



Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies

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ABSTRACT

Clinical, experimental and neuroimaging studies indicate that the cerebellum is involved in neural processes beyond the motor domain. Cerebellar somatotopy has been shown for motor control, but topographic organization of higher-order functions has not yet been established. To determine whether existing literature supports the hypothesis of functional topography in the human cerebellum, we conducted an activation likelihood estimate (ALE) meta-analysis of neuroimaging studies reporting cerebellar activation in selected task categories: motor ($n=7$ studies), somatosensory ($n=2$), language ($n=11$), verbal working memory ($n=8$), spatial ($n=8$), executive function ($n=8$) and emotional processing ($n=9$). In agreement with previous investigations, sensorimotor tasks activated anterior lobe (lobule V) and adjacent lobule VI, with additional foci in lobule VIII. Motor activation was in VIIIA/B; somatosensory activation was confined to VIIIB. The posterior lobe was involved in higher-level tasks. ALE peaks were identified in lobule VI and Crus I for language and verbal working memory; lobule VI for spatial tasks; lobules VI, Crus I and VIIIB for executive functions; and lobules VI, Crus I and medial VII for emotional processing. Language was heavily right-lateralized and spatial peaks left-lateralized, reflecting crossed cerebro-cerebellar projections. Language and executive tasks activated regions of Crus I and lobule VII proposed to be involved in prefrontal-cerebellar loops. Emotional processing involved vermal lobule VII, implicated in cerebellar-limbic circuitry. These data provide support for an anterior sensorimotor vs. posterior cognitive/emotional dichotomy in the human cerebellum. Prospective studies of multiple domains within single individuals are necessary to better elucidate neurobehavioral structure–function correlations in the cerebellar posterior lobe.

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Introduction

The cerebellum is involved in a wide range of tasks, including sensorimotor control, language, spatial and executive functions. Deficits resulting from cerebellar lesions include motor dysmetria, ataxia, and intention tremor (Holmes, 1939), but also the cerebellar cognitive affective syndrome (Schmahmann and Sherman, 1998) including executive, visual–spatial, linguistic and emotional deficits, and even mutism and psychosis (Botez-Marquard et al., 1994; Grafman et al., 1992; Heath et al., 1979; Levisohn et al., 2000; Molinari et al., 2004; Rapoport et al., 2000; Riva and Giorgi, 2000; Schmahmann et al., 2007; Steinlin et al., 2003).

The anatomical basis of this proposed cerebellar role in non-motor function is the existence of cerebro-cerebellar channels (cortico-ponto-cerebellar and cerebello-thalamo-cortical loops) that link the cerebellum with motor cortices as well as with association cortices and paralimbic regions of the cerebral hemisphere (Botez et al., 1985; Kelly and Strick, 2003; Leiner et al., 1986; Middleton and Strick, 1994;

Schmahmann, 1991, 1996; Schmahmann and Pandya, 1989, 1997; Voogd and Glickstein, 1998). Experimental investigations in animals (Chambers and Sprague, 1955a,b; Snider and Eldred, 1951), imaging studies in humans (Bushara et al., 2001; Grodd et al., 2001, 2005) and clinical reports (e.g., Victor et al., 1959; Schoch et al., 2006) have supported the original hypothesis of Bolk (1906) that there is topography of motor function within the cerebellum (see Manni and Petrosini (2004) for a review). Contemporary clinical studies suggest that whereas the cerebellar anterior lobe is principally engaged in motor control, the cerebellar vermis is involved in affective processing, and the posterior cerebellum contributes to complex cognitive operations (Exner et al., 2004; Levisohn et al., 2000; Schmahmann, 2004, 2007; Schmahmann and Sherman, 1998; Schoch et al., 2006; Tavano et al., 2007). Furthermore, consistent with the crossed cerebro-cerebellar fiber pathways, linguistic impairments can arise following right cerebellar hemisphere lesions, whereas visual–spatial difficulties may follow left cerebellar hemisphere damage (Fiez et al., 1992; Gottwald et al., 2004; Gross-Tsur et al., 2006; Hokkanen et al., 2006; Riva and Giorgi, 2000; Scott et al., 2001). Yet some studies fail to detect non-motor problems after cerebellar tumor or stroke, and others find no reliable structure–function relationships (see Frank et al., 2007). Better understanding of the functional topography of the cerebellum

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would enable these contradictory results to be clarified with respect to the location of cerebellar damage.

Positron emission tomography (PET) scans first demonstrated cerebellar activation during extremity and eye movements (Fox et al., 1985), and then revealed cerebellar activation in language studies (Petersen et al., 1988; Raichle et al., 1994). Subsequent evaluations showed cerebellar activation in tasks of sensory processing (Gao et al., 1996), appreciation of timed intervals (Jueptner et al., 1995), anticipatory planning and prediction (shifting attention tasks) (Allen et al., 1997), verbal working memory (Desmond et al., 1997), classical conditioning (Logan and Grafton, 1995), and mental imagery (Ryding et al., 1993), among others. There is now a plethora of studies using PET and functional magnetic resonance imaging (fMRI) in which cerebellar activation is noted during sensorimotor, cognitive, and emotional processing paradigms. There are no published fMRI reports, however, examining multiple behavioral domains within single individuals. We therefore performed a meta-analysis of published functional imaging studies to test our hypothesis that movement, cognition, and affective processing are topographically arranged within the cerebellum (Schmahmann, 1991, 1996, 2004). We predicted that this approach would provide insights into whether different aspects of sensorimotor function, cognition, and emotional processing activate geographically distinct cerebellar regions. This meta-analysis is facilitated by the recently introduced GingerALE software (Laird et al., 2005) that enables the calculation of activation likelihood estimates for each voxel in the brain (Turkeltaub et al., 2002), and by the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000), which together make it possible to map sites of activation from multiple imaging studies onto a single representative cerebellum.

Materials and methods

Literature review

Articles were identified through a PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) search of “cerebell* AND imaging” with the limits “Humans”, “English”, and “Adult 19–44 years”, which yielded 1118 articles. Of these, we eliminated studies that did not involve functional neuroimaging (e.g., structural and morphometric studies); those that did not report cerebellar activation or the coordinates of the activation in standard units (Montreal Neurological Institute [MNI; Collins et al., 1998] or Talairach and Tournoux (1988)); studies reporting incomplete coverage of the cerebellum; studies that performed only region of interest analyses; and studies that investigated clinical populations without reporting data from a healthy control group.

Task categories

The remaining 526 articles were then broadly categorized by the task of interest (motor, learning, language, memory, pain, auditory, somatosensory, working memory, etc.). We eliminated studies which investigated different types of processing (e.g., learning, memory, timing), that could not be classified into a particular domain (see below). From the remaining 281 studies, we selected the following categories: motor (140 articles); language (67 articles); somatosensory (8); working memory (16); executive function (17); spatial processing (14); and limbic/emotional processing (15). Previous clinical and imaging studies have shown that the cerebellum is involved in these domains.

Within each category, we then narrowed the studies to include those reporting mean group coordinates during performance of a homogeneous group of tasks. This considerable pruning of studies was performed in order to achieve a greater reliability of results, with the potential trade-off of under-representing the available activation data. The categories were selected based on the number of studies falling within each category as well as prior studies indicating that the

cerebellum is involved in processing information in these domains. Our goal was to determine whether available imaging data provided an anatomical signature for where in the cerebellum information in these domains is processed. We considered it beyond the scope of this study to investigate the nature of the cerebellar transform (see Schmahmann, 2004). Hence, studies designed to investigate theoretical formulations of the transform (e.g., timing [Ivry and Keele, 1989], building internal models [Ito, 2005], anticipation and prediction [Courchesne and Allen, 1997], sensory processing [Gao et al., 1996; Bower, 1997], motor learning [Doyon, 1997]) were not included in the meta-analysis.

In the “motor” category, we focused on studies employing simple right-handed finger movement tasks, which yielded 7 publications (total 25 foci). “Somatosensory” processing included 2 articles employing tactile matching tasks (8 foci). We did not include in the somatosensory analysis a study of cerebellar somatotopy by Bushara et al. (2001), as only peak coordinates for individuals were reported; however, the results of this study are considered in the Discussion. In the “spatial” domain, complex decision-making studies were excluded, and tasks including spatial transformations (such as mental rotation of objects, mental navigation) or spatial judgments (line bisection) were included in the analysis (8 articles, 19 foci). We particularly wanted to reduce the confound between cerebellar activation due to the motor aspects of speech, and activation involved in the processing of language stimuli. Therefore, in the “language” category, 67 publications were narrowed to 11 by eliminating those involving (or not controlling for) speech output/articulation/expressive language; bilingual language; reading/writing; sign language and Braille reading. The language papers include those involving word/letter generation; word stem completion; semantic processing; phonological processing; and verbal fluency (45 foci). “Working memory” specifically included verbal working memory and *n*-back tasks (*n*=8; 19 foci). In the “executive function” domain, well-established tests such as the Tower of Hanoi/London were included in the analyses, while tasks such as arithmetic and moral reasoning were eliminated. This yielded a total of 8 articles (33 foci). In the “emotion” category, 9 articles (20 foci) were used in the meta-analysis, including those involving viewing emotional images from the International Affective Picture Scale (IAPS; Lang et al., 2005), and studies of mood and affective processing. Table 1 lists the final selected articles, with information regarding the number of subjects, the type of tasks, and the contrasts selected. Table 2 provides information about the tasks chosen and patterns of extracerebellar activation commonly seen during these tasks.

ALE meta-analysis

The ALE meta-analysis method for imaging studies described by Turkeltaub et al. (2002) has been further developed by Laird et al. (GingerALE software 1.2 beta version, www.brainmap.org/ale; see Laird et al., 2005). Because this meta-analysis method treats each focus as the center of a probability distribution, rather than a single point, this approach is able to better deal with inevitable inter-study differences in scanning parameters and imaging analyses (Turkeltaub et al., 2002). GingerALE offers an automated method by which a whole-brain map of ALE values is generated. The ALE values represent the differential likelihood of activation at each voxel. Statistical thresholding is based on a permutation test performed with randomly generated sets of foci.

The procedure using GingerALE is summarized as follows. Text files for each category were generated that contained the cerebellar foci reported in each study within each category. Foci in Talairach space were converted to MNI space using the *icbm2tal* transform (Lancaster et al., 2007) prior to analysis. Foci that were reported in Talairach space that had been transformed from MNI space using the Brett transform were converted back to MNI space using the Brett transform

Table 1
Summary of studies included in the meta-analysis by category

| Category | Imaging modality | N | Task | Number of foci |
|------------------------------|--------------------|----|---|----------------|
| <i>Motor</i> | | | | |
| Catalan et al. (1998) | PET | 13 | Auditory cued finger tapping at 0.5 Hz | 1 |
| Rijntjes et al. (1999) | 2 T fMRI | 9 | Flexion-extension 4 s movement | 3 |
| Jancke et al. (2000) | 1.5 T fMRI | 8 | Auditory and visually cued finger tapping at 2.5 Hz | 3 |
| Lutz et al. (2000) | 1.5 T fMRI | 10 | Visually-cued tapping at 1.5 Hz | 1 |
| Riecker et al. (2003) | 1.5 T fMRI | 8 | Auditory cued finger tapping at 2, 2.5, 3, 4, 5 and 6 Hz | 12 |
| Hanakawa et al. (2003) | 1.5 T fMRI | 10 | Finger tapping at 0.67 Hz | 3 |
| Hanakawa et al. (in press) | 3 T fMRI | 13 | Finger tapping | 2 |
| <i>Somatosensory</i> | | | | |
| Hadjikhani and Roland (1998) | PET | 8 | Tactile matching | 6 |
| Saito et al. (2003) | 3 T fMRI | 11 | Tactile matching | 2 |
| <i>Spatial</i> | | | | |
| Fink et al. (2000) | 1.5 T fMRI | 12 | Landmark task (line bisection) | 2 |
| Ino et al. (2002) | 1.5 T fMRI | 16 | Mental navigation | 1 |
| Vingerhoets et al. (2002) | 1.5 T fMRI | 12 | Mental rotation | 3 |
| Zacks et al. (2002) | 1.5 T fMRI | 18 | Mental spatial transformation task | 5 |
| Graydon et al. (2005) | 4 T fMRI | 24 | Rotational transformation | 1 |
| Lee et al. (2005) | 1.5 T fMRI | 10 | Judgment of spatial orientation | 4 |
| Terhune et al. (2005) | 1.5 T fMRI | 8 | Viewing non-canonical vs. canonical orientations | 1 |
| Moffat et al. (2006) | 1.5 T fMRI | 30 | Spatial navigation through virtual environment | 2 |
| <i>Language</i> | | | | |
| Ojemann et al. (1998) | PET and 1.5 T fMRI | 7 | Word stem completion (covert) vs. fixation | 7 |
| Schlosser et al. (1998) | 1.5 T fMRI | 12 | Verbal fluency | 6 |
| Lurito et al. (2000) | fMRI | 5 | Word generation vs. viewing non-letter symbols | 3 |
| Seger et al. (2000) | 1.5 T fMRI | 7 | Verb generation; Novel vs. repeated and Unusual vs. usual semantic relationships | 14 |
| Gurd et al. (2002) | 1.5 T fMRI | 11 | Semantic fluency (categories) vs. overlearned sequence fluency (days of week) | 1 |
| Noppeney and Price (2002) | PET | 12 | Semantic decision | 2 |
| McDermott et al. (2003) | 1.5 T fMRI | 20 | Semantic vs. phonological word lists | 3 |
| Xiang et al. (2003) | 1.5 T fMRI | 6 | Semantic discrimination | 1 |
| Seki et al. (2004) | 3.0 T fMRI | 19 | Vowel exchange vs. reading words and non-words | 2 |
| Tielman et al. (2005) | 1.5 T fMRI | 22 | Semantic vs. perceptual categorization | 3 |
| Frings et al. (2006) | 1.5 T fMRI | 16 | Verb generation vs. verb reading | 3 |
| <i>Working memory</i> | | | | |
| LaBar et al. (1999) | 1.5 T fMRI | 11 | 2-back task; spatial WM masked by main effect of WM vs. baseline | 1 |
| Honey et al. (2000) | 1.5 T fMRI | 20 | 2-back vs. control | 1 |
| Gruber (2001) | 3 T fMRI | 11 | Letter memory vs. uppercase/lowercase judgment | 1 |
| Cairo et al. (2004) | fMRI | 18 | Sternberg working memory; average across all loads for encoding and maintenance | 3 |
| Chen and Desmond, (2005a) | 3 T fMRI | 17 | Sternberg working memory vs. motoric rehearsal | 1 |
| Kirschen et al. (2005) | 3 T fMRI | 17 | Regions of linear and quadratic increases in activation with increasing memory load | 8 |
| Tomasi et al. (2005) | 4 T fMRI | 30 | <i>n</i> -back | 3 |
| Valera et al. (2005) | 1.5 T fMRI | 20 | <i>n</i> -back | 1 |
| <i>Executive function</i> | | | | |
| Rao et al. (1997) | 1.5 T fMRI | 11 | Conceptual reasoning vs. sensorimotor control | 3 |
| Jahanshahi et al. (2000) | PET | 6 | Random number generation vs. counting | 2 |
| Liddle et al. (2001) | 1.5 T fMRI | 16 | Go-No-Go task: Go and No-Go vs. baseline; Go>No-Go; No-Go>Go | 10 |
| Ernst et al. (2002) | PET | 20 | Risk-taking task vs. choosing cards in sequential order | 5 |
| Daniels et al. (2003) | 1.5 T fMRI | 8 | Random number generation vs. counting | 2 |
| Schall et al. (2003) | PET/1.5 T fMRI | 6 | Tower of London task | 5 |
| Blackwood et al. (2004) | 1.5 T fMRI | 8 | Decision-making (uncertain vs. certain conditions) | 2 |
| Harrington et al. (2004) | 1.5 T fMRI | 24 | Decision-making (interval timing) | 4 |
| <i>Limbic/emotion</i> | | | | |
| Imaizumi et al. (1997) | PET | 6 | Emotion in speaker voice vs. identification of speaker | 5 |
| Lane et al. (1997) | PET | 12 | IAPS pictures; unpleasant vs. neutral | 2 |
| Paradiso et al. (1999) | PET | 17 | IAPS pictures; unpleasant vs. neutral | 1 |
| Gundel et al. (2003) | 1.5 T fMRI | 8 | Grief | 2 |
| Lee et al. (2004) | 1.5 T fMRI | 10 | IAPS pictures; unpleasant vs. neutral | 3 |
| Takahashi et al. (2004) | 1.5 T fMRI | 15 | IAPS pictures; unpleasant vs. neutral | 1 |
| Habel et al. (2005) | 1.5 T fMRI | 26 | Happy vs. sad faces | 2 |
| Bermphol et al. (2006) | 3 T fMRI | 17 | IAPS pictures; emotional perception vs. emotional expectancy | 2 |
| Hofer et al. (2007) | 1.5 T fMRI | 38 | IAPS pictures; emotional vs. neutral | 2 |

PET, positron emission tomography; fMRI, functional magnetic resonance imaging; WM, working memory; T = Tesla; N = number of subjects.

(mni2tal) rather than icbm2tal. The ALE values for each voxel were computed with a full-width half-maximum value of 12 mm. The null distribution of the ALE statistic at each voxel was determined with a permutation test (5000 permutations); these *p* values were then used to compute the threshold for the ALE map (false discovery rate was set to *p*=0.001; see Laird et al., 2005). Cluster analysis with a minimum

cluster volume of 150 mm³ was performed on the final thresholded map. The data were viewed using Mango (Research Imaging Center, UTHSCSA) with the thresholded maps for each task as the overlay, and the colin27_T1_seg_MNI.nii brain template as the underlay.

Statistical comparisons between the ALE maps of two sets of foci are possible using GingerALE. This procedure was used to determine

Table 2
Description of tasks

| Category/task | Description | Study |
|--|--|--|
| Motor/ finger tapping | Subjects tap their right index finger in time with external cue (auditory beeps or metronome; visually presented numbers). Cortical regions in the left somatomotor cortex, bilateral supplementary motor area, bilateral superior temporal gyrus, and bilateral inferior parietal lobule are active during finger tapping. | Catalan et al. (1998), Rijntjes et al. (1999), Riecker et al. (2003), Jancke et al. (2000), Lutz et al. (2000), Hanakawa et al. (2003, in press) |
| Somatosensory/ tactile matching | Tactile shapes are presented to subjects via raised shapes on flat discs. These tasks also activate the cerebral cortex in: left primary somatosensory cortex, primary and secondary sensorimotor cortex, dorsal premotor area, superior parietal lobule and anterior portion of the intraparietal sulcus. | Hadjikhani and Roland (1998), Saito et al. (2003) |
| Spatial/ landmark task | In the Landmark Task subjects are presented with a bisected line and determine whether it is bisected evenly or not. Areas of activation during this task include the right posterior parietal cortex, inferior parietal cortex, and occipital regions. | Fink et al. (2000) |
| Spatial/ mental rotation | Subjects must conduct a rotational transformation to solve the task. Objects, bodies or letters are presented at different angles of rotation. Participants determine whether two objects are the same or whether they are mirror-orientated to one another. These tasks activate bilateral occipital (lingual gyrus, precuneus, superior occipital gyrus), parietal (angular gyrus, postcentral gyrus, superior parietal lobule, left supramarginal gyrus), frontal (frontal pole, inferior and medial frontal gyri), and left temporal (inferior and middle temporal gyrus) regions. | Vingerhoets et al. (2002), Zacks et al. (2002), Graydon et al. (2005), Lee et al. (2005), Terhune et al. (2005) |
| Spatial/navigation | The subject navigates through a known vs. unknown space/place. Activation patterns highlight left premotor area, as well as the angular gyrus, parahippocampal gyrus and retrosplenial region, cuneus/precuneus, occipital regions, medial frontal gyrus, and inferior parietal lobule. | Ino et al. (2002), Moffat et al. (2006) |
| Working memory/ <i>n</i> -back | Subjects view a series of letters, and signal when the letter presented is the same as the letter “n” places previously, in contrast with a vigilance task, in which subjects signal when they see the letter “X” (or another target). These tasks activate the (sometimes left-lateralized) working memory network, including prefrontal regions (inferior, middle, and superior frontal and anterior cingulate gyri), the inferior and superior parietal lobules, the precuneus, and inferior temporal gyrus. | LaBar et al. (1999), Honey et al. (2000), Tomasi et al. (2005), Valera et al. (2005) |
| Working memory/ Sternberg | The Sternberg working memory paradigm consists of an encoding phase (a string of letters to remember), a maintenance delay phase, and then a retrieval phase (subjects indicate whether a probe was part of the originally-memorized list). A network of areas is activated, including prefrontal (inferior, middle and superior frontal and anterior cingulate gyri), precuneus, inferior and superior parietal lobules, and temporal lobe regions. | Cairo et al. (2004), Chen and Desmond (2005a), Kirschen et al. (2005) |
| Language/ word generation | In word generation tasks a word or letter is presented, and subjects generate an appropriate word in response. Verb-for-noun generation tasks are the most common, such as generating “drive” for “car”. These tasks activate bilateral prefrontal cortex regions, right orbitofrontal cortex, bilateral middle and superior temporal gyri, and left inferior parietal regions. | Lurito et al. (2000), Frings et al. (2006) |
| Language/ verbal fluency | Subjects generate words based on categories (semantic fluency) or letters (phonemic fluency). These tasks involve the anterior cingulate, middle and inferior frontal gyri and frontal operculum (prefrontal activity can be left-lateralized). | Schlosser et al. (1998), Gurd et al. (2002) |
| Language/word stem completion | Subjects are presented with three-letter stems (e.g. “che”) and are asked to complete the stem to make a word (e.g. “cheese”). These tasks activate cortical regions including left inferior and superior prefrontal areas, supplementary motor area, and bilateral superior parietal cortices. | Ojemann et al. (1998) |
| Language/semantic judgment | Semantic judgment tasks require subjects to make a judgment about the meaning of a word, including classification. These tasks engage left inferior prefrontal and lateral temporal regions. | Seiger et al. (2000), Noppeney and Price (2001), McDermott et al. (2003), Xiang et al. (2003), Tielman et al. (2005) |
| Executive function/ random number generation | Random number generation engages several executive processes – such as attention and working memory – while subjects say the numbers 1 to 9 in a random fashion. Bilateral frontal “executive” areas, including the dorsolateral prefrontal cortex and anterior cingulate cortex; temporal regions such as the superior temporal cortex; and the precuneus and inferior and superior parietal lobules are all involved. | Jahanshahi et al. (2000), Daniels et al. (2003) |
| Executive function/ Tower of London | Subjects move colored balls to achieve a specific configuration within a given number of moves. This task activates a similar bilateral “executive network” of cortical areas, including inferior, middle and superior frontal gyri (particularly the dorsolateral prefrontal cortex), cingulate cortex and the left parietal lobe. | Schall et al. (2003) |
| Executive function/ decision-making | These tasks involve decision-making during various procedures – such as risk-taking, gambling, or judgments about time intervals. These tasks activate frontal areas, such as the cingulate cortex and middle and superior frontal gyri; middle and superior temporal gyri; superior and inferior parietal lobules. | Rao et al. (1997), Ernst et al. (2002), Blackwood et al. (2004), Harrington et al. (2004) |
| Emotion/ IAPS pictures | The International Affective Picture Scale (IAPS) is a standardized scale of images that can be used to induce positive or negative emotional states. Viewing “emotional” (negative or positive) vs. neutral images leads to activation in sensorimotor cortex, prefrontal cortex and cingulate gyrus, supplementary motor area and hippocampus/parahippocampal gyrus/amygdala. | Lane et al. (1997), Paradiso et al. (1999), Lee et al. (2004), Takahashi et al. (2004), Hofer et al. (2007), Bermpohl et al. (2006) |
| Emotion/emotional intonation | Subjects listen to utterances and identify the emotion (surprise, disgust, happiness, anger) of a speaker. This highlights a network of regions including the left middle frontal gyrus, insula, right inferior frontal gyrus, parahippocampal gyrus and lingual gyrus. | Imaizumi et al. (1997) |
| Emotion/mood | Subjects are asked to adopt the mood conveyed by pictures of actors with happy or sad facial expressions or through viewing images of recently deceased relatives. A similar network is activated as in IAPS viewing, including prefrontal regions, cingulate gyrus, and superior temporal gyrus. | Gundel et al. (2003), Habel et al. (2005) |

whether there were significant activation differences between the ALE maps for the various task domains (e.g. somatosensory vs. motor; language vs. spatial). The parameters, output and visualization procedures were the same as described above.

Anatomical localization of results

The GingerALE program outputs the size, extent, weighted center, peak coordinates, and ALE values for each cluster. We used the MRI

Atlas of the Human Cerebellum (Schmahmann et al., 2000) to localize the cluster peak coordinates to different lobules of the cerebellum.

Methodological considerations

We specifically selected a small subset of articles reporting cerebellar activation for the purpose of addressing our hypothesis. In particular, the goal of the study was not to determine what the cerebellum does, but rather where in the cerebellum different types of information are dealt with. Therefore, we did not attempt in this meta-analysis to provide a complete rendering of the reported cerebellar activation patterns in the literature. However, every attempt was made to include studies that appropriately investigated the specific task categories and contrasts of interest that we selected.

Intrinsic to this type of meta-analysis are registration problems that result from grouping coordinates from different studies, and then projecting them onto a standard brain. This can be a particular problem for the fissures and lobules in the cerebellum, depending on the transform that is used. The SPM nonlinear normalization algorithm to the MNI template can lead to an elongated cerebellum, which may alter the lobular localization of certain coordinates (Diedrichsen, 2006). This is a limitation of our meta-analysis, and results are interpreted accordingly. In our study we included coordinates that were reported as being located within the cerebel-

lum. However, in some instances, activation voxels spread into adjacent non-cerebellar regions. This likely occurs due to inter-subject variability, particularly near the boundaries between structures, and data processing differences between studies. The reported results are based on the centers of the activation clusters, although the extent of the activation patterns was of interest, and is commented on.

A weakness inherent in the ALE meta-analysis is that only peak activation coordinates are entered into the analysis. Factors such as the size of clusters and the level of statistical significance of the findings are not taken into account. Additionally, the number of subjects in each study was not considered, although we did not include case studies in our analyses. The ALE program addresses these limitations by treating the foci as the centers of probability distributions (see above). Furthermore, a large number of permutations (5000) were run during the permutation testing to protect against Type I statistical errors.

Results

Peak coordinates

Table 3 shows the cluster sizes, weighted centers, peak coordinates and cerebellar lobules of the significant ALE maxima for each category of task. Fig. 1 shows the thresholded ALE activation maps for four representative rostral-caudal coronal sections. A rostral-caudal

Table 3
Peak ALE coordinates

| Task type | Cluster size (mm ³) | Extent and weighted center (x, y, z) | Local extrema (x, y, z) | Location | ALE value* ($\times 10^{-3}$) |
|---------------------------|---------------------------------|---|----------------------------|---------------------------------------|---------------------------------|
| <i>Motor</i> | | | | | |
| Cluster 1 | 9168 | From (2, -70, -54) to (34, -42, -16) centered at (18.7, -56.3, -31.6) | 22 -56 -28 12 -64 -46 | Right lobule VI Right lobule VIIIB | 18.89 8.45 |
| Cluster 2 | 3328 | From (22, -74, -64) to (38, -50, -48) centered at (30.3, -63.8, -55.9) | 30 -66 -56 | Right lobule VIIIA | 14.02 |
| Cluster 3 | 1136 | From (0, -70, -16) to (10, -54, -4) centered at (5.2, -61.7, -10.8) | 6 -64 -10 | Right lobule V | 7.12 |
| <i>Somatosensory</i> | | | | | |
| Cluster 1 | 1992 | From (14, -58, -28) to (30, -44, -12) centered at (20.9, -51.6, -22.0) | 20 -52 -22 | Right lobule V | 10.25 |
| Cluster 2 | 488 | From (16, -64, -56) to (24, -56, -42) centered at (18.8, -59.6, -49.2) | 18 -62 -46 20 -58 -52 | Right VIIIB Right VIIIB | 4.35 4.34 |
| <i>Spatial</i> | | | | | |
| Cluster 1 | 1400 | From (-34, -72, -30) to (-22, -58, -16) centered at (-28.5, -64.8, -23.1) | -28 -64 -22 | Left lobule VI | 7.85 |
| Cluster 2 | 920 | From (-8, -80, -28) to (2, -70, -12) centered at (-3.2, -74.1, -19.5) | -4 -72 -18 | Left lobule VI | 6.76 |
| Cluster 3 | 440 | From (32, -44, -42) to (40, -38, -30) centered at (35.9, -41.4, -35.9) | 36 -42 -36 | Right lobule VI | 4.79 |
| <i>Language</i> | | | | | |
| Cluster 1 | 10,544 | From (22, -86, -44) to (56, -48, -16) centered at (37.9, -63.7, -29.7) | 36 -62 -28 34 -82 -36 | Right lobule VI Right Crus I | 12.18 6.95 |
| Cluster 2 | 3328 | From (-2, -94, -44) to (24, -74, -20) centered at (12.5, -86.1, -32.9) | 14 -86 -34 4 -82 -26 | Right Crus I/II Right lobule VIIAt | 9.91 5.86 |
| Cluster 3 | 368 | From (-46, -62, -28) to (-38, -54, -24) centered at (-42, -58, -24) | -42 -58 -24 | Left lobule VI | 6.36 |
| <i>Working memory</i> | | | | | |
| Cluster 1 | 3416 | From (22, -76, -42) to (46, -58, -14) centered at (32.9, -66.8, -23.4) | 30 -70 -20 40 -64 -36 | Right lobule VI Right Crus I | 8.03 6.96 |
| Cluster 2 | 1024 | From (-44, -64, -44) to (-28, -50, -30) centered at (-38.4, -56.5, -28.4) | -40 -56 -38 -30 -62 -32 | Left Crus I Left lobule VI | 6.94 4.04 |
| Cluster 3 | 608 | From (20, -76, -62) to (30, -66, -54) centered at (24.9, -70.7, -58.6) | 26 -70 -60 | Right VIIIA | 6.89 |
| Cluster 4 | 480 | From (6, -78, -26) to (18, -70, -18) centered at (11.6, -74.2, -22.0) | 12 -74 -22 | Right lobule VI | 6.45 |
| Cluster 5 | 424 | From (-14, -88, -20) to (-8, -72, -12) centered at (-11.3, -81.4, -16.7) | -10 -84 -18 | Left lobule VI/Crus I | 5.11 |
| <i>Executive function</i> | | | | | |
| Cluster 1 | 4512 | From (-42, -82, -38) to (-6, -52, -22) centered at (-28.3, -68.5, -30.5) | -36 -66 -28 -12 -78 -28 | Left lobule VI Left Crus I | 8.90 7.05 |
| Cluster 2 | 728 | From (18, -72, -40) to (32, -64, -26) centered at (26.5, -67.8, -33.4) | 30 -68 -34 | Right Crus I | 5.89 |
| Cluster 3 | 1128 | From (-30, -80, -56) to (-22, -70, -48) centered at (-26.4, -75.5, -51.8) | -28 -78 -52 | Left VIIIB | 7.33 |
| <i>Limbic/emotion</i> | | | | | |
| Cluster 1 | 1216 | From (-54, -70, -32) to (-40, -60, -16) centered at (-47.8, -65.7, -23.8) | -50 -66 -26 | Left Crus I | 6.17 |
| Cluster 2 | 992 | From (18, -72, -44) to (30, -58, -28) centered at (25.1, -65.5, -35.0) | 26 -64 -34 | Right lobule VI | 5.75 |
| Cluster 3 | 248 | From (-6, -82, -38) to (-2, -78, -26) centered at (-3.8, -80.4, -32.2) | -4 -82 -28 -4 -80 -34 | Left VIIAt Left VIIAt | 4.42 4.40 |

Coordinates are given in MNI space. "Local extrema" refer to peaks of activation extending along the volume of the activated cluster. Locations were determined using the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000). *All ALE values are significant based on an FDR (False Discovery Rate) of $p < 0.001$.

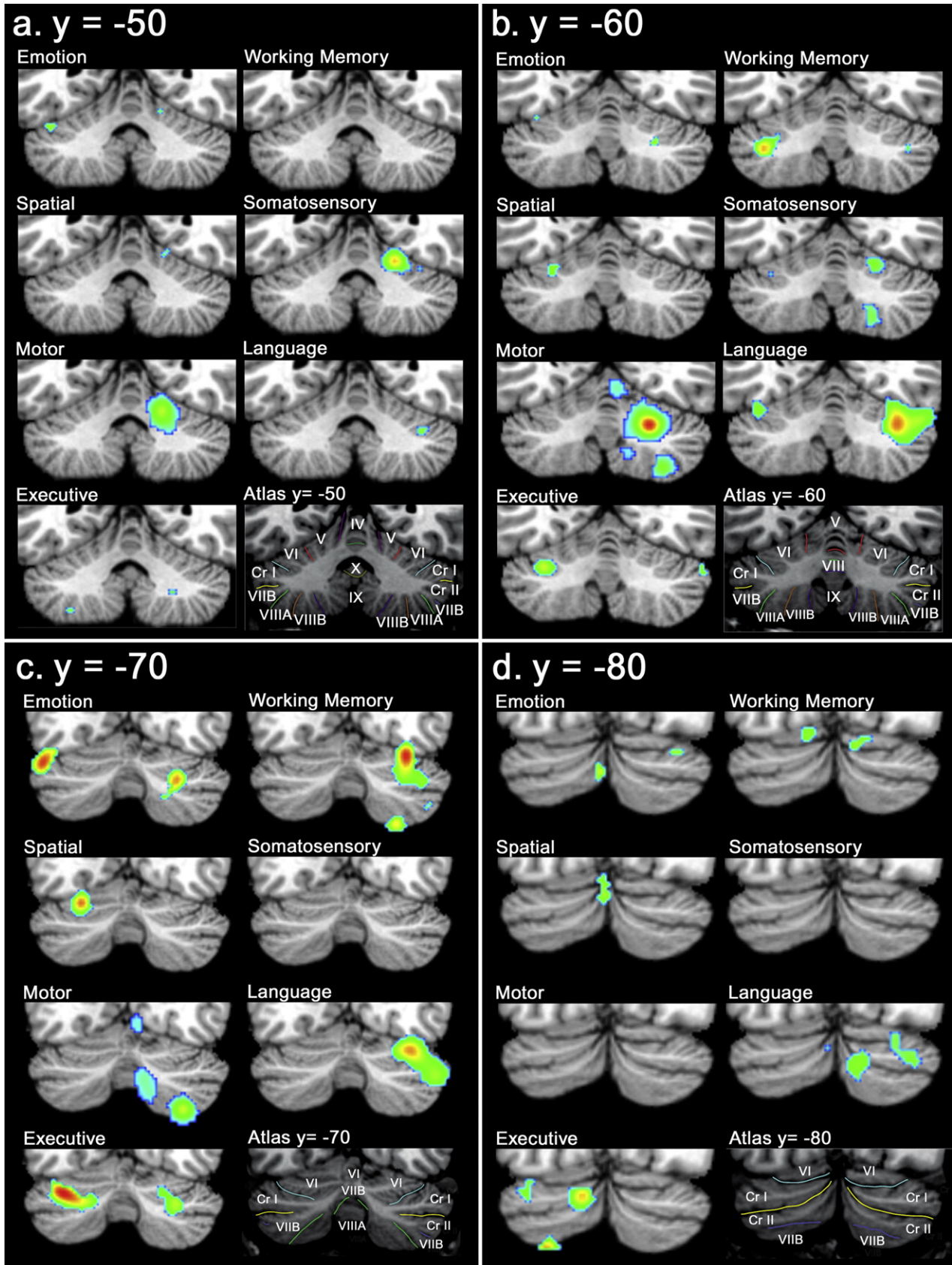


Fig. 1. ALE activation maps for each domain at (a) $y = -50$, (b) $y = -60$, (c) $y = -70$ and (d) $y = -80$ mapped onto representative coronal sections of the Colin27 brain (left cerebellar hemisphere is shown on the left). For each coronal level, at the bottom right are corresponding coronal sections from the MRI Atlas (Schmahmann et al., 2000) with the cerebellar fissures and lobules demarcated and labeled.

dimension to the activation patterns is evident, as is medial–lateral and lobular organization.

Sensorimotor tasks

Motor and somatosensory representations show largely overlapping activation patterns, with the major cluster focused in lobule V and the adjacent part of lobule VI, and a second cluster in lobule VIII. The motor and somatosensory coordinates were right-lateralized; as these were right-handed tasks, this finding is consistent with established ipsilateral cerebellar somatotopy.

Language

The strongest activation peaks for the language tasks were lateralized to right lobule VI, Crus I/Crus II, and midline lobule VIIAt. There was a small lateral cluster in left-hemisphere lobule VI.

Verbal working memory

There was considerable overlap between peak activation coordinates for the verbal working memory tasks, and those found in the language measures. For verbal working memory tasks, the strongest activation peaks were at the junction of lobule VI/Crus I in the right hemisphere, with a comparable left-hemisphere cluster in VI/Crus I. In addition to these more lateral clusters, there were medial peaks in both the left ($x=-10, y=-84, z=-18$) and right ($x=12, y=-74, z=-22$) hemispheres in lobule VI. Finally, there was a small cluster in right lobule VIIIA that showed a significant ALE peak for working memory tasks.

Spatial processing

In contrast to the language/verbal working memory processes that were more right-lateralized, spatial processing showed greater left-hemisphere activation, predominantly in lobule VI. There was also one small significant cluster in right lobule VI.

Emotional processing

Processing of emotional stimuli activated a cluster extending from the midline into medial regions of left lobule VIIAt. A large left cerebellar hemisphere cluster involving lobules VI and Crus I was also present, as was a cluster in right lobule VI.

Executive function

The executive function tasks highlighted a number of cerebellar regions, including Crus I bilaterally, and left lobules VI and VIIIB. These tasks are likely to include processing in multiple domains, depending on the demands of the paradigm. We therefore performed the comparison analyses (below) that highlight the potential contributions of spatial processing, language, and working memory to these executive tasks.

Comparison of task categories

Because the ALE clusters in several categories mapped onto similar regions of the cerebellum, we compared these foci using GingerALE software. For example, the somatosensory and motor tasks mapped to overlapping regions of the cerebellum. When the ALE maps for these categories were compared, three right-lateralized clusters, 1016–6200 mm³ in size, had significantly higher ALE values during the motor than the somatosensory conditions. These were situated in lobules V, VI and VIII (Table 4).

Studies of a number of cognitive domains resulted in activation localized to lobules VI and Crus I. We therefore conducted comparisons between these task categories to determine areas of overlapping versus unique activation patterns (see Table 4). Language and working memory activation patterns overlapped to some extent, but when the two sets of foci were compared, three significantly different clusters emerged. Language tasks were more likely to show prominent activation in right Crus I, with a small cluster in left lobule VI. In contrast, a higher activation likelihood for the working memory task was found in a small cluster in right VIIIA.

Table 4
Comparisons of task activations

| Comparison | Cluster size *ALE × 10 ⁻³ | Peak | Location | Cluster size *ALE × 10 ⁻³ | Peak | Location |
|-----------------------------------|--------------------------------------|-------------|-----------------------------------|--------------------------------------|-------------|-------------|
| <i>Motor>somatosensory</i> | | | <i>Somatosensory>motor</i> | | | |
| Cluster 1 | 6200 mm ³ | 24 -56 -32 | Right VI | None | | |
| | ALE 7.0–17.4 | 8 -64 -32 | Rt VIIIA | | | |
| | | 10 -64 -46 | Rt VIIIB | | | |
| Cluster 2 | 3200 mm ³ | 30 -66 -56 | Right VIIIA | | | |
| Cluster 3 | 1016 mm ³ | 6 -64 -10 | Right V | | | |
| | ALE 7.12 | | | | | |
| <i>Language>working memory</i> | | | <i>Working memory>language</i> | | | |
| Cluster 1 | 4256 mm ³ | 41 -60 -30 | Right Crus I | 160 mm ³ | 24 -72 -60 | Right VIIIA |
| | ALE 6.2–9.4 | | | | | |
| Cluster 2 | 3248 mm ³ | 13 -86 -33 | Right Cr I/II | ALE 5.63 | | |
| | ALE 5.7–9.8 | | | | | |
| Cluster 3 | 544 mm ³ | 35 -82 -33 | Right Cr I | | | |
| Cluster 4 | 312 mm ³ | -43 -58 -23 | Left VI | | | |
| | ALE 6.23 | | | | | |
| <i>Language>spatial</i> | | | <i>Spatial>language</i> | | | |
| Cluster 1 | 7816 mm ³ | 39 -64 -30 | Right VI/Crus I | 200 mm ³ | -28 -66 -20 | Left VI |
| | ALE 6.87–11.09 | | | | | |
| Cluster 2 | 2776 mm ³ | 12 -86 -33 | Rt Crus I/II | 184 mm ³ | -4 -72 -16 | Left VI |
| | ALE 5.76–9.87 | | | | | |
| Cluster 3 | 200 mm ³ | -42 -58 -24 | Left VI | ALE 6.15 | | |
| | ALE 6.00 | | | | | |

Coordinates are given in MNI space. Locations were determined using the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000). *All ALE values are significant based on an FDR of $p<0.001$.

Table 5
Significant ALE differences between executive and other higher-order tasks

| Comparison | Cluster size *ALE $\times 10^{-3}$ | Peak | Location | Cluster size *ALE $\times 10^{-3}$ | Peak | Location |
|--------------------------------------|---------------------------------------|-------------|--------------------------------------|-------------------------------------|-------------|-----------------|
| <i>Executive > emotion</i> | | | <i>Emotion > executive</i> | | | |
| Cluster 1 | 1776 mm ³ ALE 8.01 | -34 -68 -28 | Left VI/Crus I ⁺ | 216 mm ³ ALE 5.59 | -50 -66 -26 | Left Crus I |
| Cluster 2 | 728 mm ³ ALE 7.33 | -28 -78 -52 | Left VIIIB ⁺⁺ | | | |
| Cluster 3 | 216 mm ³ ALE 6.33 | -12 -76 -28 | Left Crus I | | | |
| <i>Executive > language</i> | | | <i>Language > executive</i> | | | |
| Cluster 1 | 1520 mm ³ ALE 7.90 | -34 -68 -30 | Left VI/Crus I ⁺ | 4448 mm ³ ALE 7.2–9.7 | 36 -63 -29 | Right VI/Crus I |
| Cluster 2 | 408 mm ³ ALE 7.25 | -28 -78 -52 | Left VIIIB ⁺⁺ | 2248 mm ³ ALE 9.84 | 14 -86 -32 | Right Crus I |
| <i>Executive > working memory</i> | | | <i>working memory > executive</i> | | | |
| Cluster 1 | 2776 mm ³ ALE 6.1–7.98 | -30 -71 -29 | Left VI/Crus I ⁺ | 496 mm ³ ALE 7.58 | 30 -70 -20 | Right VI |
| Cluster 2 | 416 mm ³ ALE 7.26 | -28 -78 -52 | Left VIIIB ⁺⁺ | 280 mm ³ ALE 6.12 | 12 -74 -22 | Right VI |
| <i>Executive > spatial</i> | | | <i>Spatial > executive</i> | | | |
| Cluster 1 | 2368 mm ³ ALE 6.52–7.16 | -27 -70 -30 | Left VI/Crus I ⁺ | 360 mm ³ ALE 6.13 | -4 -72 -18 | Left VI |
| Cluster 2 | 616 mm ³ ALE 7.33 | -28 -78 -52 | Left VIIIB ⁺⁺ | 272 mm ³ ALE 6.47 | -28 -64 -20 | Left VI |
| Cluster 3 | 296 mm ³ ALE 5.11 | 52 -58 -32 | Right Crus I | | | |

^{+/++}Regions specific to executive function in all comparisons. Coordinates are given in MNI space. Locations were determined using the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000). *All ALE values are significant based on an FDR of $p < 0.001$.

Several clusters highlight the differences between the ALE patterns for the language and spatial coordinates. Unique activation for the language condition was found in right lobules VI, Crus I and Crus II, along with a small cluster in left lobule VI. Spatial tasks compared to language measures showed two clusters of left-hemisphere activation in lobule VI, one more medial (-4, -72, -16) and one lateral (-28, -66, -20) cluster.

Analysis of the executive function tasks showed several clusters located throughout the cerebellum, with no clear lateralization or lobular pattern. Because these tasks are complex and require the processing of many different types of information, we compared the executive function coordinates with those in the other cognitive tasks. Table 5 reports the significant clusters and peak coordinates for each comparison. Two regions unique to executive function emerge from these analyses – one in left lobule VI at the border with Crus I (⁺ in Table 5) and one in left lobule VIIIB (⁺⁺ in Table 5). Language and working memory both had clusters that were uniquely separate from executive function clusters in right lobules VI (working memory) and Crus I (language). Compared to the activation sites for executive information, emotional processing activated a region in lateral left Crus I. The medial and lateral left lobule VI activation clusters for spatial processing were separate from the region of left lobule VI involved in executive functions.

Discussion

This activation likelihood estimate (ALE) meta-analysis provides a quantitative summary of patterns of cerebellar activation found in healthy adults for tasks in which different types of information are being processed. The results indicate that there is a functional topography of the cerebellum, particularly with regard to sensorimotor vs. language, spatial, and working memory tasks. In agreement with known cerebellar homunculi (Snider and Eldred, 1951), sensorimotor tasks showed significant ALE peaks in lobule V in the anterior lobe encroaching on lobule VI, with a secondary representation in lobule VIII. Language, working memory and spatial processing were largely localized to lobules VI, Crus I and Crus II. Emotional processing included a midline peak in lobule VIIAt, and hemispheric activation

peaks in lobules VI and Crus I. Executive functions showed a distributed pattern, and included bilateral regions in lobule VI, Crus I, and VIIIB.

Sensorimotor vs. cognitive regions of the cerebellum

A dichotomy between the “sensorimotor” and “cognitive” cerebellum has been proposed (Schmahmann, 1991, 1996, 2004), and is supported by clinical findings in stroke patients (Exner et al., 2004; Schmahmann, 2007; Schmahmann and Sherman, 1998; Schoch et al., 2006). Our meta-analysis findings corroborate this dichotomy: motor tasks were localized to the anterior lobe, with a secondary representation in lobules VIIIA/B; somatosensory tasks also involved the anterior lobe, with a secondary representation in lobule VIIIB. None of the “higher-level” language, working memory, spatial or executive tasks showed ALE peaks in the anterior lobe.

Our findings are concordant with previous fMRI studies (Bushara et al., 2001; Grodd et al., 2001; Nitschke et al., 1996) that have established the somatotopic representation of the body in the human cerebellum. Grodd et al. (2001) found that movement of the right hand was localized to right lobule V with a secondary representation in right lobule VIII. Bushara et al. (2001) reported activation for individual participants during tactile stimulation of the hand and foot; the representation of the hand was largely ipsilateral, with a lobule V component and a secondary component in lobules VIIIB and IX, depending on the individual subject. These findings correspond to our meta-analysis results, particularly for tactile tasks, which highlighted ipsilateral lobules V and VIIIB. Thus, imaging data in humans support the conclusions of Snider and Eldred (1951) that there are two representations of the body in the cerebellum, one in the anterior lobe and a second in the posterior lobe. Further, our results suggest a potential dichotomy between somatosensory and motor processing in lobule VIII. Whereas motor activation was observed in both lobules VIIIA and VIIIB, somatosensory foci were located only in VIIIB. In the mediolateral dimension in lobule VIIIB, the somatosensory coordinates were more laterally situated, at $x = 18, 20$; the motor coordinates in lobule VIIIB were more medial, at $x = 12$. We remain circumspect

about these findings given the inherent limitations of meta-analyses, but the possibility that tactile and motor processing involve different regions of lobule VIII appears to be a novel observation that requires further prospective investigation.

Lateralization of function in the cerebellar hemispheres

Clinical and imaging studies have indicated that language representation in the cerebellum is more right-lateralized, while spatial functions are more left-lateralized (see clinical work by Fiez et al. (1992), Gottwald et al. (2004), Gross-Tsur et al. (2006), Hokkanen et al. (2006), Leggio et al. (2008), Riva and Giorgi (2000), Scott et al. (2001) and imaging studies investigating crossed cerebellar-cerebral activation during language and working memory tasks, including those by Hubrich-Ungureanu et al. (2002), Jansen et al. (2005) and Ziemus et al. (2007)). Our meta-analysis findings show a degree of laterality in language and spatial tasks: the right cerebellar hemisphere is more likely to be active during language paradigms, and the left during spatial tasks. However, both domains show bilateral activation, involving a small component of the opposite lobule VI. These results are in agreement with findings in non-human primates suggesting that not all cerebro-ponto-cerebellar projections are crossed: in macaques, the majority (about 90% of projections to the hemispheres and 70% of projections to the vermis) of ponto-cerebellar fibers project contralaterally, with 10–30% projecting to the ipsilateral side (Brodal, 1979).

Parietal vs. prefrontal loops?

Anatomical and physiological studies in cats and non-human primates indicate that association areas in both parietal and prefrontal cortical areas are interconnected with the hemispheric extensions of lobule VII, i.e. Crus I and Crus II (Allen and Tsukahara, 1974; Brodal, 1983; Brodal and Bjaalie, 1997; Brodal and Steen, 1983; Kelly and Strick, 2003). The degree to which the Crus I/II connections are specific for these different cerebral association areas has not definitively been established, although there is some indication that Crus II is more closely linked with the prefrontal cortex. There are likely to be differences between non-human primates and humans with respect to parietal and prefrontal cortico-cerebellar loops, as reflected in the observation that the largest segment in the monkey cerebral peduncle contains fibers derived from the motor cortex, whereas most fibers in the human cerebral peduncle arise from prefrontal regions (Ramnani et al., 2006). In our meta-analysis, left Crus I was activated by working memory, executive and emotional conditions, whereas significant ALE values were found in both Crus I and Crus II in the right cerebellar hemisphere in language tasks. In the studies included in the meta-analysis, cortical activations were present in both frontal and parietal regions. Based on the current analyses therefore, it is difficult to discern whether these prefrontal- vs. parietal-cerebellar anatomical loops are reflected in the imaging data. Further work investigating the relationship between parietal and prefrontal activity and cerebellar activation patterns is needed to explore the localization and functional significance of the parietal and prefrontal cerebro-cerebellar loops in humans. An example of this is a recent study by Hayter et al. (2007), in which performance on the Paced Auditory Serial Addition task, a working memory task, was used to study the relationship between prefrontal regions and specific cerebellar areas. Relative to a control task, the working memory measure activated medial regions of lobules VI and VII along with prefrontal and premotor cortical areas.

The limbic cerebellum

It has been proposed that the posterior vermis can be considered the “limbic cerebellum”, based on the connections between this region and limbic structures of the brain (see Heath et al., 1979;

Schmahmann, 1991, 1996, 2004). Patients with the cerebellar cognitive affective syndrome (CCAS) can present with emotional lability, inappropriate laughing or crying, and changes in affect (Levisohn et al., 2000; Parvizi et al., 2007; Parvizi and Schiffer, 2007; Rapoport et al., 2000; Schmahmann and Sherman, 1998; Schmahmann et al., 2007; Steinlin et al., 2003), suggesting that these cerebello-limbic connections are involved in the modulation of emotional processing. The meta-analysis of coordinates active while viewing “emotional” vs. “neutral” pictures from the IAPS scale and judging emotional intonation in speakers' voices activated a variety of regions within the cerebellum, including a cluster in lobule VIIA extending from the midline (–2, –82, –38) into the medial left-hemisphere (–6, –82, –38); a large left-lateralized cluster in Crus I; and an area in right lobule VI. The midline lobule VII component may be important for the affective aspects of the CCAS and posterior fossa syndrome (Famularo et al., 2007; Pollack et al., 1995; Richter et al., 2005), and malformations of the posterior vermis have been associated with emotional symptoms (see Tavano et al., 2007). These posterior vermal regions are among the brain areas that show significant structural differences in autistic spectrum disorders (Bauman and Kemper, 2005; Courchesne et al., 1988; Penn, 2006).

Agreement with other imaging studies

The results of the meta-analysis are supported by findings of other imaging studies employing similar tasks that did not meet the criteria for inclusion in this analysis.

Language processing

Language-related activation during phonological, semantic and word generation paradigms has generally been observed in the right posterolateral cerebellum, with more involvement of the anterior lobe when articulation is a factor (see Fiez and Raichle, 1997; and clinical work by Ackermann et al., 1992). In Jansen et al. (2005), subjects with right- or left-hemisphere language dominance performed a word generation paradigm. Performance of the task was associated with activity in the cerebellar hemisphere contralateral to the dominant cerebral hemisphere. As in the present meta-analysis results, the activity was focused in lateral, posterior cerebellar regions, including lobules VI and Crus I/II. These findings are similar to earlier studies showing right cerebellar activation during verbal fluency tasks in right-handed subjects (Le et al., 1998; Petersen et al., 1988; Raichle et al., 1994), and a study of crossed cerebro-cerebellar activation during a verbal fluency task in one left-handed subject and one right-handed subject (Hubrich-Ungureanu et al., 2002).

Working memory

Earlier imaging studies have highlighted the role of the cerebellum in working memory (e.g. Desmond et al., 1997; Fiez et al., 1996). Our results reveal that regions involved in verbal working memory tasks showed overlap with those involved in language tasks, consistent with the proposed role of verbal rehearsal in working memory (Baddeley, 1992). Based on their findings during a Sternberg working memory task, Chen and Desmond (2005a) hypothesized that the cerebellum has two different roles during verbal working memory: the first, involving a cerebello-frontal loop between right cerebellar lobules VI and Crus I and Broca's area, is involved in articulatory rehearsal; the second, involving a cerebello-parietal loop between right cerebellar lobules VIIIB and VIIIA and the inferior parietal lobule, is involved in the maintenance/storage of information. To further investigate these ideas, Chen and Desmond (2005b) used event-related fMRI to study the differences in cerebellar activation during encoding, maintenance and retrieval in the Sternberg task. During task encoding, right lobule VI and Crus I were active, along with the left inferior frontal gyrus. The left inferior parietal lobe and right cerebellar lobules VIIIB and VIIIA activation started during encoding,

but continued to increase, peaking during the maintenance phase. Activation in vermal lobule VI was related to retrieval. These findings of different cerebellar patterns during the various phases of the working memory task correspond well with the distributed areas highlighted by our meta-analysis. Further, they suggest that within-task variation in localization may be dependent on the demands during different phases of the task.

Spatial processing

Clinical, animal studies, and imaging data provide support for a role for the cerebellum in spatial functions (for review, see [Molinari and Leggio, 2007](#)). The cerebellum receives strong inputs from the parietal lobe ([Glickstein et al., 1985](#); [Schmahmann and Pandya, 1989](#)), and cerebellar damage leads to spatial deficits ([Botez et al., 1985](#); [Levisohn et al., 2000](#); [Molinari et al., 2004](#); [Nawrot and Rizzo, 1998](#); [Schmahmann and Sherman, 1998](#); [Tavano et al., 2007](#); [Wallesch and Horn, 1990](#)). Three types of spatial tasks were chosen for the meta-analysis: line bisection; tasks that involved mental rotation; and those that involved spatial navigation. The finding that spatial tasks showed more left-lateralized activation patterns are concordant with imaging data showing that the right cerebral hemisphere is more active during spatial tasks; for example, [Fink et al. \(2000\)](#) found that line bisection tasks particularly involved the left cerebellum and the right parietal cortex. Two early studies of mental rotation reported strong cerebellar activation ([Bonda et al., 1995](#); [Parsons et al., 1995](#)). Mental rotation seems to involve both cerebral hemispheres (see [Jordan et al., 2001](#)), particularly compared to the predominantly left-sided cerebellar activation during the line bisection tasks. [Molinari and Leggio \(2007\)](#) propose that the cerebellum plays a specific role in both the extraction of relevant information from the environment, and the acquisition of procedures related to this spatial information.

Executive function

“Executive” tasks are thought to tap prefrontal cognitive control mechanisms involved in the planning and integration of the different processes required to attain a specific goal. Many types of tasks can be categorized as executive – including directing attention, decision-making, working memory, and inhibition of a previously-correct strategy following rule changes. These tasks activate widely distributed brain networks depending on the nature of the task (see [Table 2](#)). In this meta-analysis, we have included examples of executive function tasks in which cerebellar activation is reported. However, it may not be possible to highlight purely executive cerebellar regions. As in the language and spatial findings, the areas of the cerebellum recruited by executive functions include regions involved in processing task- and domain-specific information. For example, the Sternberg task (regarded here as a working memory paradigm) may also be considered an executive function task. There were areas of overlap between the regions involved in working memory and executive function; however, there were also regions in right lobule VI that were specific to working memory. There were two regions in the comparison analyses, both in the left cerebellar hemisphere, that were specific to executive functions across all comparisons (vs. emotional processing, language, working memory and spatial processing): one cluster in lobule VI/Crus I, and another in lobule VIIIB. Anatomical studies in monkeys show interconnections between the prefrontal cortex and lobule VII (Crus I, Crus II, and lobule VIIIB; [Kelly and Strick, 2003](#)). Therefore, these findings are consistent with the concept of cerebro-cerebellar circuits that may underlie the involvement of the cerebellum in executive functions (see [Bellebaum and Daum \(2007\)](#) for a review of the cerebellum and executive control).

Emotional processing

Several imaging studies have found cerebellar activation in response to viewing emotional images or facial expressions (e.g., [George et al., 1993](#); [Paradiso et al., 1997, 2003](#)). A study investigating

empathy for another's pain ([Singer et al., 2004](#)) found cerebellar activation in symmetrical left and right regions of lobule VI. [Wildgruber et al. \(2005\)](#) investigated the neural correlates of identifying emotional intonation and found cerebellar activation during the emotion vs. baseline condition (left lobule VI, midline lobule VII, right lobule VI and Crus I), but not when the emotion condition was contrasted with the vowel identification condition. The areas of cerebellar activation found in the emotion vs. baseline contrast correspond to some of the regions reported in the PET study by [Imaizumi et al. \(1997\)](#) during a similar task. In both studies, cerebellar activation was found in midline lobule VII and the lateral posterior hemisphere (lobule VI and Crus I). The activation of vermal lobule VII is quite consistent in these studies, as shown also in our meta-analysis. Perhaps the hemispheric activation is related to the decision-making aspects of these tasks, whereas the vermal lobule VII component may be more specifically related to emotion processing. The clinical relevance of the putative limbic cerebellum in the posterior vermis is further substantiated by the finding that patients with cerebellar stroke have differences in PET responses in prefrontal and limbic regions compared with control subjects ([Turner et al., 2007](#)). Patients showed increased activation in prefrontal regions and decreased activation in limbic structures in response to unpleasant stimuli.

Theoretical implications

The notion that the cerebellum is somatotopically arranged originated with Lodewijk (Louis) (Bolk, 1866–1930; [Bolk, 1906](#)). Subsequent experimental studies, clinical reports and imaging findings have confirmed the observation ([Snider, 1950](#); [Snider and Eldred, 1951](#); [Snider and Stowell, 1944](#)) that the cerebellum contains one somatotopic representation in the anterior lobe, and a secondary representation in lobule VIII (see [Manni and Petrosini \(2004\)](#) for a review). Outside of the motor domain the picture is less clear, although clinical findings support regional functional neuroanatomical specialization of the cerebellum for motor, cognitive and affective processes (e.g., [Exner et al., 2004](#); [Heath et al., 1979](#); [Schmahmann, 2007](#); [Schmahmann and Sherman, 1998](#); [Schoch et al., 2006](#); [Tavano et al., 2007](#)). Our meta-analysis shows that sensorimotor processing activates the anterior lobe and parts of lobule VIII, in agreement with earlier observations. In contrast, the activations during cognitive and emotional paradigms are localized to the cerebellar posterior lobe in lobules VI and VII, involving both Crus I and Crus II, with no anterior lobe involvement. This sensorimotor vs. cognitive/emotional dichotomy confirms clinical observations of functional differences between the anterior lobe and posterior lobe. However, while there is evidence that different information is processed in the left and right cerebellar hemispheres, and some support for the presence of parietal vs. prefrontal-cerebellar loops, the present meta-analysis is unable to confirm strict functional topography for non-motor tasks.

These observations have relevance for the dysmetria of thought theory ([Schmahmann, 1991, 1996](#)), which postulates a cerebellar role in cognition and emotion in addition to its traditional engagement in motor control. In this view, the essentially homogeneous cerebellar cortex and repeating corticonuclear microcomplexes ([Ito, 1993](#)) are the anatomical and physiological substrates that subservise a constant cerebellar computation ([Dow, 1974](#); [Schmahmann, 1991](#)); the resulting universal cerebellar transform (UCT; [Schmahmann, 2000, 2004](#)) is applied to diverse anatomical loops of afferents and efferents linking the cerebellum with the cerebral cortex, brainstem and spinal cord, thus enabling the cerebellum to modulate diverse streams of information. The functional domains of these loops, to which the UCT is applied, are determined by their origins and targets in extra-cerebellar structures.

The dysmetria of thought theory is thus predicated on the near-uniformity of the cerebellar cortex, coupled with the rich heterogeneity of cerebellar connections, and topographic organization of

function in the cerebellum. This meta-analysis provides at least partial support for one aspect of this theory, namely, that there is topographic organization of function in the cerebellum.

Limitations

Essential considerations in the conduct of any meta-analysis are the selection of studies to be included in the analysis, the division of tasks into broad functional domains, and the determination of the locations of activations across different imaging experiments. These challenges are substantial, but not insurmountable. As described in our Materials and methods section, we defined exclusion and inclusion criteria based on study parameters (functional imaging studies in healthy controls that reported standard coordinates based on whole-brain analyses), regardless of the domain investigated; we then restricted tasks to focused sensorimotor paradigms, and to selected, well-defined cognitive domains known to activate the cerebellum (spatial processing, language, executive function, emotion processing); and we excluded cognitive task comparisons in which motor output was not subtracted out. We addressed potential meta-analysis pitfalls by using an automated procedure (GingerALE) that allows for the quantitative analysis of activation sites as centers of activation probability distributions, which is thought to be more robust to inter-study differences in parameters, and we sacrificed voluminous data from large numbers of studies in favor of a focused group of paradigms that reliably report cerebellar activation. In this manner, we achieved our principal goal of determining whether different types of information are processed in different cerebellar regions. The problem of matching activation sites from multiple individuals and studies (both fMRI and PET) with the template of a single cerebellum, for reasons related to true inter-individual variability as well as technical factors determined by different methods, scanners, cognitive tasks, and issues of registration, indicates that further studies are needed to investigate cerebellar functional topography prospectively within single individuals.

Conclusion

The results of this meta-analysis show that different regions of the cerebellum process information from different domains. Our findings provide support for anatomical, physiological and clinical studies reporting the existence of sensorimotor (anterior lobe, lobule VIII), cognitive (posterior lobe, particularly lobules VI and VII [Crus I and Crus II]), and emotional (posterior vermis) regions of the cerebellum. The areas of overlap, and the inherent limitations of the meta-analysis approach, mandate a prospective study to clarify the functional topography of the cerebellum, particularly with respect to cognition.

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