphere. However, it is important to note that E and colleagues (E et al., 2012) found bilateral activation associated with language in Crus I and lobule VI, though they investigated both expressive and receptive language tasks. Our findings in control participants may therefore be a result of the tasks available for inclusion in our meta-analysis, resulting in the similarity between our findings with those of E and colleagues. In motor tasks, our activation for controls was largely focused in the secondary motor representation of the cerebellum. While it is certainly surprising to not see the strong right hemisphere activation which was demonstrated in previous cerebellar meta analyses (Bernard & Seidler, 2013; Stoodley & Schmahmann, 2009), the handedness of participants included in patient studies is more variable. In healthy populations investigations are typically restricted to right-handed individuals, whereas investigations of patient populations will often include left handed individuals, in both the patient and control groups.

The functional topography in patients however, did seem to differ, particularly when compared to controls. This was represented primarily as decreased activation in some tasks and cerebellar regions, but also as increased activation. In both cases, this is indicative of cerebellar dysfunction. The decreases likely indicate that patients with schizophrenia are not appropriately engaging the cerebellum, and associated cortical regions during task performance. However, the increases are also quite interesting. In this case, it implies that patients with schizophrenia are over activating regions, but most likely it is because they are relying upon *different* cerebellar regions (and their associated cortical areas as well). The

greater activation in executive function and motor tasks was in anterior motor regions that were not activated in the control group. This may be related to the execution of the tasks, and perhaps additional reliance upon motor regions to make responses and process information. In other words, the over activation may be a form of compensation for a wide array of cerebellar, or other neural dysfunction. The greater activation in emotion is likely an artifact due to cerebellar imaging methods (please see “Limitations” for a more in depth discussion of this issue). Interestingly, recent structural imaging evidence in patients with schizophrenia provides a possible structural basis for these functional topographical alterations (Kim et al., In Press). Kim and colleagues investigated the modular structural architecture of the cerebellum in patients and controls, and found that there were slight differences in the patient group, primarily in Crus II.

Regional Activation Differences

The vast majority of group differences in cerebellar functional activation were primarily localized to lobules VI and Crus I (Table 3). This was generally consistent across all task domains with the exception of language activations where group differences were seen in secondary motor regions (lobules VIIIa and VIIIb). Importantly, these regions are associated with prefrontal cortical areas (Bernard et al., 2012; Kelly & Strick, 2003; Salmi et al., 2010). Furthermore, these regions are also adjacent to Crus II, which was recently implicated by Kim and colleagues with respect to differences in the structural modularity of the cerebellum in patients with schizophrenia (Kim et al., In Press). These aspects of the cerebellum are active during the performance of working memory tasks (Chen & Desmond, 2005), and are associated with cognitive functions as demonstrated with meta-analysis (Bernard & Seidler, 2013; E et al., 2012; Stoodley et al., 2012). Thus, it seems as though patients with schizophrenia do not effectively utilize cerebellar regions associated with higher order cognitive function and the prefrontal cortex. Interestingly, differences in activation of these posterior-lateral aspects of the cerebellum (lobule VI and Crus I) were also seen with motor tasks. While motor activation is typically associated with the anterior cerebellum along with lobules VIIIa and VIIIb, these regions are engaged during more complex motor task performance (Schlerf, Verstynen, Ivry, & Spencer, 2010), and lobule VI is also associated with premotor regions as revealed by resting state connectivity analysis (Bernard et al., 2012). With that said, the activation differences in these lateral cerebellar regions may also be due to prefrontal cortical dysfunction, given the interaction between the regions. With these analyses we are unable to dissociate whether or not this is truly cerebellar dysfunction, or an additional indicator of prefrontal cortical dysfunction. Future functional imaging work targeting this question specifically is needed.

However, it is important to note that these regional findings differ somewhat from those of Lungu and colleagues (Lungu et al., 2012). They noted that cerebellar hypoactivation in patients with schizophrenia (relative to controls) was located medially in lobules IV and V, with some lateral hypoactivations associated with cognitive tasks. One factor that may contribute to these differences are the papers included in the analyses, as we surveyed work that included newer references not available at the time of their analyses, and differences in inclusion criteria. However, the methodological limitations of their study likely account for the differences seen when compared with the findings reported here. Specifically, they used

methods that do not take into account the complexity of neuroimaging data, particularly given the varying subject numbers in each study, and the additional statistical considerations related to the large number of voxels in the brain. Their topographical findings were based off of plotting points in studies showing cerebellar activation in patients and controls, but were not the result of statistical comparisons across the two groups (Lungu et al., 2012). While the work of Lungu and colleagues (Lungu et al., 2012) represents an important first step towards understanding the cerebellum in schizophrenia across studies, the interpretation of their results is limited due to the somewhat rudimentary methodological approach that the authors took. More modern state-of-the-art meta-analytic methods, such as ALE as used here, take into account many additional variables associated with neuroimaging, particularly with respect to the number of subjects included in each analysis (Eickhoff et al., 2012; Turkeltaub et al., 2012). Specifically, instead of comparing findings with a chi-squared test based on the number of studies that do or do not show a result, or just plotting foci as done by Lungu and colleagues (Lungu et al., 2012), the ALE method used here models the activation foci as probability distributions, with the peak centered at the coordinate from a particular study. These probability distributions are then compared and modeled with respect to the probability of activation occurring in a given voxel in the brain, using multiple permutations (Turkeltaub et al., 2002). Our findings presented here are the result of state-of-the-art statistical meta-analytic comparisons that allow us to make stronger inferences regarding these group differences in activation.

Cerebellar Internal Models in Schizophrenia

The cerebellum is thought to be a crucial structure for the formation of new internal models of both motor and cognitive behaviors (Ito, 2008; Ramnani, 2006). These internal models then allow for the smooth and coordinated performance of behaviors by integrating information (for example, sensory information during a motor task) as the task is ongoing (Ito, 2008; Ramnani, 2006). Internal models are typically divided into two classes, forward and inverse models. Forward models involve efference copies of a particular command, and the actual behavioral outcomes are compared with the predicted outcomes. Inverse models use copies of the reciprocal of the command and it works as a feed-forward model that does not receive feedback (Ito, 2008). Though the two types of internal models work differently, Ito (2008) has suggested that they may work together. Given that there are functional differences in the cerebellum across an array of tasks, and that internal model processing is thought to be a primary function of the cerebellum, we suggest that the decreased activity in the cerebellum may be indicative of internal model dysfunction, particularly with respect to forward models, though inverse models may also be impacted.

There is evidence indicating that patients with schizophrenia and those at ultra high-risk for psychosis are impaired at sensorimotor integration, as evidenced by deficits in postural sway (Bernard, Dean, et al., In Press; Kent et al., 2012; Marvel, Schwartz, & Rosse, 2004). The inability to effectively modify the body position during a postural sway task may be indicative of a cerebellar deficit as the structure may not be appropriately updating and modifying the ongoing behavior, and in at-risk populations postural sway has been linked to cerebellar resting state networks (Bernard, Dean, et al., In Press). One possibility is that this

is due to dysfunctional internal models, particular with respect to forward model processing (that is, the ongoing evaluation and updating of behavior based on an efference copy).

Cerebellar internal model dysfunction may be manifest in several different patterns of cerebellar activation. First, if the cerebellum is not being appropriately engaged during task processing, this would be seen as decreased activation relative to a control group that is appropriately relying upon this mechanism. This would imply that individuals may not be utilizing existing internal models. Second, the topography of cerebellar activation may be altered because the modularity of the internal models is altered. That is, if individuals need to rely upon additional neural circuits for processing, this may result in an inefficient model, that is differently stored in the cerebellum. Our results provide evidence for both of these circumstances, and are discussed further below. Finally, in motor learning tasks, the formation of a new internal model is associated with decreased activation in the cerebellum over the course of learning (Imamizu et al., 2000). The same pattern might therefore be expected in the non-motor domains. If internal model formation is altered, we would not expect to see this decreasing pattern of activation over the course of learning. This would be manifest as an interaction between a group of patients with schizophrenia and controls, wherein cerebellar activity would be modulated in the control group, but not in the patient group. This would provide a more direct test with respect to the formation and reliance upon internal models in patients with schizophrenia. Unfortunately however, our meta-analytic methods do not allow us to test this hypothesis, and to date there is little work available in the literature to provide evidence either for or against this pattern of activity. Future work is clearly necessary to better understand forward models and the cerebellum in schizophrenia.

As briefly described previously, within the cerebellum, it is thought that there is a modular organization with distinct representations for internal models as proposed by the MOSAIC computational model (Hiroshi Imamizu et al., 2003; Wolpert & Ghahramani, 2000). While one might expect some redundancy across similar tasks, recent evidence from multiple domains of motor learning support this modularity (Bernard & Seidler, 2013). Though the MOSAIC model was initially conceptualized for motor tasks, assuming similar modularity in the cognitive domain is a reasonable extension of the model. Indeed, the recently revealed functional topography of the cerebellum, along with the distinct motor and cognitive cerebello-cortical loops support this (Bernard, Peltier, et al., In Press; Bernard et al., 2012; Stoodley & Schmahmann, 2009; Stoodley et al., 2012), and such a functional topography may be indicative of healthy cerebellar function and internal model processing.

Dysfunctional internal models would result in a wide range of behavioral deficits, resulting in uncoordinated behavior and thought, and may be manifest in part as an altered cerebellar functional topography. In particular, individuals would have difficulty learning and reaching automaticity in task performance. For example, when performing a working memory task, an individual has to hold and manipulate information in their mind. In addition to the cortical processing, the cerebellum would also be involved to modify the forward model of the thought and processing involved in such a task, and as performance continues, individuals are better able to quickly and implicitly perform a working memory manipulation task (Ito, 2008). Over time, as the forward model is fine-tuned, performance could be described as implicit and “intuitive” (Ito, 2008), as opposed to early on in task performance where performance is very effortful and heavily reliant upon prefrontal cortical

processing (for additional task domain specific evidence related to forward models in the non-motor domain, please see Ito, 2008). However, in patients with schizophrenia, this forward model may not be appropriately updated and fine-tuned over time, so errors will continue and performance will not improve or become automatic. Thus, a better understanding of cerebellar topography in schizophrenia has important implications for understanding the cerebellar representations of these internal models, that may give rise to the varying symptoms and deficits that these patients face.

Across all investigated task domains, there were differences (either increases or decreases) in cerebellar activation in patients with schizophrenia relative to controls. The instances of decreased activation indicate that patients with schizophrenia may not be appropriately engaging the cerebellum for task performance, and areas of increase relative to controls have similar implications. The latter is indicative of reliance upon different, and perhaps less efficient, neural circuits. Together, this is indicative of dysfunctional activation likely due to the formation and engagement of internal models of behavior (both motor and cognitive). Furthermore, we suggest that a well-defined topography may be indicative of healthy cerebellar function, given the assertions of the MOSAIC model wherein internal models for a variety of behaviors are distinct in their representations. The reliance upon different regions is perhaps indicative of abnormal processing.

Finally, though work investigating forward models in patients with schizophrenia has been limited, recent findings from Shergill and colleagues (Shergill et al., 2014) provide important insight with respect to sensory prediction errors. The authors found that in a task involving sensory prediction error, the cerebellum was behaving normally in its role as a comparator. However, there was a main effect of group such that patients with schizophrenia showed decreased activation relative to controls across all conditions. Shergill and colleagues thus suggest that this may have downstream effects on sensory prediction (Shergill et al., 2014). At first glance, this seems potentially problematic for our suggestion that cerebellar forward model processing is dysfunctional in patients with schizophrenia. However, there are several considerations with respect to this work. First, they did not look at learning over time, and the formation of new internal models of a behavior. Indeed the cerebellum functioned well as a comparator with respect to the predicted and actual sensory consequences of a movement. But, it is unclear whether or not cerebellar activation would be modulated over time in ways that are consistent with the formation of new internal models of behavior (e.g., Imamizu et al., 2000). Second, as described above, the cerebellum is made up of anatomically segregated functional units. The regions associated with sensorimotor processing are anatomically and relatively functionally distinct from those associated with higher-level cognitive processing (Stoodley & Schmahmann, 2009; Stoodley et al., 2012). The majority of group differences in our work were seen in the latter areas (lobule VI and Crus I). Thus, it is certainly possible that in patients with schizophrenia there is a greater impact on internal models related to higher order processing or affect. However, this notion in general is speculative. Further testing using cerebellar tasks that eliminate motor demands such as those developed by Balsters and colleagues (Balsters, Whelan, Robertson, & Ramnani, 2013) and those involving affect are needed to test this explicitly. Additionally, this will provide further information as to the specificity of internal model deficits across motor and cognitive domains.

Cerebellar Dysfunction and Deficits in Schizophrenia

Of note, both working memory and emotion tasks showed significantly reduced cerebellar activation, and no regions of increased activation. Given that both emotion and working memory are commonly impacted in schizophrenia (Carter et al., 1998; Kring & Moran, 2008), this lack of activation is especially interesting. General deficits in internal models related to affect and cognitive factors may play into many of the negative symptoms experienced by patients with schizophrenia (Andreasen & Olsen, 1982). For example, if patients with schizophrenia have difficulty understanding facial emotion or process affect differently due to dysfunctional internal models associated with this domain (as suggested here by the significantly reduced cerebellar activation), this may result in social withdrawal or anhedonia if patients struggle to understand emotional information, including their own feelings. Indeed affective deficits have been postulated to play a role in social role function as well, (Keltner & Kring, 1998) further highlighting the broad impact of these deficits. This is consistent with our recent work in ultra high-risk individuals showing associations between negative symptom severity and both cerebellar-mediated tasks, and resting-state network connectivity (Bernard, Dean, et al., In Press). The inability to appropriately monitor these complex behaviors therefore has key implications for symptomatology and general day-to-day functioning.

Similarly, it is also possible that an internal model deficit may contribute to the positive symptoms of schizophrenia such as psychosis. For example, in the somatosensory field and study of the cerebellum, one fascinating finding is that one cannot tickle oneself (Blakemore, Wolpert, & Frith, 1998). This has been linked to cerebellar and somatosensory cortex processing. In a study of healthy individuals, Blakemore and colleagues (1998) observed that the somatosensory cortex was active during external tickling stimulation to the palm of the hand, but not so during self-generated tickling. Furthermore, cerebellar involvement differed between self-generated movements that resulted in tickling and those that did not, and the authors proposed that this is due to the role of the cerebellum in predicting the sensory consequences of movements through efference copies and forward models (Blakemore et al., 1998). Although this has not been tested, we therefore might expect patients with schizophrenia to be more able to tickle themselves given the proposed internal model dysfunction. Extrapolating to other sensory systems, if a sensation is generated internally, perhaps the sound of a voice, a healthy individual would quickly recognize this as being an internally generated voice or thought. A patient with schizophrenia however may not do so given the proposed cerebellar internal model deficits, as the cerebellum may not recognize this as an internal signal. This could then result in many of the abnormal sensory experiences associated with positive symptomatology and psychosis. However, it is critical to note that this would likely also rely upon abnormal processing in the sensory cortices in the first place. The role of the cerebellum is secondary in this instance, but may contribute to the severity of the symptoms. Additionally, these links are highly speculative, and remain untested. Future work to test these ideas and links more directly is needed particularly in different cognitive domains and with respect to affect.

Finally, though we propose here that cerebellar dysfunction may be related to internal model dysfunction contributing to the variety of deficits and symptoms seen in patients with

schizophrenia, we have alluded to several alternative explanations worthy of further discussion. First, the regions of the cerebellum with the most pronounced decreases in activation (lobule VI and Crus I) are strongly associated with the prefrontal cortex. As we briefly acknowledged above, though this might be due to cerebellar dysfunction, it also may further evidence of marked prefrontal cortical function. This is largely consistent with the perspective that neither system operates independently, and abnormal functioning and communication between both is likely to contribute to pathophysiology. That is, cerebellar activation is decreased due to abnormal processing in the prefrontal cortex. However, it is also possible that the end result, more poorly monitored behavior or thought due to the abnormal cerebellar activation, is the same. Future work looking at cerebellar-prefrontal co-activation patterns are needed to better tease apart this important question.

Relatedly, it also may be the case that the altered cerebellar activation is not due to cerebellar dysfunction per se, but due to degraded connections between the cerebellum, thalamus and cortex. Indeed, we recently discussed this potential issue in older adults with respect to internal models (Bernard & Seidler, In Press) as aging populations have decreased cerebellar resting state connections, and there is evidence of decreased cerebellar white matter integrity as well. In this case, while the deficit may be external to the cerebellum, the degraded inputs would result in decreased reliance upon cerebellar processing during task performance. The cerebellum may be completing the appropriate neural computations based on the provided afferent information, but the dysfunctional connections with the rest of the brain are the primary culprit. Investigations coupling functional activation in the cerebellum with measures of both resting state and white matter connectivity are needed to investigate this further. Along these lines, because the cerebellum is important for comparing actual actions to the consequences of those actions (particularly in the sensory domain) (Blakemore et al., 1998), if there are abnormalities in sensory cortices or inputs in patients with schizophrenia, this may also influence cerebellar processing. The information the cerebellum receives may not be correct resulting in performance deficits and symptoms.

Finally, it may be that the altered cerebellar topography serves as compensation for other widespread deficits (such as those discussed above). This is a particularly intriguing hypothesis with respect to the cases where patients with schizophrenia showed *increased* cerebellar activation with respect to controls. This may very well be because patients are relying upon different, less efficient neural circuits to perform a particular task. However, this does not necessarily explain the decreased activation in similar regions that are activated by controls. While this may indicate a difference in neural processing efficiency, the internal models hypothesis is a more parsimonious explanation. Regardless, these findings of dysfunctional cerebellar activation in patients with schizophrenia open up many new and interesting questions, and further highlight the potential role of this important structure in the pathophysiology of the illness. Ongoing and future work will serve to better elucidate and solidify the role of the cerebellum in schizophrenia.

Limitations

While our meta-analytic review has provided important new insights into the cerebellum in schizophrenia, there are also several limitations to consider. First, there is a great deal of

heterogeneity amongst patients with schizophrenia, in terms of symptom types and severity, time since first episode, antipsychotic medications, and additional substance use and abuse. Our findings cut across numerous studies with variable patient populations, and these findings need to be viewed in light of this patient heterogeneity. This is particularly notable given our motor findings, as some antipsychotic medications have side effects that impact the motor system (Tandon & Jibson, 2002). Relatedly, some of the studies included in our analyses included individuals with schizoaffective disorder in their patient samples. Thus, though we present differences between patients with schizophrenia and healthy controls, these differences are may be due in part to medication and substance use, and may vary in their degree across individuals based on symptoms or time since first episode. Second are issues associated with neuroimaging of the cerebellum. Standard image normalization algorithms often result in stretching and warping of the cerebellum along with bleeding over of ventral visual areas due to smoothing (Diedrichsen et al., 2009; Diedrichsen, 2006), and only recently have cerebellar-specific methodologies been developed (Diedrichsen et al., 2009; Diedrichsen, 2006). Because of this, some of the foci included in our study may be due to ventral visual activations. Indeed, this appears to be the case in our contrast indicating more ventral visual activation in patients during emotion tasks, though this was based on cerebellar coordinates. Third, within our task domains, a variety of different tasks were included (for example, the language domain included both word reading and listening to speech). While this is consistent with previous meta-analyses of the cerebellum (Bernard & Seidler, 2013; E et al., 2012; Stoodley & Schmahmann, 2009), this does introduce further heterogeneity into our analyses. We are only able to look at general domains of processing, as opposed to specific tasks, though this is necessary in order to have the power to look at these domains. Individual task types on their own would not provide enough foci for analysis. Relatedly, the contrasts used in a given study can vary. In our analyses, we were careful to only include contrasts related to the task in question (that is, we did not include the control only contrast results), and provided information about the aspects of the task that were evaluated in each study in Table 1. While there is variability across the specific included tasks, there is some general consistency in the areas activated within the cerebellum across task domains, as previously demonstrated by investigations of cerebellar functional topography (E et al., 2012; Stoodley et al., 2012; Stoodley & Schmahmann, 2009). Finally, while the number of study inclusions are comparable to prior cerebellar meta-analyses (Bernard & Seidler, 2013; E et al., 2012; Stoodley & Schmahmann, 2009) only 42 studies were included here, though there are many more functional neuroimaging investigations of schizophrenia. We restricted our investigation to *only* studies showing cerebellar activation in either the control or patient groups, along with those using standard neuroimaging analyses (general linear model/contrast approach versus independent component analysis, for example). However, there are additional neuroimaging studies in the literature that do not show such activation, likely for a variety of reasons including statistical power, potential group differences in the ability to appropriately perform the task, and/or unique performance strategies that do not engage the cerebellum. As such, our results are somewhat biased towards activation in the cerebellum, as the additional studies that were excluded showed no activation in neither the patient nor the control group, though this may be due to a variety of methodological factors which would potentially confound the results, and may not just be due to a lack of involvement in the structure.

Conclusions

Using advanced neuroimaging meta-analysis techniques, we provide a detailed review of cerebellar dysfunction in patients with schizophrenia. Most notably, these patients show different activation patterns within the cerebellum (both increases and decreases) that may reflect dysfunctional internal models, particularly forward models. Finally, this cerebellar dysfunction in a wide array of task domains including cognitive, provide additional support for cerebellar involvement in cognitive dysmetria (Andreasen et al., 1996, 1998).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Within group activation patterns by task type
Significant cerebellar activations within each task domain are presented for each group (warm colors: controls; cool colors: patients). All areas are significant using a $p<.001$ cluster forming threshold, with a FDR $p<.05$ cluster level correction. Coronal slices are presented. All images are presented such that the right hemisphere is presented on the right, and the left hemisphere on the left.

Figure 2. Group differences in activation by task type

Significant group differences as well as significant regions of activation overlap are presented for each task domain. All areas are significant using $p < .05$, with a minimum cluster size of 50 mm^3 . Coronal slices are presented. All images are presented such that the right hemisphere is presented on the right, and the left hemisphere on the left. Red: controls > patients; Blue: patients > controls; Purple: overlap.

Table 1

Studies included in our meta-analysis, including imaging modality, sample size, a general task description, and the number of foci per group.

Study	Imaging Modality	Emotion			Task	# SCZ Foci	# CON Foci
		N, SCZ	N, CON				
Lakis, Jiménez, Mancini-Marié, Stip, Lavoie, & Mendrek (2011), <i>Psychiat Res-Neuroim</i> , 194, 245–56.	3 T fMRI	37	37		Retrieval of high arousal emotional images relative to neutral images	3*	1
Kumari, Fannon, Peters, flyche, Sumich, Permkumar, et al. (2011), <i>Brain</i> , 134, 2396–407.	1.5 T fMRI	38	0		Emotional faces & participants indicated gender. Fear and anger relative to a control oval included here only at baseline assessment	3	n/a
Taylor, Chen, Tso, Liberzon, & Welsh (2011), <i>J Psychiat Res</i> , 45, 526–38.	3 T fMRI	21	21		Preference (yes or no to the prompt “Like”) in emotional faces (positive, negative, fear) contrasted with gender discrimination condition	2	5
Sugurladze, Chu, Marshall, Evans, Anilkumar, Tinehin et al. (2011), <i>J Psychopharm</i> , 25, 722–33.	1.5 T fMRI	16	16		Implicit emotion task where participants assessed gender of faces showing varying degrees of emotion. Only baseline assessment included	4	5
Mendrek, Mancini-Marié, Fahim, & Stip (2007), <i>Aust N: J Psychiat</i> , 41, 136–42.	1.5 T fMRI	10	0		Passive viewing of negative and neutral emotional faces in women	2	n/a
Dowd & Barch (2010), <i>Biol Psychiat</i> , 67, 902–11.	3 T fMRI	40	32		Evaluation of emotional pictures, contrasting high and low to neutral faces	1	1
Diaz, He, Gaddie, Bellion, Belger, Voyvodie et al. (2011). <i>J Psychiat Res</i> , 45, 1184–93.	3 T fMRI	11	17		Passive viewing of emotional and neutral stimuli during the maintenance period of a working memory task. Only the maintenance activity included	0	2
Taylor, Phan, Britton, & Liberzon (2005). <i>Neuropsychopharmacol</i> , 30, 984–95.	PET	18	10		Rating of emotional images (IAPS); contrasted emotional and non-aversive images	0	1
Phillips, Williams, Senior, Bullmore, Brammer, Andrew, et al. (1999). <i>Psychiat Res-Neuroim</i> , 92, 11–31.	1.5 T fMRI	10	5		Patients in two groups of 5 (paranoid and non paranoid); Implicit emotion task with gender discrimination	5	4
Executive Function/Attention							
Tragellas, Smucny, Eichman, & Rojas (2012). <i>Schizophr Res</i> , 142, 230–236	3 T fMRI	17	22		Selective attention, auditory oddball task during background noise condition and silence	3	2
Backes, Kellermann, Voss, Kramer, Depner, Schneider, et al. (2011). <i>Eur Arch Psychiat Clin Neurosci</i> , 261 (Suppl 2), S155–60.	fMRI**	17	17		Attention network test; alertness and conflict components	8	0
Dichter, Belion, Casp, & Belger (2010). <i>Schizophrenia Bull</i> , 36, 595–606.	4T fMRI	12	13		Target detection; contrasted with aversive images	3	1
Jamadar, Michie, & Karyanidis (2010). <i>Neuropsychologia</i> , 48, 1305–23.	1.5T fMRI	11	11		Task switching; switch greater than repeat contrast	1	4
Tu, Yang, Juo, Hsieh, & Su (2006). <i>J Psychiat Res</i> , 40, 606–12.	3T fMRI	10	10		Antisaccade task	2	2

Study	Imaging Modality	N, SCZ	N, CON	Task	# SCZ Foci	# CON Foci
Harrison, Yücel, Shaw, Brewer, Nathan, Strother, et al. (2006). <i>Psychiat Res-Neuroim</i> , 148, 23–31.	PET	8	8	Stroop task	2	3
Liddle, Laurens, Kiehl, & Ngan (2006). <i>Psychol Med</i> , 8, 1097–1108.	1.5T fMRI	28	28	Selective attention, auditory oddball; targets relative to baseline and novel stimuli	4	4
Eyler, Olsen, Jeste, & Brown (2004). <i>Psychiat Res-Neuroim</i> , 130, 245–57.	1.5T fMRI	9	10	Visual vigilance task, relative to fixation	3	1
Ojeda, Ortuño, Arbizu, López, Martí-Climent, Peñuelas, et al. (2002). <i>Hum Brain Mapp</i> , 17, 116–30.	PET	11	10	Sustained attention, mental counting with auditory stimulation	3	3
Language						
John, Halahalli, Vasudev, Jayakumar, Jain. (2011). <i>Brit J Psychiat</i> , 198, 213–22.	3T fMRI	24	24	Word generation and word repetition	1	6
Smee, Krabbendam, O'Daly, Prins, Nalesnik Morley, et al. (2011). <i>Acta Psychiatr Scand</i> , 123, 440–450.	1.5T fMRI	9	9	Word generation (letter based) assessed at baseline	1	1
Ragland, Moeller, Bhati, Valdez, Kohler, Siegel (2008). <i>Schizophr Res</i> , 99, 312–23.	3T fMRI	14	13	Semantic word generation	2	3
Stephane, Hagen, Lee, Uecker, Pardo, Kislowski, et al. (2006). <i>J Psychiatry Neurosci</i> , 31, 396–405.	PET	18	12	Word reading, relative to looking at words	1	1
Weinstein, Werker, Vouloumanos, Woodward, & Ngan (2006). <i>Schizophr Res</i> , 86, 130–7.	1.5T fMRI	12	11	Listening to speech (English, Mandarin, and reversed English)	2	2
Koeda, Takahashi, Yahata, Matsuura, Asai, Okubo, et al. (2006). <i>Biol Psychiatry</i> , 59, 948–57.	1.5T fMRI	14	14	Listening to speech (sentences, reverse sentences, and non-vocal sounds) with comprehension questions	0	1
Motor						
Marvel, Turner, O'Leary, Johnson, Pierson, Ponto, et al. (2007). <i>Neuropsychology</i> , 21, 761–77.	PET	12	11	Implicit sequence learning and random button presses	5	4
Müller, Röder, Scheuerer, & Klein (2002). <i>Prog Neuro-Psychoph</i> , 26, 421–6.	1.5T fMRI	30	10	Unilateral, finger-to-thumb opposition task (sequential movement); Patients divided into 3 groups of 10 based on medication, contrasts considered separately by group	2	1
Kumari, Gray, Honey, Soni, Bullmore, Williams, et al. (2002). <i>Schizophr Res</i> , 57, 97–107.	1.5T fMRI	6	6	Implicit sequence learning	0	1
Müller & Klein (2000). <i>Psychiat Clin Neuros</i> , 54, 653–8.	1.5T fMRI	3	3	Self-paced finger tapping	1	1
Mattay, Callicott, Bertolino, Santha, Tallent, Goldberg, et al. (1997). <i>Neuroreport</i> , 8, 2977–84.	1.5T fMRI	8	8	Sequential finger-to-thumb opposition and individually created random movement sequence	0	1
Working Memory						
Dreher, Koch, Kohn, Apud, Weinberger, & Berman (2012). <i>Biol Psychiatry</i> , 71, 890–7.	PET	17	19	N-back (2- versus 0- back)	0	2
Hensler, Falkai, & Gruber (2009). <i>Eur J Neurosci</i> , 30, 693–702.	1.5T fMRI	12	12	Delayed matching to sample with articulatory rehearsal	1	1

Study	Imaging Modality	N, SCZ	N, CON	Task	# SCZ Foci	# CON Foci
Luck, Danion, Marrer, Pham, Gounot, & Foucher (2010). <i>Hippocampus</i> , 20, 936–48.	2T fMRI	16	17	Verbal working memory Sternberg variant with incorrect lures	1	0
Kircher, Thienel, Wagner, Reske, Habel, Kellerman, et al. (2009). <i>Eur Arch Psychiatry Clin Neurosci</i> , 259, 72–9.	1.5T fMRI	14	0	N-back (2- versus 0- back)	1	n/a
Pae, Juh, Yoo, Choi, Lim, Lee, et al. (2008). <i>Int J Neurosci</i> , 118, 1467–87.	1.5T fMRI	12	11	N-back (2-back)	2	3
Koch, Wagner, Nenadic, Schachtzabel, Roebel, Schultz, et al. (2007). <i>Neuroscience</i> , 146, 1474–83.	1.5T fMRI	13	13	Verbal working memory Sternberg variant, with investigation of improvement (speed of response) over time	1	2
Spence, Green, Wilkinson, & Hunter (2005). <i>Brit J Psychol</i> , 187, 55–61.	1.5T fMRI	17	0	N-back (2- versus 0- back) during placebo condition	1	n/a
Yoo & Choi (2005). <i>Int J Neurosci</i> , 115, 351–66.	1.5T fMRI	10	10	N-back (2-back)	2	4
Mendrek, Kiehl, Irwin, Forster, & Liddle (2004). <i>Psychol Med</i> , 34, 1–10.	1.5T fMRI	12	12	N-back (2- versus 0- back)	2	2
Mendrek, Laurens, Kiehl, Ngan, Stip, & Liddle (2004). <i>Brit J Psychol</i> , 185, 205–14.	1.5T fMRI	8	8	N-back (2- versus 0- back)	2	4
Kim, Kwon, Park, Youn, Kang, Kim (2003). <i>Am J Psychiatry</i> , 160, 919–23.	PET	12	12	N-back (2-back versus button press control)	3	0
Honey, Bullmore, & Sharma (2002). <i>Schizophr Res</i> , 53, 45–56.	1.5T fMRI	20	20	N-back (2-back versus button press control)	1	1

* One focus in this study included a missing negative sign in the z coordinate. Addition of the negative sign placed the coordinate in the cerebellum, and was included in this manner.

** Scanner information was not provided, and only the use of fMRI was indicated.

Table 2

Peak ALE coordinates by task category and group. Only statistically significant coordinates are included.

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
Emotion						
Controls						
Cluster 1	1104	From (-36, -82, -38) to (-24, -72, -26) centered at (29.84, -77.71, -33.01)	-35, -76, -34	Crus I	10.83	Cognitive: WM, EF, LNG, EMO
Cluster 2	664	From (-18, -78, -40) to (-10, -70, -30) centered at (-14.13, -73.23, -35.31)	-26, -78, -34	Crus I	10.44	Cognitive: WM, EF, LNG, EMO
Cluster 3	232	From (44, -60, -42) to (50, -54, -36) centered at (47.47, -56.52, -38.35)	-14, -74, -36	Crus II	12.52	Cognitive: WM, LNG
Cluster 4	208	From (36, -52, -30) to (42, -46, -26) centered at (39.59, -48.19, -28.09)	48, -56, -38	Crus I	8.89	Cognitive: WM, EF, LNG, EMO
			40, -48, -28	Lobule VI/Crus I	8.53	Motor & Cognitive: WM, EF, LNG, EMO
Patients						
Cluster 1	392	From (-42, -76, -20) to (-28, -68, -14) centered at (-35.04, -72.77, -16.82)	-40, -74, -16	Cortex	7.93	--
Cluster 2	288	From (-40, -50, -28) to (-34, -46, -24) centered at (-37, -48, -26)	-32, -72, -16	Lobule VI/Cortex	7.69	Cognitive & Motor: WM, LNG, EF
Cluster 3	240	From (36, -54, -28) to (42, -48, -24) centered at (38.15, -50.24, -26.06)	-38, -48, -26	Lobule VI	9.54	Cognitive & Motor: WM, LNG, EF
Cluster 4	160	From (4, -36, -38) to (8, -30, -34) centered at (6, -33, -36)	38, -50, -26	Lobule VI	9.81	Cognitive & Motor: WM, LNG, EF
			6, -32, -36	Brainstem	8.23	--
Executive Function/Attention						
Controls						
Cluster 1	1192	From (-8, -82, -24) to (8, -68, -10) centered at (1.27, -73.67, -16.37)	0, -72, -16	Lobule VI	10.19	Cognitive & Motor: WM, LNG, EF
Cluster 2	832	From (-32, -74, -30) to (-22, -58, -22) centered at (-27.14, -64.35, -25.47)	-26, -62, -26	Lobule VI	10.19	Cognitive & Motor: WM, LNG, EF
Cluster 3	640	From (14, -62, -28) to (22, -52, -18) centered at (18, -57.62, -23.19)	-30, -72, -26	Crus I	7.21	Cognitive: WM, EF, LNG, EMO
Cluster 4	240	From (-32, -76, -40) to (-26, -72, -34) centered at (-29.01, -74, -37.74)	18, -58, -24	Lobule VI	10.65	Cognitive & Motor: WM, LNG, EF
Cluster 5	216	From (-22, -88, -26) to (-18, -84, -20) centered at (-20, -85.94, -23.09)	-30, -74, -38	Crus I	8.88	Cognitive: WM, EF, LNG, EMO
			-20, -86, -24	Crus I	8.76	Cognitive: WM, EF, LNG, EMO

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
Cluster 6	160	From (16, -30, -36) to (20, -26, -30) centered at (18, -28, -33)	18, -28, -33	Brainstem	8.76	--
Patients						
Cluster 1	2240	From (-38, -76, -36) to (-12, -54, -16) centered at (-25.69, -65.39, -23.05)	-30, -72, -22	Lobule VI	11.88	Cognitive & Motor: WM, LNG, EF
			-24, -64, -24	Lobule VI	10.58	Cognitive & Motor: WM, LNG, EF
			-20, -58, -20	Lobule VI	10.41	Cognitive & Motor: WM, LNG, EF
			-22, -62, -34	Lobule VI	8.48	Cognitive & Motor: WM, LNG, EF
Cluster 2	1896	From (8, -66, -28) to (26, -50, -12) centered at (17.7, -56.54, -20.7)	18, -56, -20	Lobule VI	14.11	Cognitive & Motor: WM, LNG, EF
			10, -56, -12	Lobule V	7.27	Motor
Cluster 3	840	From (-46, -74, -44) to (-30, -68, -32) centered at (-38.05, -70.44, -37.33)	-38, -70, -36	Crus I	10.36	Cognitive: WM, EF, LNG, EMO
Cluster 4	672	From (24, -58, -34) to (36, -44, -24) centered at (31.54, -49.59, -28.52)	28, -46, -28	Lobule VIIIb	8.85	Secondary motor representation
			34, -56, -32	Crus I	8.34	Cognitive: WM, EF, LNG, EMO
			34, -48, -26	Lobule VI	8.21	Cognitive & Motor: WM, LNG, EF
Cluster 5	352	From (10, -72, -36) to (16, -62, -32) centered at (13.06, -67.32, -34.32)	14, -68, -34	Crus I/WM	8.92	Cognitive: WM, EF, LNG, EMO
Cluster 6	320	From (-4, -78, -22) to (4, -70, -18) centered at (-32, -73.63, -20.27)	0, -74, -20	Lobule VI	8.54	Cognitive & Motor: WM, LNG, EF
Language						
Controls						
Cluster 1	440	From (-24, -66, -30) to (-18, -56, -24) centered at (-20.99, -61.04, -26.51)	-22, -58, -26	Lobule VI	8.78	Cognitive & Motor: WM, LNG, EF
			-20, -64, -26	Lobule VI	8.49	Cognitive & Motor: WM, LNG, EF
Cluster 2	400	From (-4, -78, -46) to (6, -70, -40) centered at (-93, -73.87, -42.46)	2, -74, -44	Lobule VIIa	9.92	Secondary motor representation
Cluster 3	216	From (-32, -36, -22) to (-28, -32, -18) centered at (-30, -34, -20)	-30, -34, -20	Cortex	8.78	--
Cluster 4	160	From (-16, -72, -28) to (-12, -66, -22) centered at (-14, -69, -25)	-14, -70, -26	Lobule VI	8.21	Cognitive & Motor: WM, LNG, EF
Cluster 5	160	From (-32, -54, -22) to (-28, -48, -16) centered at (-30, -51, -19)	-30, -52, -20	Cortex/Lobule VI	8.21	Cognitive & Motor: WM, LNG, EF
Cluster 6	160	From (-34, -60, -10) to (-30, -54, -4) centered at (-32, -57, -7)	-32, -58, -8	Cortex	8.21	--
Patients						

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
Cluster 1	512	From (20, -72, -46) to (34, -64, -34) centered at (27.8, -68.47, -38.95)	32, -68, -36 22, -68, -42	Crus I Crus II	7.26 6.12	Cognitive: WM, EF, LNG, EMO Cognitive: WM, LNG
Cluster 2	352	From (32, -64, -24) to (40, -58, -16) centered at (36, -61, -20)	36, -60, -20	Lobule VI/Cortex	8.49	Cognitive & Motor: WM, LNG, EF
Cluster 3	352	From (4, -78, -20) to (10, -70, -12) centered at (7, -74, -16)	6, -47, -16	Lobule V	7.91	Motor
Cluster 4	288	From (-18, -78, -28) to (-12, -74, -22) centered at (-15, -76, -25)	-14, -76, -24	Lobule VI	7.11	Cognitive & Motor: WM, LNG, EF
Motor						
Controls						
Cluster 1	888	From (-14, -76, -44) to (-4, -64, -30) centered at (-8.71, -70.2, -36.83)	-10, -68, -40	Lobule VIIa	7.61	Secondary motor representation
Cluster 2	568	From (-24, -66, -34) to (-16, -58, -26) centered at (-20.72, -62.19, -30.59)	-20, -62, -30	Lobule VI	7.48	Cognitive & Motor: WM, LNG, EF
Cluster 3	352	From (34, -48, -58) to (42, -42, -50) centered at (38, -45, -54)	38, -45, -54	Lobule VIIa	6.71	Secondary motor representation
Cluster 4	312	From (-32, -76, -42) to (-26, -70, -36) centered at (-28.98, -73.74, -38.98)	-28, -74, -38	Crus I	6.54	Cognitive: WM, EF, LNG, EMO
Cluster 5	288	From (6, -56, -48) to (10, -50, -42) centered at (8, -53, -45)	8, -53, -45	Lobule IX	6.52	DMN
Patients						
Cluster 1	1800	From (-32, -58, -46) to (-12, -42, -16) centered at (-21.32, -51.06, -27.49)	-28, -54, -24	Lobule VI	8.06	Cognitive & Motor: WM, LNG, EF
			-20, -54, -20	Lobule V	7.36	Motor
			-16, -44, -42	Lobule IX	6.90	DMN
			-18, -48, -30	Lobule V	6.47	Motor
Cluster 2	256	From (14, -60, -46) to (20, -54, -40) centered at (17, -57, -43)	17, -57, -43	Lobule VIIIb	6.55	Secondary motor representation
Working Memory						
Controls						
Cluster 1	2128	From (-44, -70, -48) to (-30, -54, -36) centered at (-36.9, -62.33, -42.44)	-36, -62, -42	Crus II	17.27	Cognitive: WM, LNG
Cluster 2	1384	From (40, -76, -42) to (48, -48, -30) centered at (43.15, -65.48, -36.87)	44, -70, -38	Crus I	10.93	Cognitive: WM, EF, LNG, EMO
			42, -60, -36	Crus I	9.15	Cognitive: WM, EF, LNG, EMO

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
			42, -50, -32	Crus I	7.14	Cognitive: WM, EF, LNG, EMO
Cluster 3	1240	From (26, -70, -30) to (54, -58, -20) centered at (37.67, -63.88, -25.9)	32, -66, -28	Crus I	9.16	Cognitive: WM, EF, LNG, EMO
			50, -60, -24	Crus I	7.48	Cognitive: WM, EF, LNG, EMO
			46, -60, -24	Crus I	7.40	Cognitive: WM, EF, LNG, EMO
Patients						
Cluster 1	1144	From (28, -78, -44) to (40, -66, -34) centered at (33.48, -71.77, -38.06)	34, -72, -38	Crus I	13.21	Cognitive: WM, EF, LNG, EMO
Cluster 2	720	From (-40, -74, -42) to (-30, -66, -34) centered at (-35.44, -70, -38)	-36, -70, -38	Crus I	11.63	Cognitive: WM, EF, LNG, EMO
Cluster 3	440	From (44, -64, -34) to (48, -56, -22) centered at (46, -59.37, -28.5)	46, -58, -30	Crus I	8.25	Cognitive: WM, EF, LNG, EMO
Cluster 4	416	From (-38, -56, -52) to (-32, -44, -42) centered at (-35.54, -49.78, -46.86)	-36, -46, -44	Crus II	7.73	Cognitive: WM, LNG
			-36, -54, -50	Crus II	7.31	Cognitive: WM, LNG
Cluster 5	256	From (36, -74, -22) to (42, -68, -16) centered at (39.01, -70.98, -19.01)	40, -70, -20	Crus I	7.83	Cognitive: WM, EF, LNG, EMO

The functional category associated with each lobule is based on investigations of the cerebellar functional topography (Stoodley & Schmahmann, 2009; Stoodley et al., 2012). However, these studies were not exhaustive and the regions may be involved in other functions. Default mode network (DMN) associations are based off of resting state connectivity analyses (Bernard et al., 2012; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011). WM: working memory; EF: executive function; EMO: emotion; LNG: language

Table 3

Significant group differences and overlap by task type. Only statistically significant coordinates are included.

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
Emotion						
Controls>Patients						
Cluster 1	440	From (-18, -78, -40) to (-10, -70, -30) centered at (-14.9, -74.01, -36.18)	-12, -74, -38	Crus II	1956.55	Cognitive: WM, LNG
Cluster 2	272	From (-32, -80, -38) to (-24, -74, -32) centered at (-27.26, -77.42, -35.96)	-16.11, -73.94, -35.33	Crus I	1821.04	Cognitive: WM, EF, LNG, EMO
			-29.6, -76.8, -37.6	Crus II	2241.40	Cognitive: WM, LNG
Patients>Controls						
Cluster 1	144	From (-34, -74, -18) to (-28, -70, -24) centered at (-31.44, -72.11, -15.99)	-31.44, -72.11, -15.99	Cortex	1726.82	--
Overlap						
Cluster 1	72	From (36, -50, -28) to (40, -48, -26) centered at (38.71, -48.88, -27.09)	38, -48, -26	Lobule VI	7.87	Cognitive & Motor: WM, LNG, EF
Executive Function/Attention						
Patients>Controls						
Cluster 1	184	From (24, -50, -30) to (30, -44, -26) centered at (26.94, -46.52, -28.09)	25.33, -46.22, -28.89	Lobule VI	1684.49	Cognitive & Motor: WM, LNG, EF
			30, -48, -27	Lobule VI	1656.60	Cognitive & Motor: WM, LNG, EF
Overlap						
Cluster 1	504	From (-32, -74, -28) to (-22, -58, -22) centered at (-26.11, -65.12, -25.11)	-24, -62, -26	Lobule VI	9.53	Cognitive & Motor: WM, LNG, EF
Cluster 2	488	From (14, -62, -26) to (22, -52, -18) centered at (17.9, -56.79, -22.03)	-30, -72, -26	Lobule VI	7.21	Cognitive & Motor: WM, LNG, EF
Cluster 3	248	From (-4, -76, -22) to (4, -70, -18) centered at (-22, -73.07, -19.97)	18, -56, -22	Lobule VI	10.31	Cognitive & Motor: WM, LNG, EF
			2, -72, -20	Lobule VI	7.96	Cognitive & Motor: WM, LNG, EF
Language						
Controls>Patients						
Cluster 1	88	From (-4, -76, -42) to (0, -70, -40) centered at (-1.3, -73.42, -40.7)	-2, -70, -42	Lobule VIIa/VIII b	2012.19	Secondary motor representation
			-2, -75, -40	Lobule VIIa	1991.74	Secondary motor representation
Patients>Controls						

Cluster	Cluster Size (mm ³)	Extent & Weighted Center (x, y, z)	Local Extrema (x, y, z)	Location	ALE Value (x10 ⁻³)	Lobular Function
Cluster 1	152	From (30, -70, -38) to (34, -64, -34) centered at (31.97, -67.02, -35.5)	31.5, -66.25, -34.75	Crus I	2115.35	Cognitive: WM, EF, LNG, EMO
Motor						
Controls>Patients						
Cluster 1	712	From (-14, -74, -44) to (-4, -64, -30) centered at (-9.02, -69.32, -37.07)	-11.11, -71.78, -34.67	Crus II	1980.92	Cognitive: WM, LNG
			-12, -66, -36	Lobule VIIa	1839.78	Secondary motor representation
			-7.81, -68, -39.37	Lobule VIII	1738.06	Secondary motor representation
Cluster 2	160	From (-32, -76, -40) to (-26, -70, -36) centered at (-28.61, -73.45, -37.63)	-28, -73, -36	Crus I	2117.70	Cognitive: WM, EF, LNG, EMO
			-26, -72, -40	Crus I	1980.92	Cognitive: WM, EF, LNG, EMO
			-32, -76, -38	Crus I	1959.96	Cognitive: WM, EF, LNG, EMO
Cluster 3	88	From (-20, -66, -34) to (-16, -62, -30) centered at (-18.03, -64.61, -31.64)	-20, -66, -32	Lobule VI	2154.51	Cognitive & Motor: WM, LNG, EF
			-16, -62, -32	Lobule VI	1738.06	Cognitive & Motor: WM, LNG, EF
Patients>Controls						
Cluster 1	768	From (-30, -58, -26) to (-16, -50, -16) centered at (-22.53, -53.53, -21.08)	-19, -52.2, -19.4	Lobule VI	2404.38	Cognitive & Motor: WM, LNG, EF
			-26.8, -51.2, -21.6	Lobule VI	2151.97	Cognitive & Motor: WM, LNG, EF
			-20, -50, -24	Lobule V	2110.68	Motor
			-25, -58, -21	Lobule VI	1857.78	Cognitive & Motor: WM, LNG, EF
Working Memory						
Controls>Patients						
Cluster 1	1216	From (-44, -66, -48) to (-30, -54, -36) centered at (-37.19, -61.22, -42.67)	-40, -60, -38	Crus I	2280.13	Cognitive: WM, EF, LNG, EMO
			-37.85, -60.58, -42.88	Crus II	2226.21	Cognitive: WM, LNG
Cluster 2	88	From (36, -66, -32) to (42, -62, -28) centered at (38.35, -64.34, -30.17)	38, -64, -30	Crus I	1888.19	Cognitive: WM, EF, LNG, EMO
			42, -66, -32	Crus I	1787.85	Cognitive: WM, EF, LNG, EMO
Overlap						
Cluster 1	184	From (-40, -70, -42) to (-32, -66, -38) centered at (-36.4, -67.81, -39.81)	-36, -68, -40	Crus I	8.98	Cognitive: WM, EF, LNG, EMO
Cluster 2	128	From (44, -64, -26) to (48, -58, -22) centered at (45.98, -60.99, -24.52)	46, -60, -24	Crus I	7.40	Cognitive: WM, EF, LNG, EMO
Cluster 3	64	From (40, -74, -40) to (40, -70, -36) centered at (40, -71.7, -38.22)	50, -70, -38	Crus I	7.17	Cognitive: WM, EF, LNG, EMO

The functional category associated with each lobule is based on investigations of the cerebellar functional topography (Stoodley et al., 2012). However, these studies were not exhaustive and the regions may be involved in other functions. Default mode network (DMN) associations are based off of resting state connectivity analyses (Bernard et al., 2012; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011). WM: working memory; EF: executive function; EMO: emotion; LNG: language

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