Chapter 8

Big Challenges from the "Little Brain" — Imaging the Cerebellum

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1. Introduction

The cerebellum is a compact structure that has about one-ninth of the volume of the neocortex, but comprises more than half of the neurons in the central nervous system. While the cerebellum has historically been understood to assist with movement and balance (e.g., Holmes, 1917, 1939), today we know that the cerebellum is also involved in non-motor functions (for review, see Stoodley & Schmahmann, 2009). Indeed, the cerebellum appears to play a role in nearly as many separate functions as the neocortex. This functional diversity within a restricted area poses unique challenges for the study of the cerebellum using functional magnetic resonance imaging (fMRI).

While no additional equipment or specialized pulse sequences are required to obtain fMRI data from the cerebellum, most so-called "whole brain" fMRI experiments focus on the study of the neocortex, often excluding inferior aspects of the cerebellum from data acquisition altogether. Furthermore, most common analysis methods are designed with the neocortex in mind and may be suboptimal for the analysis of cerebellar data, thus necessitating novel approaches to obtain insights about cerebellar function.

In this chapter we will highlight the current "best practices" to cerebellar fMRI experiments and address methodological challenges such as anatomical realignment, cerebellar atlases, cardiac artifacts on functional data, and the physiological source of the cerebellar blood-oxygen-level-dependent (BOLD) signal. We also review important research findings about the cerebellum, highlighting the role of fMRI studies in shaping our understanding of cerebellar function.

2. Methodological concerns for cerebellar imaging

2.1. Anatomical methods

Hypothesis testing using fMRI often requires data from multiple individuals; therefore we need a common anatomical frame of reference. Most widely-used normalization methods result in poor alignment of regions within the cerebellar cortex, which weakens statistical power (Diedrichsen, 2006). The deep cerebellar nuclei (the output of the cerebellum) are small and lie adjacent to the fourth ventricle and vascular supply, and therefore pose a special challenge to spatial normalization.

2.2. Localization within the cerebellar cortex

Like the neocortex, the cerebellar cortex is intricately folded. There are clearly defined lobules and sub-lobules within this cortex, separated by a number of fissures that can be reliably identified across individuals (Figure 1). Each lobule has its own pattern of connectivity with the neocortex (Kelly & Strick, 2003), and likely its own functional role (Stoodley & Schmahmann, 2009). Since each lobule is relatively small (5-10mm), inaccuracies in normalization will lead to functional data being averaged across neighboring structures. Indeed, if one uses standard spatial normalization procedures (which result in satisfactory overlap of structures within the cerebrum), the location of the primary fissure in the cerebellum (which forms the boundary between the anterior and posterior lobes) can be mis-localized by 1-2 cm (Diedrichsen, 2006). The top row of Figure 2 illustrates this overlap following the standard nonlinear SPM normalization to the MNI group template. When averaging anatomical scans across participants after normalization, most spatial details of the underlying anatomy are lost.

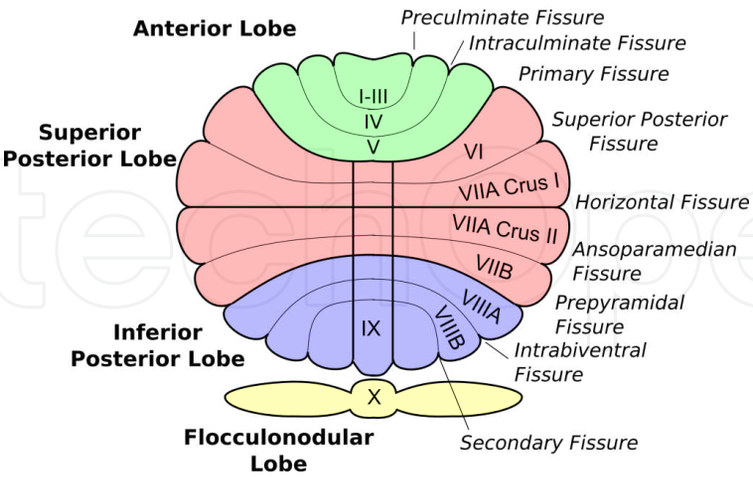

Figure 1. Anatomy of the cerebellar cortex. Traditionally, the cerebellum is split into the Anterior (green), Posterior (red and blue), and Flocculonodular (yellow) Lobes. Since the posterior lobe in the human cerebellum is large, researchers often subdivide it into Superior (red) and Inferior (blue) aspects. The cortex is subdivided longitudinally into lobules (Roman Numerals) by deep fissures. The current consensus on anatomical nomenclature is based on work by Larsell (1952, 1953), as laid out (along with excellent translations of prior nomenclature systems) by Schmahmann and colleagues (1999).

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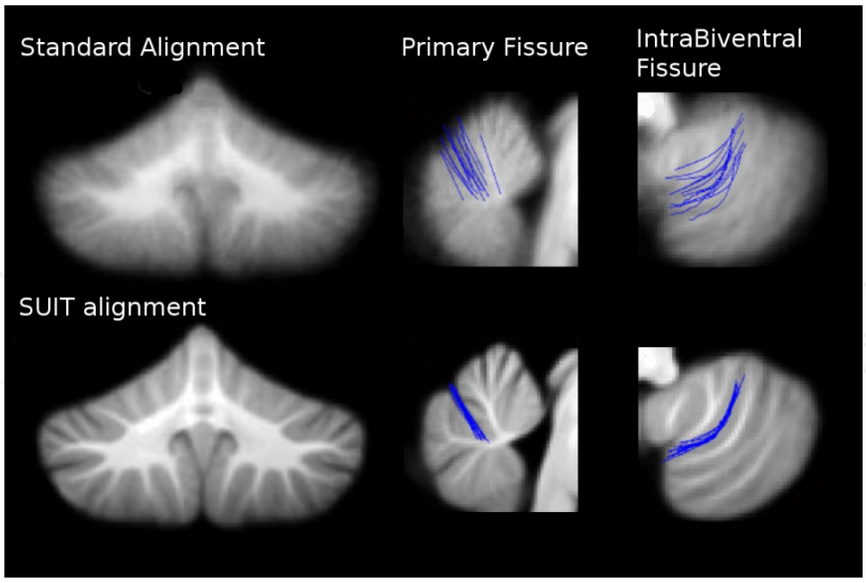

Figure 2. Comparison of normalization procedures. The top row demonstrates the normalization and coregistration of 21 individuals using the SPM standard normalization procedure to the MNI 152 template, which is not specialized for the cerebellum. Note the loss of detail, and the poor alignment of the Primary and Intrabiventral fissures. The second row shows the same 20 brains normalized using the SUIT template.

An equally serious problem is anatomical 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 (Diedrichsen et al., 2009). For example, it has become common to identify the anatomical location of cerebellar coordinates using the MRI atlas of the human cerebellum (Schmahmann et al., 1999). While this atlas provides a framework for subdividing the structure into individual lobules, the atlas is based on a single individual with a unique anatomy. Examination of 20 participants after normalization in SPM suggests that coordinate-based assignment using this atlas is correct for only 38% of the voxels in the cerebellar cortex (Diedrichsen et al., 2009).

Better normalization should be achievable, as cerebellar fissures are stereotyped and consistent across individuals (Makris et al., 2003, 2005). This makes it possible to use higher resolution anatomical normalization methods combined with a template that preserves anatomical detail within the cerebellum, implemented in the SUIT toolbox (Diedrichsen, 2006). This template is spatially unbiased relative to the space defined by the MNI 152 template, so each cerebellar structure is located where it would end up – on average-after affine alignment to the MNI 152 template. Thus, the resultant coordinates can be directly compared to results obtained in other studies. The use of the toolbox dramatically improves overlap of individual fissures (Figure 2, bottom row).

Since the development of the SUIT method, other methods have been published that use similar high-resolution warps and detailed nonlinear templates. While these methods improve the alignment of cerebellar structures, SUIT still improves the overlap of individual lobules by about 8% (Diedrichsen et al., 2009). The advantage of the SUIT approach likely arises from the initial segmentation into cerebellum and neocortex, as only subtentorial structures drive the

normalization. Segmentation also reduces the likelihood that activity from nearby neocortex will be misattributed to the cerebellum.

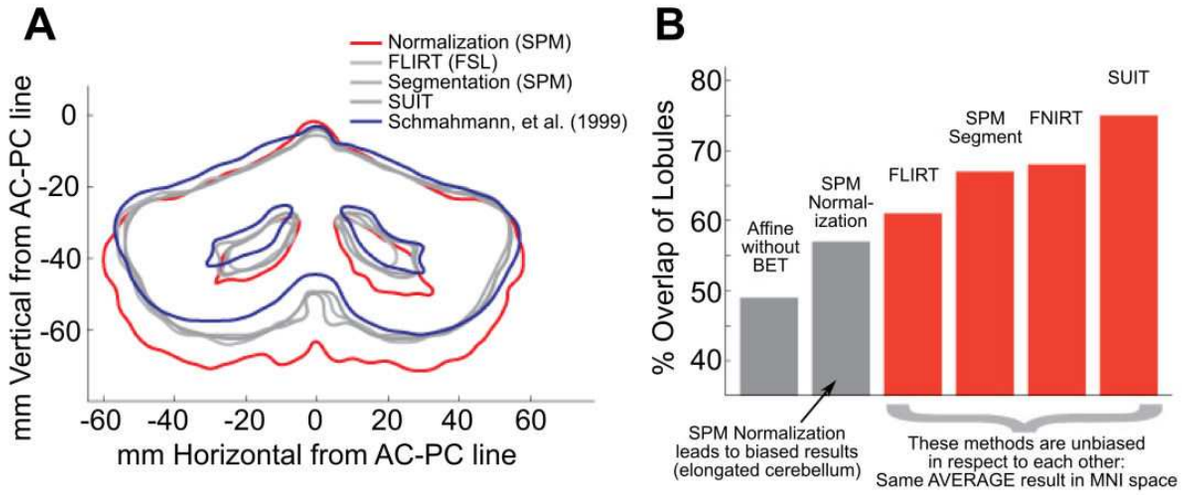

Figure 3. Overlap and bias of different normalization methods. A) When the outline of the cerebella are overlaid, the standard SPM normalization method (red outline) is clearly biased, particularly with respect to the Schmahmann atlas (blue outline). The other methods (including SUIT) are unbiased with respect to each other. B) Comparing the percent overlap of individual lobules, we can see some differences even among methods which result in the same overall spatial location.

To overcome bias in labeling the anatomical locations of activated regions, a probabilistic atlas for the cerebellum has been developed (Diedrichsen et al., 2009) to allow for accurate anatomical description of cerebellar activations observed in group analyses. This atlas can also facilitate analyses that eschew the group-overlap approach in favor of analysis based on anatomical regions of interest (ROIs). While it is possible to identify cerebellar lobules manually to constrain the anatomical extent of analysis (Makris et al., 2003, 2005), doing this by hand is tedious, and requires specialized knowledge to be reliable. The use of independently validated probabilistic atlases is much more efficient.

2.2.1. Imaging the nuclei

While SUIT-normalization and the associated probabilistic atlas provide sufficient accuracy for fMRI studies of the cerebellar cortex, more specialized techniques are required for the alignment of the deep cerebellar nuclei (DCN). These structures can be difficult to identify using conventional anatomical scans, as they can appear contiguous with the cerebellar white matter. Due to the high concentration of iron in these nuclei, they can be visualized more easily in T1-weighted images in older individuals (Dimitrova et al., 2002b) or by using T2-weighted images (Dimitrova et al., 2006).

Because the deep cerebellar nuclei are small, the inter-individual overlap using typical normalization methods is quite poor. Good superposition of the nuclei in group analyses is essential, especially because the T2* signal from the DCN is lower than the surrounding white

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matter and the nearby gray matter (Dimitrova et al., 2006). Since variability in fMRI is proportional to the average raw signal, this means that the functionally induced signal variations in the dentate nucleus are very low compared with functional activation in nearby gray matter. If these signals are averaged together with the signal from areas where both the raw signal and noise is twice as large (a consequence of spatial smoothing), it is extremely unlikely that they will be detected. This problem is exacerbated by high field strength, where the differences in T2* are even more pronounced.

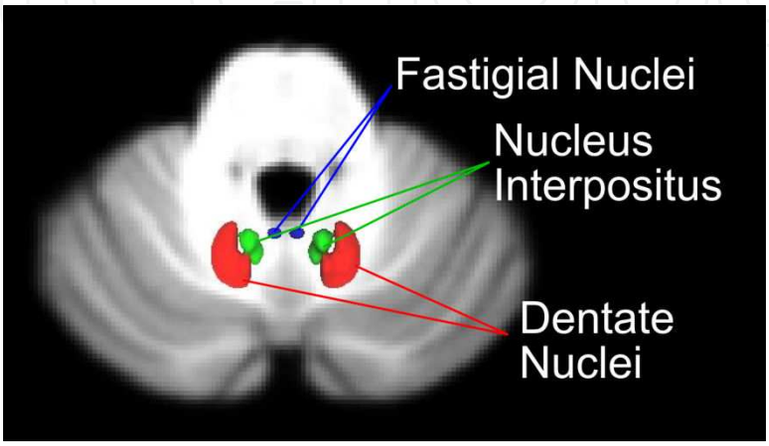

Figure 4. Overview and approximate location of the deep cerebellar nuclei. Adapted from (Diedrichsen et al., 2011).

A refined method for the normalization of the cerebellum and the dentate nucleus has recently been developed in conjunction with a probabilistic atlas for the DCN (Diedrichsen et al., 2011). As with the cerebellar cortical atlas (Diedrichsen et al., 2009), inter-individual anatomical variability depends on the normalization method chosen. Traditional MNI-alignment methods perform the worst, while segmentation-based methods perform slightly better (Diedrichsen et al., 2011). The best overlap for the deep cerebellar nuclei was obtained by using a variation of the SUIT-normalization method, combining white matter segmentation with an anatomical ROI that covers the deep cerebellar nuclei. Currently, this ROI must be traced by hand, and is most reliable when traced onto the phase image of susceptibility-weighted scans collected at 7T (Diedrichsen et al., 2011).

Using these techniques, Timmann and colleagues have shown that the dentate nucleus can be subdivided into cognitive and sensorimotor components (Küper et al., 2011a). They were able to demonstrate a somatotopic gradient between hand and foot movement in the motor portion of the dentate nucleus at 7T (Küper et al., 2011b). These studies provide important and exciting advances into our understanding of the human dentate nucleus. They also, however, highlight the limits of current fMRI techniques and the need for further development. Both magnetic inhomogeneity artifacts as well as physiological noise near arterial vessels make the detection of these weak signals challenging. As high-field scanners become more accessible and functional imaging at this field strength matures, we hope to see these techniques used for testing specific hypotheses about the deep cerebellar nuclei.

2.3. Interpretation of the cerebellar bold signal

FMRI involves repeatedly imaging the brain and analyzing small changes caused by variations in blood oxygenation. It is important to know which neurophysiological processes drive the cerebellar BOLD signal. Neural activity increases the cerebral metabolic rate of oxygen consumption ($CMRO_2$), which causes an increase in the local concentration of deoxy-hemoglobin, whose magnetic properties decrease BOLD. Neuronal activity also leads to a compensatory increase in cerebral blood flow (CBF), which raises the local concentration of oxygenated hemoglobin and thus increases the BOLD signal. In the neocortex, these two quantities have been measured and the relationship between them appears to be relatively fixed: the increased oxygenated hemoglobin from increased CBF outstrips the increased deoxy-hemoglobin from increased $CMRO_2$ by ratio of 2:1 (Hoge et al., 1999). As a result, neural activity in the cerebral cortex increases the BOLD signal. However, the architecture of the cerebellar cortex is dramatically different from that of the neocortex, and the same ratios may not apply. Careful thought and experimental work are needed to illuminate the relationship between neural activity and BOLD in the cerebellum.

2.3.1. Neural sources

There are two primary input systems to the cerebellar cortex (Figure 5). The first is the mossy fiber inputs that project to granule cells, which give rise to parallel fibers. Each parallel fiber synapses onto the dendritic trees of thousands of Punkinje cells-the only output cell of the cerebellar cortex. A single Purkinje cell can receive weak synapses from tens of thousands of parallel fibers. The second input system is the climbing fibers that arise from the inferior olive. Each Purkinje cell receives a very strong synaptic input from a single climbing fiber. Stimulation of each of these two pathways leads to time-locked increases in blood flow at the cerebellar cortex (Mathiesen et al., 2000), which by inference suggests that activity in both pathways may be contributing to the BOLD signal.

To understand the source of the cerebellar BOLD signal under physiologically plausible conditions, it is informative to understand how much energy (and hence oxygen) neural processes within the cerebellum demand. Calculations based on cell numbers, spontaneous firing rates and membrane potentials (Howarth et al., 2009) lead to the estimation that approximately 18% of the energy in the rat cerebellar cortex is consumed by Purkinje cells. In contrast, granule cells use 67% of the energy, most of which is consumed by the process of relaying mossy fiber input to cells in the cerebellar cortex. During sensory stimulation, mossy fibers have been shown to fire bursts of action potentials exceeding 700 Hz, compared to baseline firing rates at rest on the order of 3 Hz (Rancz et al., 2007). If the proportional increases of blood flow and energy use observed in the cerebral cortex hold for the cerebellum, we would be tempted to conclude that activity-dependent BOLD signal changes are mostly caused by increased signaling in the mossy fiber input pathway.

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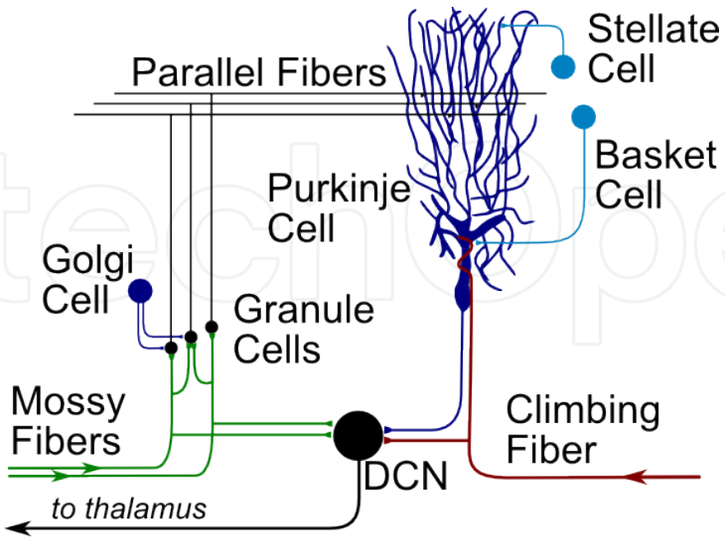

Figure 5. Overview of the cerebellar circuit. The input pathways are the mossy and climbing fibers, which are excitatory. Mossy fibers (green) synapse onto granule cells, which give rise to excitatory parallel fibers which synapse onto Purkinje cells, the output of the cerebellar cortex. Climbing fibers (red) synapse directly onto the Purkinje cells. Stellate, Basket, Golgi, and Purkinje cells are all inhibitory. Both input pathways, as well as Purkinje cells, synapse on the Deep Cerebellar Nuclei (DCN), the output of the cerebellum. (Adapted from Ito, 2001)

When the parallel fibers of anesthetized rats are electrically stimulated, blood flow to the region increases (Iadecola et al., 1996). This increased blood flow outstrips the increased $CMRO_2$, thereby leading to increased tissue oxygen (Thomsen et al., 2009). By inference, this suggests that increased activity in the mossy fiber/parallel fiber system will be tightly coupled with an increase in the BOLD signal. In line with energy use predictions outlined in the previous paragraph, increased neural activity within Purkinje cells alone does not seem to be strong enough to increase blood flow (Thomsen et al., 2004).

The possible response of the BOLD signal to activity within the climbing fiber system is less clear. After lesions of the inferior olive, stimulation of the whiskers of a rat produced only 42% of the blood flow increase observed in control animals (Zhang et al., 2003). This suggests that climbing fibers may be responsible for approximately half of the activity-dependent modulation of the BOLD signal. However, when complex (and simple) spike firing rates in Purkinje cells are increased by pharmacologically removing inhibitory input from interneurons, increases are observed in $CMRO_2$, but not in CBF (Thomsen et al., 2009). According to these results, increasing the complex spike rate by increasing the climbing fiber input could actually decrease the BOLD signal.

Clearly, the question of which neural processes are reflected in the cerebellar BOLD signal remains unanswered. While it appears likely that increased mossy/parallel fiber input would lead to robust increases in the BOLD signal at the cerebellar cortex, it remains unclear how

climbing fiber input would modulate BOLD, if at all. Parallel electrophysiological recording and BOLD measurements would constitute an important step forward.

2.3.2. Physiological artifacts

Since the BOLD signal depends on the rate of blood flow and oxygenation, it should come as no surprise that it is sensitive to changes in respiration and cardiac function. This is especially true in the cerebellum and brainstem, which are surrounded by a dense vascular bed. Problematically, these physiological processes have been shown to change in response to behavior. Systematic heart rate changes are known to occur in many tasks involving the control of action (Damen & Brunia, 1987; Jennings et al., 1991, 1992, 1993; Jennings & van der Molen, 2002) as well as feedback processing in cognitive (Crone et al., 2004, 2005, 2006) and motor tasks (Schlerf et al., 2012). Thus, we may misinterpret BOLD signal changes caused by physiological processes as changes caused by neural activity.

Fortunately, physiological signals (respiration, heart rate) are easily recorded. The main challenge, then, becomes one of data analysis: how should one best remove physiological artifacts from the fMRI signals using 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 (Figure 6A and B). The rate of blood flow varies for different phases of the cardiac cycle, and the brainstem shows movement with every heartbeat. The rise and fall of the chest during breathing induces subtle changes in the magnetic field. An efficient way to deal with changes related to the phase of these processes without any *a priori* knowledge of how the BOLD signal will change with these events is to use the RETROICOR method (Glover et al., 2000). This method deals with this by including both the sine and the cosine-and higher harmonics-of the phase of the physiological process as nuisance covariates within a standard GLM analysis. Thus, variability within a voxel's time series due to phasic changes of the signals measured will be modeled, instead of merely adding residual noise to the estimate of the BOLD response. This method was developed for the cerebral cortex, but provides efficient noise reduction for sub-tentorial structures as well. Within the brainstem, it has been demonstrated that the BOLD signal contains physiological noise which can be best modeled by three harmonics of respiration, two harmonics of heart rate, as well as a multiplicative term (Harvey et al., 2008). For areas around the cerebellum and brain stem, our own observations suggest that more than 30% of the variance in the raw fMRI signal can be explained by the first two harmonics of heart and breathing rate (Figure 6C). More recent methods have also been proposed for modeling other physiological artifacts in the BOLD signal, like spontaneous variations in breathing rate (Birn et al., 2006, 2008) and cardiac output (Chang & Glover, 2009). This approach can be quite important for correctly identifying neurally relevant portions of the cerebellar BOLD signal (Schlerf et al. 2012). While the proper balance between noise reduction and over-fitting 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 physiological processes.

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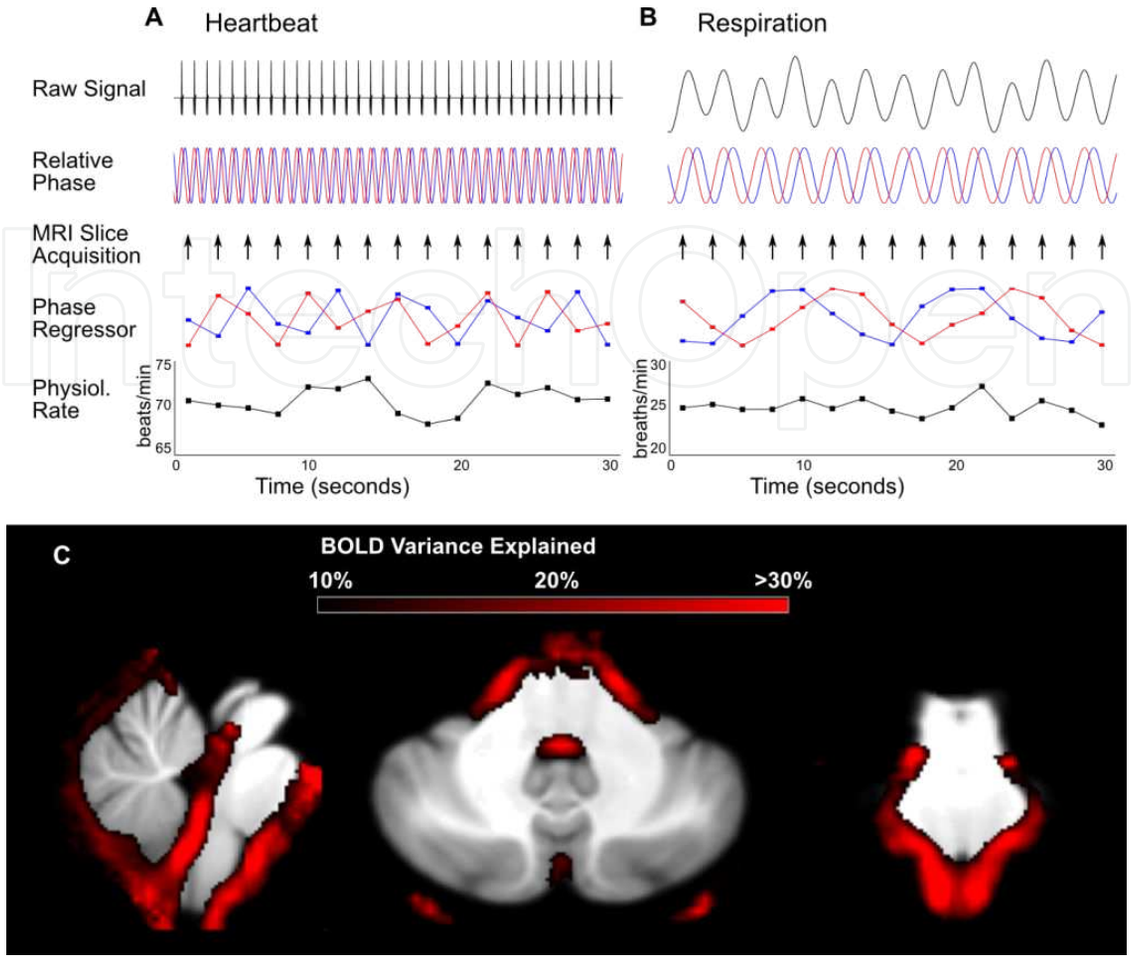

Figure 6. Influence of heart rate onto the BOLD signal. A) As a demonstration, a representative individual's heartbeat is shown. The top row shows the raw EKG trace of the hearbeat, and the next shows the first Fourier expansion (both sine and cosine waves) of the relative phase of the heartbets. Since fMRI data is acquired at regular intervals, BOLD artifacts may arise related to the phase of the heartbeat the data was acquired. The bottom row demonstrates heart rate effects. B) A representative individuals breathing is shown. The top row is the raw trace from a pneumatic compression belt, and the next rows show the instantaneous phase, as well as the phase and rate regressors. Note that breathing rate is substantially slower than heart rate. C) Data from a study conducted of the cerebellum (Schlerf et al., 2012) showing a high level of variability (greater than 30% of BOLD variance) accounted for by cardiac and respiratory phase regressors in CSF and arteries surrounding the cerebellum.

3. Functional studies of the cerebellum

3.1. Sensorimotor function

Because damage or removal of the cerebellum results first and foremost in movement impairments, the cerebellum has historically been categorized as a sensorimotor structure (Holmes, 1917, 1939). While it is now understood that the functional domain of the cerebellum extends beyond movement, sensorimotor processing remains one of the most active and important areas of cerebellar research.

Movement is one of the most efficient tasks for modulating BOLD-signal within the cerebellum. Below we review a few important fMRI results that have shaped our thinking of the function of this structure.

3.1.1. Maps of the body

Physiological work has suggested the presence of multiple body maps within the cerebellum. Two somatotopic maps were initially observed in the non-human primate cerebellum: one in the anterior lobe and the other in the inferior posterior lobe (Snider & Eldred, 1952). Both of these maps are somatotopically organized on a gross level (Figure 7). This organization has also been shown in humans using functional imaging. Indeed, the first published imaging study of the cerebellum (using PET) revealed spatially specific activations in response to finger and eye movements in the cerebellum (Fox et al., 1985).

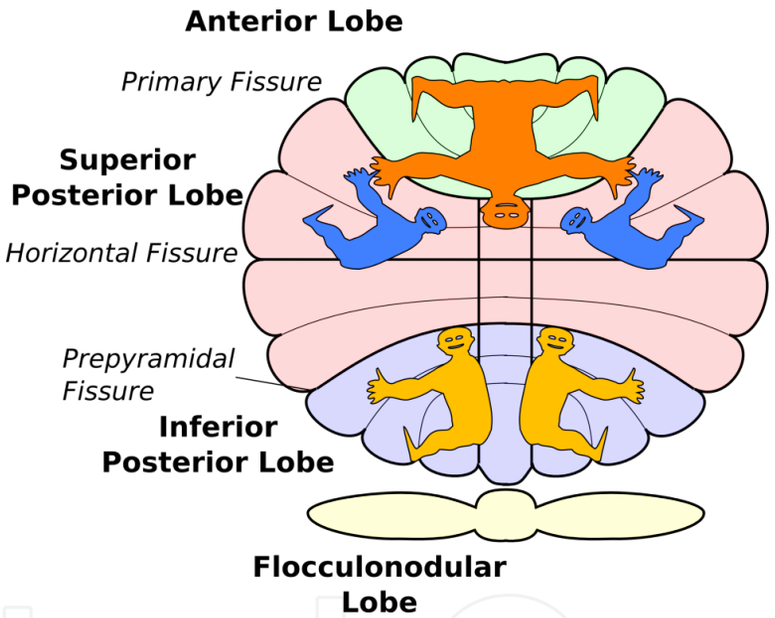

Figure 7. Multiple body representations within the cerebellum. The lobes are shaded to match the regions in Figure 1. Shown are the anterior (top, orange) and inferior posterior (bottom, yellow) body representations, as well as the newly identified superior posterior representation (blue). (Adapted from Snider & Eldred, 1952; Grodd et al., 2001; Schlerf et al., 2010)

Using fMRI, researchers have confirmed and extended these results. Rijntjes and colleagues (1999) confirmed that both sensory-motor representations show a somatopic gradient using finger and toe movements. Grodd et al. (2001) built upon this finding, demonstrating anterior and posterior representations for the hand, lips, tongue, and feet. These distinct maps were observed in the anterior and posterior lobes, in good agreement with animal physiology. The representation within the anterior lobe (lobules I-V; see Schmahmann et al., 1999) is generally unilateral, with each cerebellar hemisphere representing the movement of the ipsilateral limb. Within the somatomotor representation in the posterior lobe (chiefly lobule VIII), the observed

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activations are usually also stronger on the ipsilateral side, but bilateral activation is commonly observed (Grodd et al., 2001; Schlerf et al., 2010).

A number of studies have tried to dissociate the function of the anterior and posterior body maps. Thickbroom et al. (2003) explored the functional response to both active and passive movements of single fingers. Activation was observed to both types of movement in both the anterior lobe and the inferior aspect of the posterior lobe, suggesting that these regions have both sensory and motor functions. Habas et al. (2004a, 2004b) explored the response of the anterior map and the inferior posterior map during bimanual movements. Contrasting with the Thickbroom study, they found that passive bimanual movements did not activate the representation in lobule VIII, while active bimanual movements did (Habas et al., 2004a). A second study found that the inferior representation is more strongly activated by out-of-phase bimanual movements than in-phase movements, suggesting that this region may be specifically engaged by movements requiring the coordination of multiple effectors (Habas et al., 2004b).

A recent study, designed to explore the cerebellar response to coordination between individual fingers, tested simple rhythmic movements of all digits (fingers or toes) as well as complex sequential movements of individual digits (Schlerf et al., 2010). The body map within the anterior lobe was not strongly affected by movement complexity. Interestingly, there was evidence for a new map in lobules VI and VIIA Crus I, which was much more strongly activated for sequential movements of both the fingers (medially) and toes (laterally, see Figure 7). This suggests that these regions (thought to have cognitive functions) may be more involved in motor behavior than previously thought (Schlerf et al., 2010).

The aforementioned fMRI studies reveal somatotopic organization on a gross anatomical level, with neighboring voxels activating in response to different body parts. Physiological experiments, however, suggest that neighboring patches of cerebellar cortex respond to stimulation of quite different areas of the skin within the same bodypart. The term "fractured somatotopy" has been coined to capture this disjointed organization (Shambes et al., 1978; Bower & Woolston, 1983; Kassel et al., 1984). This organization poses a challenge to cerebellar imaging, as each voxel averages the activity over several of these patches of cerebellar cortex. Thus, conventional fMRI analyses will reach a resolution limit. A recent study was able to explore finer resolution maps of individual fingers using advanced analysis techniques (Wiestler et al., 2011). The analysis approach rests on the assumption that even if the average level of BOLD signal change across a region is not sensitive to individual finger movement, the spatial pattern of activity across multiple voxels may be specific for fingers and can be detected by multivariate analyses. The authors used local voxel patterns to train a linear classifier, and then predicted which finger was moved or stimulated in an independent test dataset. Better-than-chance prediction indicates that the region contains a finger representation. Two finger maps were identified: one in lobule V, and a second in lobule VIII. The activation patterns in these two representations were equally informative of finger identity for movement and tactile stimulation. This suggests that motor as well as sensory events are encoded with equal fidelity in the cerebellum. In contrast to the finger representations in the neocortex, which are ~3-4mm in size, the authors showed that the cerebellar representations are ~1-2mm in size, smaller than

an individual voxel. Such "hyper-acuity" of multivariate analysis has also been demonstrated for the case of orientation columns in visual cortex (Swisher et al., 2010). Thus, multivariate analysis promises to be an excellent tool to study fractured somatotopy within the cerebellum.

3.1.2. Motor learning

In addition to studying topographic organization, fMRI has been used to explore the cerebellar involvement in motor learning. A large body of evidence shows that the cerebellum is involved in the process of error-based learning (Martin et al., 1996; Straube et al., 2001; Maschke et al., 2004; Pisella et al., 2005; Smith & Shadmehr, 2005; Morton & Bastian, 2006; Tseng et al., 2007; Alahyane et al., 2008). One example of such a task is saccade adaptation, in which the length of an eye-movement is adjusted on a trial-by-trial basis, based on whether the eye movement under-or over-shot the target during the previous saccade. This rapid learning process is impaired in cerebellar patients (Golla et al., 2008).

A seminal model proposed by Marr (1969) and Albus (1971) suggests that the architecture of the cerebellar cortex is ideally suited for such error-based learning. The model suggests that context information about the planned or ongoing movement is signaled over the mossy-fiber-parallel-fiber system. The climbing fiber input to the cerebellar cortex then provides an error signal that leads to plasticity at the parallel-fiber-Purkinje cell synapses. Through this mechanism, the cerebellar output associated with the same movement (parallel fiber input) is rapidly adjusted.

Researchers have used error-based learning tasks to test the involvement of the cerebellum in motor adaptation, albeit with mixed results. Generally, two types of learning responses can be predicted for the blood oxygenation level dependent (BOLD) signal. The first, based directly on the Marr/Albus model (Marr, 1969; Albus, 1971), is that the BOLD response should reflect an error-signal, and therefore should be high early in learning when errors are large and then taper off as performance improves. The second type of activity change is related to the storage of the learned representation. This idea predicts that as participants learn to produce more accurate movements (often referred to by motor control researchers as "acquiring an internal model") the BOLD response in regions that support those accurate movements should increase, because they perform more, or more accurate computations. Early-learning related activity was observed during a study of skill learning, with increased activity in the ipsilateral anterior lobe early during a pinch-force training task (Floyer-Lea & Matthews, 2005). An adaptation study conducted by Imamizu and colleagues (2000) reported activation patterns during a visuomotor adaptation task which were consistent with both error-processing and storage. With learning, activity decayed in broad regions throughout the anterior and lateral cerebellum, while the most lateral regions (bilaterally) increased in activation as the new rule was stored. A more recent study using a similar adaptation task observed chiefly storage related activity in the ipsilateral anterior lobe (Luauté et al., 2009). Storage related activity in PET has also been observed for saccade adaptation, with bilateral cerebellar lobules VI and VII showing increased activity when performing the adapted movement (Desmurget et al., 2000).

Learning is a slow process when compared with the time-course of the BOLD signal measured in fMRI, and it is not easy to repeat, which reduces the reliability of the measured brain

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response. Finally, many behavioral changes can be conflated with learning. For example, Seidler and colleagues (2002) argue that storage-related changes in cerebellar activation reflect performance parameters rather than learning per se. Similarly, the error-related component of the learning response may result from increased corrective movements when errors are prevalent. A study looking for signatures of error processing using a design containing random perturbations found no cerebellar regions which were significantly active in a contrast of trials containing errors and corrective movements against trials containing corrective movements without errors, while cerebral voxels in the postcentral gyrus were active in this contrast (Diedrichsen et al., 2005). A very recent study used a task in which corrective movements were impossible, and observed proprioceptive error-related activity in lobules V and VI (Schlerf et al., 2012).

The cerebellum may also play a role in other forms of learning. The serial reaction time task (SRTT) is a classic paradigm used to study motor sequence learning (Nissen & Bullemer, 1987). Typically, a set of stimuli appear on a computer screen, telling participants which keys to press. If these cues appear in a sequential order, responses will get faster as participants learn the sequence. Patients with cerebellar damage have consistently shown impairments in learning during the SRTT (Doyon et al., 1997; Molinari et al., 1997; Gómez-Beldarrain et al., 1998; Shin & Ivry, 2003). Yet, imaging studies using fMRI and PET have consistently shown either no change in cerebellar responses during learning (Seidler et al., 2002; van der Graaf et al., 2006) or slight decreases in the anterior lobe ipsilateral to the moving hand (Hazeltine et al., 1997; Doyon et al., 2002). Thus, while patient studies suggest some role of the cerebellum in sequence learning, evicence from brain imaging is much more limited.

3.1.3. Timing and coordination

Patients with cerebellar lesions show consistent impairment in tasks that require timing and coordination (in addition to deficits in error-based learning). The relationship between these two functions, and the cerebellar involvement in both, has been a very active area of research that has sparked substantial controversies in the last years.

There is a longstanding debate about the cerebellar contribution to movement timing, and fMRI has provided evidence for both sides. Work on eyeblink conditioning, where a tone is predictably delivered prior to an aversive stimulus delivered to the eyelid, has historically provided strong evidence for the role of the cerebellum in timing (Gellman & Miles, 1985; Steinmetz et al., 1986; Ivry & Keele, 1989). This task has been successfully adapted to the MR environment, revealing activation in lobules VI and VIIA Crus I during eye-blink conditioning (Ramnani et al., 2000; Dimitrova et al., 2002a; Miller et al., 2003; Gerwig et al., 2007; Cheng et al., 2008). Timed movement tasks, such as the production of rhythmic finger movements, reveal strong cerebellar activation (Lutz et al., 2000; Dhamala et al., 2003; Garraux et al., 2005; Jantzen et al., 2005; Spencer et al., 2007). Studies have also examined the response to timing without movement, and found cerebellar activation in response to sensory estimates of temporal delay in left lobules VI and VIIA Crus I (Harrington et al., 2004) and broad activation throughout the anterior lobe in response to deviations from predictable rhythmic sequences (Liu et al., 2008).

While the link between timing and the cerebellum may be somewhat controversial (Rao et al., 2001; Hinton et al., 2004), the link between the cerebellum and coordination is not. A cardinal symptom of cerebellar disease is ataxia, or the lack of movement coordination. This deficit is especially pronounced when the movement task involves the coordination of movement across multiple joints (Thach et al., 1992; Bastian et al., 1996; Thach, 1998). In healthy participants, increased cerebellar activation in fMRI studies is commonly observed when the coordination requirements of the task increase. For example, during eye-hand coordination the cerebellum increases its activation parametrically with increased temporal offset between the required eye and hand movements (Miall et al., 2001).

Many researchers assume that the precise sequential activation of separate muscles in the context of a coordinated movement relies on the same neural mechanisms that underlie explicit timing tasks (Ivry et al., 2002; Ivry & Spencer, 2004). In this view, deficits in timing are the cause of coordination deficits. Coordinating across effectors (e.g., the shoulder and hand muscles when pitching a baseball) would thus require accurately timing the serial order of events. Incorrect timing of the release of a baseball during the shoulder swing of a pitch would result in highly uncoordinated and inaccurate pitching. However, recent behavioral studies have shown that the motor system controls the moment of ball release based on a predictive estimate of the arm position, rather than "timing" the ball release based on the state of an internal clock triggered by a particular event (Hore & Watts, 2005). An imaging study comparing the role of the cerebellum in timing and coordination using a single task showed that these are dissociable processes with lateral lobule V being more strongly engaged during coordination than timing (Diedrichsen et al., 2007).

3.2. Nonmotor function

While the cerebral neocortex is divided into cytoarchitectonic regions that delineate functional specialization, the cerebellar cortex is nearly uniform. Functional specificity is likely determined by the connections between the cerebellum and other parts of the brain (Schmahmann, 2004). Virus tracer studies in primates have demonstrated connections between the cerebellum and cortical association areas, such as the prefrontal and parietal cortices (Strick et al., 2009). FMRI connectivity studies confirm the existence of these networks in humans (Krienen & Buckner, 2009; Buckner et al., 2011), with connections largely involving the lateral cerebellar hemispheres, especially lobules VI and VIIA (Crus I and II). Since the prefrontal and parietal association areas within the neocortex are believed to play important roles in executive function and language, connected regions within the cerebellum should contribute to these functions as well.

3.2.1. Executive control

FMRI has provided important evidence for the role of the cerebellum in executive functions such as attention and working memory. Attention is the cognitive process of focusing on a particular feature in the environment. Working memory is the short-term storage (on the order of seconds) of information for later processing. Humans with damaged cerebella have been

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observed to have deficits in both attention (e.g., Akshoomoff & Courchesne, 1992) and working memory (e.g., Ravizza et al., 2006).

An early fMRI study of the cerebellar role in attention asked participants to attend to visual stimuli and count certain targets, or make repetitive finger movements without attention (Allen et al., 1997). Motor responses were mostly contained within lobule V, while attentional responses were more posterior, chiefly lobules VI and VIIA, which are connected with the prefrontal cortex. A third task combined these processes (asking participants to press a button every time the target stimulus appeared), and revealed activation in both of these regions (Allen et al., 1997). This finding corroborated an early patient study of the cerebellar role in attention (Akshoomoff & Courchesne, 1992). At any given point, participants were asked to respond to either colored flashes or tones, detecting a target item in that series. During a "switch" condition, participants were asked to wait for a target in the other sensory modality following the successful identification of a target. Patients with damage to the cerebellum responded particularly slowly during this condition, suggesting that attention switching may be an important function of the cerebellum (Akshoomoff & Courchesne, 1992). An fMRI study was conducted using a similar task, asking participants to attend to either the shape or color of a visual stimulus. Increased and reproducible cerebellar activation near right lobule VI was observed during the attention switching condition compared to the sustained attention condition (Le et al., 1998). Bischoff-Grethe and colleagues (2002) pointed out that these switching tasks did not control for motor demands, as separate stimulus-response mappings must be maintained and switched in addition to attention. This study replicated the previous task of Le et al (1998), and included a control condition where participants performed the same attention switch but only responded to one of the two features. Since the control condition involved identical attentional processes, any differences would support a motor explanation of this effect. Analysis of this data found increased activity in right lobule VI when two response mappings were required, suggesting that response reassignment was more important than attention switching (Bischoff-Grethe et al., 2002).

Individuals with cerebellar damage have impaired verbal working memory, but intact spatial working memory (Ravizza et al., 2006). Transcranial magnetic stimulation over right lobule VI selectively impairs response time on verbal working memory tasks (Desmond et al., 2005). FMRI has also supported a cerebellar role in working memory. Studies have compared activation during the Sternberg working memory task (Sternberg, 1966) to a control task of silent rehearsal, where participants continuously read a list of items for later matching. Cerebellar activity in bilateral lobules VI and VIIa crus I is observed during both tasks, while Lobule VIII is specifically activated in response to working memory (Desmond et al., 1997; Chen & Desmond, 2005a). Activity in all of these regions, bilateral lobules VI and VIIa Crus I and right lobule VIII, increases parametrically with working memory load (Kirschen et al., 2005).

The Sternberg task (Sternberg, 1966) can be used in event-related fMRI studies, where distinct components of working memory can be explored. Lobules VI and VIIA Crus I are chiefly involved during the encoding phase, while lobules VIIB and VIIIA were involved in encoding as well as maintenance across delay (Chen & Desmond, 2005b).

3.2.2. Language

While overt language disturbances such as aphasia are not commonly observed following cerebellar damage, speech disturbances have been documented (e.g., Holmes, 1917), which may mask subtle linguistic effects. FMRI has become an important tool for exploring the cerebellar contribution to language.

The first study to observe cerebellar activation in a cognitive task detected activity in the right cerebellum during verb generation (Petersen et al., 1989). Verb generation has since been successfully used to demonstrate functional activation of bilateral lobules VI and right VIIA Crus I by a number of researchers (e.g., Seger et al., 2000; Frings et al., 2006). A similar task is word-stem completion, where words are generated to complete a command prompt of a few letters. An early study observed that the right cerebellum (chiefily lobule VIIA Crus I, extending into midline lobules VI through VIIB) is more active when there are a limited number of correct completions of the word compared to when there are many (Desmond et al., 1998). This suggests that the search for correct words requires more cerebellar computation than selection among a number of easily identified options.

Despite the ease of observing activation during linguistic tasks, the role of the cerebellum in language is not without controversy. Participants with cerebellar degeneration do not have impairments in verb-generation tasks (Richter et al., 2004). Furthermore, while most fMRI studies control for speech articulation using noun repetition tasks, some investigators argue that this is not a strong enough control. Ackermann and colleagues (1998) observed cerebellar activity in right lobule VI by asking participants to perform a self-guided repetition task by rehearsing the months of the year repeatedly. This suggests that the cerebellum's role may still be fundamentally articulatory, as well-learned sequences of words are not demanding to recite. While the cerebellar contribution to language is not the only example of the difficulty in reconciling brain imaging studies with clinical investigation, it does underscore the need for elegant experimental manipulations when exploring cerebellar activity.

4. Conclusion

This chapter has provided a brief overview of some of the specialized techniques for imaging this particular part of the brain. We discussed some specialized anatomical methods for normalization and inter-individual alignment, as well as region-of-interest identification. We also discussed the importance of removing physiological nuisance covariates, and the promise of future innovation by multivariate analysis methods. Brain scientists who are interested in the cerebellum should become familiar with these methods.

We also discussed literature covering the functional specificity of this structure. Cerebellar regions likely play a role in many different functions, ranging from sensorimotor functions to higher cognitive functions. We provided an overview of the major areas of research, attempting to highlight some of the current controversies with regard to the role of the cerebellum. As MRI scanners and pulse sequences improve and researchers make better use of specialized

cerebellar analysis techniques, some of these controversies may be resolved. Fortunately, new controversies will undoubtedly emerge to take their place.

The cerebellum is a fascinating structure that poses unique challenges to MRI. As new solutions to some of these challenges come of age, we expect that imaging the "little brain" will continue to provide fresh and important insights to cerebellar function for years to come.

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