Advances in functional imaging of the human cerebellum

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Purpose of review

A quarter century of functional neuroimaging has provided a number of insights into the function of the human cerebellum. However, progress has been relatively slow, partly because cerebellar imaging poses a number of unique challenges for functional magnetic resonance imaging (fMRI). This review provides a guide to problems and recent solutions in the design, analysis and interpretation of neuroimaging studies of the human cerebellum.

Recent findings

One major problem in the interpretation of functional imaging studies is that it is still unclear what type of neural activity is reflected in the cerebellar blood-oxygenation-level-dependent signal. We summarize recent work that has provided partly contradictory insights. We then highlight some technical challenges, specifically the susceptibility to physiological artifacts, and recently developed techniques to account for them. Furthermore, the small size and functional heterogeneity of the cerebellum poses a challenge for normalization and atlas methods, which demands different analysis techniques than those used in the neocortex. Finally, we highlight some novel results assessing anatomical and functional connectivity with the neocortex.

Summary

Although these results clearly show the limitations of current approaches, they also show the potential of anatomical and functional MRI for the study of the human cerebellum.

Keywords

atlas methods, blood-oxygenation-level-dependent signal, cerebellum, connectivity, functional imaging

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Introduction

Exactly 25 years have passed since the first published functional imaging study of the human cerebellum. In that study, Fox and Raichle [1] showed spatially specific activations in response to finger and eye movements. Today, there is substantial evidence for the involvement of the cerebellum in both motor and nonmotor functions. Although research has begun to show some spatially specific patterns associated with these processes [2••], the functional role of the cerebellum in these tasks remains far from clear. Why has progress been so slow? Here we review three factors that make neuroimaging of cerebellar structures especially challenging. First, it is still unclear which neuronal processes are reflected in the cerebellar blood-oxygenation-level-dependent (BOLD) signal, which is used as a marker of neuronal activity in functional magnetic resonance imaging (fMRI). Second, the BOLD signal is influenced by the cardiac and breathing cycles, and these physiological artifacts are especially pronounced for cerebellar structures. Finally, the small size of functional regions in the cerebellum poses a particular challenge to intersubject normalization of results.

Functional basis for neuroimaging signals

What neurophysiological processes drive the cerebellar BOLD signal? Unfortunately, the answer is far from clear. Neural activity increases the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Initially, this increases the local concentration of deoxyhemoglobin, whose magnetic properties decrease the BOLD signal. However, activity also leads to a compensatory increase in cerebral blood flow (CBF). In the neocortex, the relationship between these two quantities appears to be relatively fixed: the increase in oxygen supply due to CBF outstrips the $CMRO_2$ by a factor of $2:1$ [3]. As a result, neural activity leads ultimately to less deoxyhemoglobin and therefore a higher BOLD signal. The BOLD signal can be expressed as a nonlinear function of $CMRO_2$, CBF, and blood volume [4,5]. In the neocortex, both

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activity-dependent energy use [6], as well as the BOLD signal [7], appear to reflect mostly postsynaptic activity caused by efferent and recurrent excitatory input to a cortical region.

The architecture of the cerebellar cortex is dramatically different from that of the neocortex. There are two input systems to the cerebellar cortex. First, mossy fibers project to granule cells, each of which gives rise to a long parallel fiber. The parallel fiber in turn synapses on the dendritic trees of thousands of Purkinje cells – the only output cell of the cerebellar cortex. Each Purkinje cell also receives strong synaptic input from a single climbing fiber, arising from the inferior olive. To understand the source of the cerebellar BOLD signal we need to understand how much energy (and hence oxygen) these processes demand and how they influence the local blood flow.

Recent calculations based on cell numbers, spontaneous firing rates and membrane potentials [8•] led to the estimation that only 18% of the energy in the rat cerebellar cortex is consumed by Purkinje cells. Granule cells, in contrast, use 67% of the energy, much of which is used to relay mossy fiber input to other cells in the cerebellar cortex. During sensory stimulation, mossy fibers increase their firing rate from nearly 3 Hz at rest to up to 700 Hz [9]. If blood flow increased proportionally to energy use, these numbers would lead us to conclude that activity-dependent BOLD signal changes are mainly caused by increased signaling in the mossy fiber or parallel fiber system.

For the mossy fiber system, there appears to be a tight coupling between activity and blood flow. Experiments in anaesthetized rats have shown that electrical stimulation of parallel fibers leads to increases in blood flow [10]. This effect is dependent on glutamatergic signaling and on nitric oxide as a vasodilatory signal [11]. The increases in CBF outstrip the concomitant increases in $CMRO_2$, thereby leading to an increase in tissue oxygen [12••] and, by inference, the BOLD signal.

For the climbing fiber systems this relationship is less clear. One study indicates that climbing fiber input provides a major source of blood flow modulation. After lesions of the inferior olive, whisker stimulation produced only 42% of the blood flow increase observed in sham-lesioned rats [13]. This would indicate that more than half of the BOLD signal reflects climbing fiber input. In contrast, increasing complex- and simple-spike firing rate in Purkinje cells by pharmacologically removing inhibitory input from interneurons increases $CMRO_2$ but not CBF [12••]. According to these results, increases in complex-spike rates would lead to a decrease in BOLD signal.

Thus, the question of which neural processes are reflected in the cerebellar BOLD signal remains unanswered. Whereas it is clear that increased mossy fiber or parallel fiber input would lead to robust increases of the regional BOLD signal, it is still unclear whether climbing fiber input would be visible at all, and if so, to what degree. Because of possible interspecies differences, parallel electrophysiological recording and BOLD measurements in the monkey cerebellum would constitute an important step forward.

Physiological artifacts

Due to its dependence on blood flow and oxygenation, the BOLD signal is highly sensitive to changes in respiration and cardiac function. This is especially true for the cerebellum and the brainstem, which are surrounded by a dense bed of vasculature. Physiological processes may be correlated with the task that participants perform: systematic heart rate changes are known to occur in many tasks involving the control of action [14] as well as feedback processing in cognitive tasks [15]. Thus, we may easily misinterpret BOLD signal changes caused by physiological processes as being caused by neural activity.

Fortunately, physiological signals are easily recorded, as modern MRI scanners include pneumatic belts to record respiration and pulse oximeters or ECG to record heartbeats. The main challenge then becomes how to remove physiological artifacts from the fMRI signals based on these recordings.

There are two principal ways that physiological processes can influence the BOLD signal. First, the time of slice acquisition relative to the physiological event is important (Fig. 1a). The rate of flow varies for different phases of the cardiac cycle, and the brainstem shows considerable movement with every heartbeat. Furthermore, the rise and fall of the chest during breathing induces subtle changes in the magnetic field. Because we do not know *a priori* how exactly the BOLD signal changes with these events, a universal solution is to include both the sine and the cosine – as well possibly higher harmonics – of the phase of the physiological process as nuisance covariates within a standard GLM analysis. This RETROICOR method [16] was developed for the cerebral cortex, but provides an efficient way of noise reduction for subtentorial structures as well. Within the brainstem, good removal or physiological artifacts has been demonstrated utilizing three harmonics of respiration, two harmonics of heart rate, as well as a multiplicative term [17]. For areas around the cerebellum and brainstem we have found that up to 40% of the variance in the raw fMRI signal can be explained by the first two harmonics of heart and breathing (Fig. 1b).

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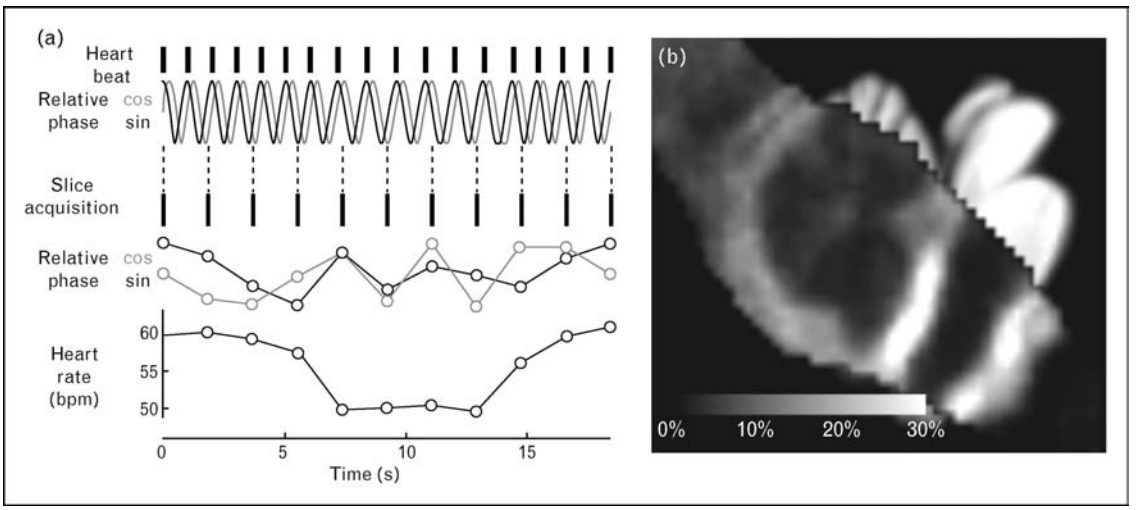
Figure 1 Influence of heart rate on the BOLD signal



(a) The time point when a slice is acquired in respect to the heart beats influences the BOLD signal. Two regressors, the sine and cosine of relative phase (second row), capture the lowest frequencies of this dependence. Because the heart rate is usually faster than image acquisition, the regressors for relative phase (fourth row) are under-sampled versions of the relative phase functions and contain low frequencies. The instantaneous heart rate (bottom row) exerts an independent effect on the BOLD signal. (b) Percentage of the variance of the raw BOLD signal that can be explained by cardiac and respiratory relative phase regressors, shown on a group-average parasagittal slice. Around the brainstem up to 35% of the imaging signal is caused by physiological artifacts.

The second type of effect on the BOLD signal comes from the instantaneous rate of the physiological process (Fig. 1a, bottom panel). Spontaneous changes in the rate of breathing have a long-lasting effect on the BOLD signal [18]. Part of the influence is likely to be related to a high correlation between breathing rate and changes in end-tidal carbon dioxide [19••], a potent vasodilator. Removing these rate effects can significantly reduce noisy signals in gray matter [18,19••]. Changes in the rate of cardiac output are also reflected in the BOLD signal. Heart rate regressors have been reported to capture approximately 1% of the variance across the brain at rest [20]. Changes in cardiac rate affect the BOLD signal with a time-course similar to the canonical hemodynamic response function [21].

Inclusion of the appropriate noise regressors can drastically improve the quality of the analysis. For functional connectivity studies (see below) these regressors are essential for reducing the Type I error rate. Even for traditional fMRI studies – especially those studying brainstem structures, such as the inferior olivary nucleus [22,23] – the inclusion is important because heart rate may vary systematically with the task in question. While the proper balance between noise reduction and overfitting has to be determined in each individual case, recording heart rate and breathing should become commonplace for cerebellar imaging studies to ensure that the effects of interest do not correlate systematically with either the phase or the rate of physiological processes.

Anatomical localization

The cerebellum consists of a number of clearly defined lobules and sublobules, each of which has its own pattern of connectivity with the neocortex [24] – and likely its own functional role [2••]. Thus, the cerebellum is perhaps as functionally diverse as the neocortex – at one-ninth of the volume. Current methods of group analysis in MRI seldom provide a sufficient level of spatial accuracy to explore functional localization in detail.

The first problem is variability. Because of difference in shape, it is not guaranteed that the lobules of two individual cerebella superimpose in group space. Indeed, using standard spatial normalization procedures, the location of the primary fissure (boundary between V and VI) spreads over 1–2 cm [25]. While averaging anatomical scans across participants, all spatial details of the underlying anatomy are lost. Therefore, it is virtually impossible to precisely assign functional activation to different lobules.

An equally serious problem is bias. Even within the same neuroimaging coordinate system (e.g. MNI152), different normalization methods may lead to substantially different locations of the same cerebellar structure in atlas space. For example, it is a common practice to use nonlinear normalization in SPM to conduct a group analysis and to then interpret the coordinates using the fMRI atlas of the human cerebellum [26]. Because the atlas is based on a single individual with a unique anatomy, and because the

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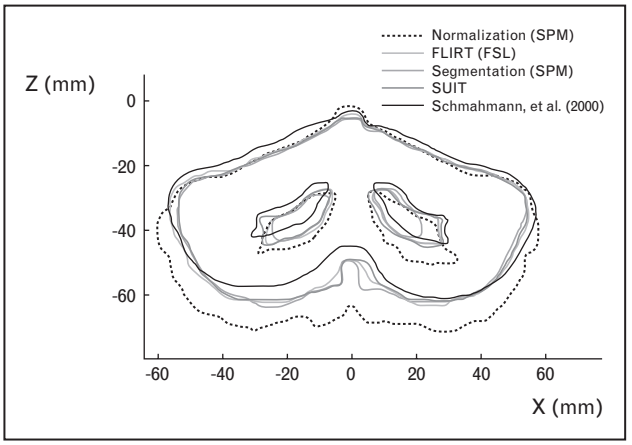
Figure 2 Anatomical bias in different normalization complicates spatial inference



The outline of the average cerebellar gray matter (>50%) of 20 participants is shown after normalization to MNI space (coronal slice $y = -66$). While most normalization methods (gray, FSL, segmentation in SPM, SUIT) are unbiased in respect to each other, standard nonlinear SPM normalization (thick black line) leads to an elongated cerebellum in atlas space. The location of the cerebellar atlas of one individual (thin black line, 26) differs slightly from each of the group averaged maps. The lobular assignment of the individual atlas agrees for only 38% of all cerebellar voxels with an SPM-normalized group analysis, and for 52–55% of all cerebellar voxels with the other normalization methods (FSL, segmentation in SPM, SUIT). These in turn agree for 76–82% of all cerebellar voxels with each other.

normalization method used for the atlas is biased differently than that typically used for the group analysis itself, large discrepancies between the two arise (Fig. 2). A systematic comparison between the most likely lobules of 20 participants after SPM normalization and the lobules in the atlas indicates that a coordinate-based assignment would only be correct for 38% of the voxels.

To ameliorate this situation, we have developed a refined population template and normalization method [spatially unbiased infratentorial template (SUIT)]. The method is able to fully align subtentorial anatomical structures to each other, reducing the anatomical variability after alignment. Even compared to recent whole-brain normalization methods, such as nonlinear normalization in FSL and unified segmentation in SPM [27], SUIT improves the overlap of individual lobules by nearly 8% [28••]. This normalization method also has the advantage of providing a segmentation mask, thereby preventing activity from the visual cortex from bleeding into the superior cerebellum. Furthermore, to overcome the problem of systematic biases, we have developed a probabilistic atlas of the cerebellum [28••]. Because this atlas is generated for different normalization methods, it allows for valid and accurate lobular annotation of activations found in group analyses. Although these techniques provide sufficient accuracy for fMRI studies of the cerebellar cortex, more specialized techniques for the alignment of the deep cerebellar and other brainstem nuclei need to be developed.

Mapping cerebellar–cortical connectivity

The function of each cerebellar lobule depends on its connections with the neocortex. However, anatomical connections between the neocortex and cerebellum synapse in the pontine nuclei, deep cerebellar nuclei, and thalamus are difficult to trace using conventional methods. The use of trans-synaptic viral tracers, however, has revealed some elements of this connectivity. A motor loop that connects lobules V and VIII with M1 and a nonmotor loop that connects Crus II with area 46 in the prefrontal cortex have been identified [29•]. Unfortunately, the connectivity of other lobules (e.g. VIIB, IX, etc.) is unknown. Because of large interspecies differences in regard to the organization of the lateral cerebellum and prefrontal cortex [30], in-vivo mapping of neocortical–cerebellar connections in humans would provide an important advance in understanding the functions of these areas.

The most widely employed MR technique to study anatomical connectivity is diffusion tensor imaging (DTI). White matter bundles have a strong asymmetry of water diffusion along their axons, and DTI measures the direction and magnitude of this diffusion. In the cerebellum, DTI has been used to generate structural integrity measures, such as fractional anisotropy (the strength of directional preference) and diffusivity (magnitude of diffusion). In the cerebellar peduncles, these measures stabilize during the first few years of development [31] and can be used to identify white matter damage in several cerebellar-linked disorders, such as dystonia [32], schizophrenia [33], and ataxia [34,35••].

General white matter integrity measures, however, are limited in their ability to distinguish which pathways are damaged in regions with multiple fiber tracts. In these situations one can apply tractography, a set of techniques that map the trajectories of clustered fiber bundles based on diffusion data. For example, probabilistic tractography [36] was recently used to reveal structural connectivity deficits in the cerebello-thalamic pathways of gene carriers for primary dystonia [37••].

Tractography methods have also been used to study healthy patterns of connectivity between cortical and cerebellar regions [38–40]. A recent study [41•] attempted to identify the connections between the cerebellar lobules and cortical areas. While these probability maps showed connectivity between VIIA Crus I and II and prefrontal cortex [24], the well-established connections between lobule V and M1 could not be demonstrated clearly. Tractography may fail in these situations because fibers

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connecting the neocortex and cerebellum navigate dense areas of the midbrain with multiple fiber crossings. Whereas the standard tensor model has been shown to have a limited capability at navigating fiber crossings [42], recent advances in high-angular-resolution diffusion imaging, such as diffusion spectrum imaging (DSI), have shown some promise solving this problem [43,44]. For example, Granziera and colleagues [45••] used DSI to track projections from the inferior olive to areas in cerebellar cortex and projections from the interpositus nucleus to the red nucleus. Although many technical difficulties still remain to be overcome, high-angular-resolution diffusion imaging methods hold promise for mapping the topography of projections to and from the human cerebellum.

A general challenge for diffusion imaging, however, is tracking polysynaptic connections through small and intricately organized regions, such as the pontine and the deep cerebellar nuclei. Functional connectivity MRI (fcMRI) [46] provides an alternative avenue to investigate neocortical–cerebellar circuits. Rather than mapping anatomical connectivity, fcMRI relies on the correlation of resting state fMRI time-series between a seed region and the rest of the brain, relying on the assumption that regions which form part of a functional network will be spontaneously correlated. Using this technique, two recent studies [47•,48••] have clearly demonstrated two distinct cortico-cerebellar networks: a motor network involving lobules V and VIII and the contralateral sensorimotor cortex; a nonmotor network involving Crus I and II and contralateral prefrontal and parietal areas. A third study further suggests that we may be able to identify additional loops. Using independent component analysis, Habas and colleagues [49••] analyzed the cerebellar constituent parts of five well-known components typically visible in resting-state fMRI data. The authors identified the two main networks found in [47•,48••], but also found that activity in lobule IX was correlated with the default-mode network involving medial prefrontal and retrosplenial cortex. Interestingly, a similar result was found in [48••]. While these results clearly need to be replicated and extended, with particular care taken to address potential physiological confounds, they indicate that fcMRI may serve as a useful application of existing methodologies to study cortico-cerebellar networks in the human.

Conclusion

Due to functional heterogeneity, small spatial size, and susceptibility to physiological artifacts, the human cerebellum poses many challenges to MRI research. We believe, however, that many of these difficulties can be overcome using specialized imaging and analysis techniques, many of which we have highlighted here. With such methods, functional and anatomical MRI provides a unique window into the function of the cerebellum in health and disease.

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