The Rate of Visuomotor Adaptation Correlates with Cerebellar White-Matter Microstructure

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Abstract: Convergent experimental evidence points to the cerebellum as a key neural structure mediating adaptation to visual and proprioceptive perturbations. In a previous study, we have shown that activity in the anterior cerebellum varies with the rate of learning, with fast learners exhibiting more activity in this region than slow learners. Here, we investigated whether this variability in behavior may partly reflect inter-individual differences in the structural properties of cerebellar white-matter output tracts. For this purpose, we used diffusion-weighted magnetic resonance imaging to estimate fractional anisotropy (FA), and correlated the FA with the rate of adaptation to an optical rotation in 11 subjects. We found that FA in a region consistent with the superior cerebellar peduncle (SCP), containing fibers connecting the cerebellar cortex with motor and premotor cortex, was positively correlated with the rate of adaptation but not with the general level of performance or the initial deviation. The same pattern was observed in a region of the lateral posterior cerebellum. In contrast, FA in the angular gyrus of the posterior parietal cortex correlated positively both with the rate of adaptation and the overall level of performance. Our results show that the rate of learning a visuomotor task is associated with FA of cerebellar pathways. *Hum Brain Mapp 30:4048–4053, 2009.* © **2009 Wiley-Liss, Inc.**

Key words: cerebellum; visuomotor adaptation; motor learning; motor control; diffusion weighted imaging; fractional anisotropy

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INTRODUCTION

Our bodies change and so does our environment. The fact that we manage to perform accurate movements despite this variability is of major interest to the field of motor control. Convergent experimental evidence from human and nonhuman primates points to the cerebellum as a key structure in adapting to visual and proprioceptive perturbations of the environment. Extensive cerebellar damage compromises both the rate of adaptation and the magnitude of the after-effect [Martin et al., 1996; Maschke et al., 2004; Smith and Shadmehr, 2005; Weiner et al., 1983; Werner et al., 2009]. Neurophysiological evidence suggests

that during adaptation activity of climbing fibers, carrying information from the spinal cord, change the efficacy of parallel fibers, carrying information from the cerebellar cortex, at the Purkinje synapses [Gilbert and Thach, 1977]. These findings are consistent with the theory that the cerebellum is the site where motor memories are formed and maintained [Albus, 1971; Marr, 1969].

The rate of adaptation and the initial movement error vary across the population [e.g. Della-Maggiore et al., 2008; Lackner, 1994]. Neuroimaging studies show that functional activity in the cerebellum covaries with the rate of learning and/or motor error. For example, total motor output correlates positively with activity in the anterior cerebellum during recall of an internal model 5.5 h after achieving adaptation to a force field [Shadmehr and Brashers-Krug, 1997]. Motor error, measured as the maximal deviation of the arm when interacting with a force field, correlates positively with activity in the deep cerebellar nuclei during adaptation and negatively with activity in the anterior cerebellum 29 days later [Nezafat et al., 2001]. On the other hand, the rate of visuomotor adaptation when using a mouse with an optical rotation to track a visual target is associated with bilateral increments of activity around the posterior superior cerebellar fissure [Imamizu et al., 2000]. In summary, functional imaging studies have demonstrated that behavioral variation is associated with differences in activation patterns across the population.

The aim of the present study was to investigate whether inter-individual variability in visuomotor adaptation may partly reflect differences in the structural microstructure of cerebellar white-matter tracts. White-matter structure have previously been shown to predict performance in different tasks such as learning of foreign speech sounds [Golestani et al., 2007] and visual memory [Begre et al., 2007]. Microstructural properties of white matter, such as axon caliber and myelin thickness, influence functionally relevant properties of axonal transduction, such as conduction velocity [Gillespie and Stein, 1983], and may thereby influence behavior. Here, we used diffusion-weighted magnetic resonance imaging to characterize structural properties of white-matter tracts through fractional anisotropy (FA), a voxel-wise measure that is modulated by local factors such as myelin thickness, axon caliber, and packing density [Beaulieu, 2002]. Subjects performed a visuo-motor adaptation task and we tested for correlation between behavioral and FA measures. We hypothesized that higher adaptation rates would be associated with greater FA values in white-matter tracts within the cerebellum and/or those containing cerebellar projections to the motor regions of the cerebral cortex. Our previous work provides evidence that allows us to generate anatomically-specific hypotheses for where such correlations may be found for this specific task. Previously, we have shown that activity of a motor network including the anterior cerebellum, the contralateral sensorimotor cortex and the cingulate motor area correlates with the rate of learning during the same adaptation task used here, with fast learners showing more ac-

tivity in these areas than slow learners (Della-Maggiore and McIntosh, 2005). The results of the current study show that the rate of learning a visuomotor task, but not the overall level of performance or the initial motor error, is associated with greater FA of cerebellar pathways.

METHODS

Experimental Procedures

Twelve right-handed healthy participants (range 21–45 year, mean ± SD = 30 ± 8) were recruited for the experiment. Participants were screened to ensure none suffered from medical, neurological, or psychiatric disorders. During the experiment, participants used their right hand to track a target moving randomly on a screen with a joystick; a cursor represented the movement of the hand. After performing this task for 5 min, an optical perturbation evidenced by a rotation in the cursor direction relative to the hand was applied [for details see Della-Maggiore and McIntosh, 2005]. Subjects performed six 5-min blocks of the task with the perturbation and a final 5-min block without the perturbation to measure after-effects. The distance between target and cursor was sampled at 200 Hz and averaged for each block; it was used as measure of visuomotor error.

MRI Acquisition

Magnetic resonance brain images were acquired on a 1.5 Tesla Sonata scanner (Siemens, Erlangen, Germany) with a one-channel head coil; this dataset has also been used in a different study [Johansen-Berg et al., 2007]. Three sets of whole-brain diffusion-weighted images were acquired (60 directions, b-value 1,000 s mm^{-2}, 2.2 × 2.2 × 2.2 mm^3, 60 slices). In addition, six images without diffusion weighting were acquired (Bo). Images were eddy-current corrected and aligned to the first nondiffusion weighted image using the FSL toolbox (www.fmrib.ox.ac.uk/fsl).

Statistical Analysis

The FSL toolbox was used for statistical analysis. Tract-based spatial statistics was used to compute correlations between behavioral measures and FA [Smith et al., 2006]. Although our working hypothesis focused on the cerebellum, we decided to compute the correlations across the whole brain so that we could also identify other brain tracts that may contribute to inter-individual variability in adaptation. Briefly, FA maps were calculated for each individual using FDT and then aligned nonlinearly to FSL's FA template (generated form 58 FA maps) using FNIRT. The aligned images were averaged to generate a mean FA image. This mean FA image was "thinned" and thresholded at an FA value of 0.2 to generate a tract skeleton that included only the major white-matter pathways. Finally, for each subject the FA values of local tract centers were projected onto this invariant tract representation.
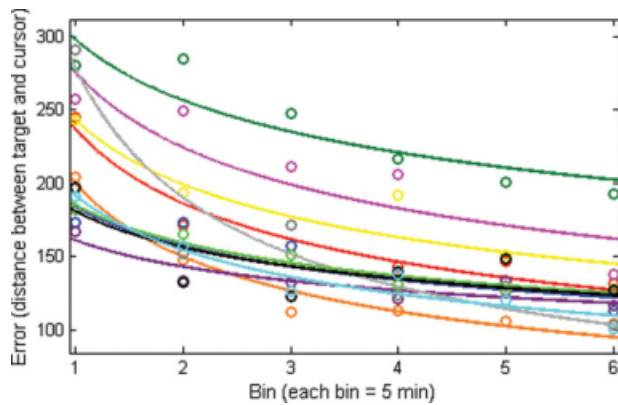
Figure 1.

Behavioral results. Shown is the visuomotor error, computed as the distance between target and cursor, corresponding to the average of 5-min blocks for all 11 subjects. Individual data was fit using a power function ($y = a * x\ ^\wedge b$). Each color represents a different subject.

Three behavioral measures were used to compute correlations with FA: the initial visuomotor error (IVE), the rate of visuomotor adaptation, and the level of performance. The rate of adaptation was quantified by fitting the time course of the visuomotor error (six data points in total) with a power function ($y = a * x\ ^\wedge b$), of which b was the learning rate. The initial visuomotor error was the average of the error obtained during the first adaptation block. The level of performance during adaptation was inferred from the standard error (SE) of the regression, assuming that higher standard errors would reflect lower levels of performance than lower standard errors [Keating and Thach, 1990]. We tested for correlation between IVE, the rate of visuomotor adaptation "b," the level of performance (SE) and FA in the whole brain after covarying for age, which has significant effects on FA [Pfefferbaum et al., 2000] and on the number of Purkinje cells after 40 years of age [Andersen et al., 2003]. We performed an exploratory, whole-brain analysis, for which we used a t threshold of 3.169 (10° of freedom; $P < 0.005$ uncorrected one-tail) and a cluster extent threshold greater than 15 voxels [Boorman et al., 2007] to define clusters of positive correlation.

RESULTS

Behavioral Results

One of the 12 participants was excluded from the analysis because the adaptation rate deviated more than three standard deviations from the sample mean.

Adaptation rate computed as the regression coefficient (b) and the IVE (first symbol) are shown for all subjects in Figure 1 ($n = 11$; $df = 5$; R^2 ranged from 0.78 to 0.95). Statistical significance for each regression coefficient was assessed for each subject using t tests (P values ranged between 0.02 and 0.001). All subjects adapted to the per-

turbation. After-effects, assessed by averaging the visuomotor error during the first minute of the last 5-min block, were also present in all subjects ($df = 10$; $t = 6.502$, $P < 0.0001$), a finding consistent with the modification or generation of an internal model for the perturbation [Shadmehr and Mussa-Ivaldi, 1994].

DWI Results

The TBSS analysis yielded four significant clusters in which FA correlated positively with the rate of adaptation (Fig. 2a). Two of these clusters were located in the
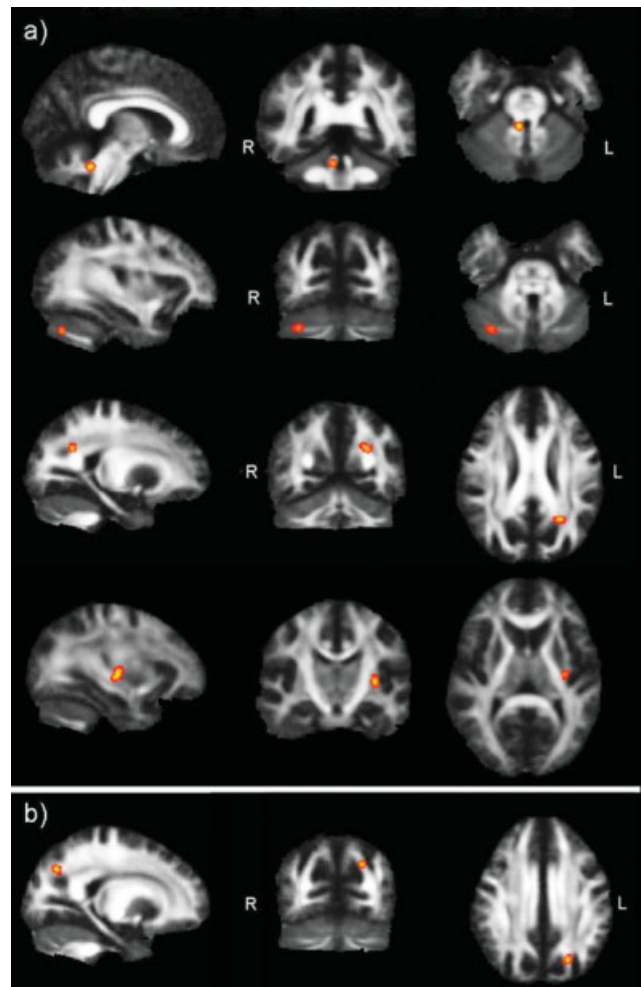

Figure 2.

Tract-based spatial statistics. (**a**) Clusters exhibiting a positive correlation between FA and the rate of visuomotor adaptation. Top panel shows the superior cerebellar peduncle cluster; second panel shows the cluster identified on the lateral cerebellum; third panel shows the cluster identified in the angular gyrus of the posterior parietal cortex and forth panel shows the cluster identified in the external capsule. (**b**) Clusters exhibiting a positive correlation between the overall level of performance and FA. Shown is the cluster identified in the angular gyurs, in the vicinity of that identified in (a).

ipsilateral (i.e. right) cerebellum; the first one in a region of the anterior cerebellar lobe consistent with the superior cerebellar peduncle ($r = 0.75$; 34 voxels; max $t = 6.81$; $x = 6$, $y = -48$, $z = -26$, $t > 3.169$, $P < 0.005$), and a second cluster, in the posterior cerebellar lobe, near the horizontal fissure (Crus I and Crus II; $r = 0.82$; 18 voxels; max $t = 3.85$; $x = 32$, $y = -71$, $z = -30$, $t > 3.169$, $P < 0.005$). The third cluster showing a positive correlation between FA and the rate of adaptation was located in the left inferior parietal lobule, in a region consistent with the angular gyrus ($r = 0.92$; 20 voxels, max $t = 6.38$, $x = -21$, $y = -56$, $z = 28$, $t > 3.169$, $P < 0.005$). Finally, a fourth cluster was identified in the left external capsule ($r = 0.9$; 28 voxels, max $t = 4.94$, $x = -31$, $y = -20$, $z = 1$, $t > 3.169$, $P < 0.005$).

As for the correlation between FA and the level of performance, only a region in the vicinity of the left parietal cluster (26 voxels, max $t = 5.46$, $x = -18$, $y = -60$, $z = 37$, $t > 3.169$, $P < 0.005$) exhibited a positive correlation between FA and the level of performance measured as the SE of the regression (Fig. 2b), suggesting that FA values in this area of the angular gyrus are not specific to the rate of learning but also contribute to the ability to perform the task. Fractional anisotropy in the cerebellum did not correlate with the SE of the regression or the IVE at the defined statistical threshold.

DISCUSSION

In this study, we explored the possibility that inter-individual differences in cerebellar structure may in part explain inter-individual variability in visuomotor adaptation. We found evidence in favor of this hypothesis. Fast learners showed higher values of fractional anisotropy than slow learners in the posterior cerebellum and in the superior cerebellar peduncle. By contrast, correlation between FA and the level of performance yielded no significant clusters in the cerebellum, indicating that anatomical variations in these areas relate to the rate of learning rather than an overall ability to perform the task. Factors that influence FA include myelination of axons, axonal diameter, or packing density of axons [Beaulieu, 2002] and any of these structural features could influence speed or efficiency of neural signals propagation, thereby influencing behavior. Our results show that the speed of visuomotor adaptation may be determined partly by cerebellar anatomy.

Neurophysiological studies point to the cortex as the site of motor-memory storage in the cerebellum [Gilbert and Thach, 1977; Keating and Thach, 1990]. Our results identified a cluster in the posterior cerebellum, near the horizontal fissure (between Crus I and Crus II: HVIIA). Two different hand-representations have been described in the cerebellum using fMRI [Grodd et al., 2001]. The larger is located in the anterior cerebellum (Lobules IV, V). The second smaller representation is located in the posterior cerebellum (HVIII), and is nearby the posterior cluster identified with TBSS. Given its anatomical location in the

lateral cerebellum, this cluster may be part of a pathway connecting the cerebellar cortex with the dentate nucleus. The second cluster is located in the superior cerebellar peduncle. The SCP contains the main efferent connections to the thalamus. Most fibers passing through the SCP originate in the dentate nucleus, continue rostrally to the brain stem and decussate at the level of the inferior colliculus [Dum and Strick, 2003]. In addition, some of the fibers that pass through the SCP originate in the interposed nucleus. The majority of SCP fibers connect the cerebellum with motor and premotor areas of the cerebral cortex via the thalamus [Rouiller et al., 1994].

Although abundant experimental evidence points to a critical role of the cerebellum in adaptation, the site of adaptation in the cerebellar cortex is controversial. Neuroimaging studies looking for functional correlates of the rate of adaptation to proprioceptive perturbations have shown increased activity in regions corresponding to the anterior cerebellum and/or the dentate nucleus [Nezafat et al., 2001; Shadmehr and Holcomb, 1997]. On the other hand, adaptation to visual perturbations has been associated with activation of the anterior cerebellum [Della-Maggiore and McIntosh, 2005], bilateral activation of the area around the posterior cerebellar fissure [Imamizu et al., 2000], and the posterior cerebellum [Krakauer et al., 2004]. Given that only the most anterior part of the cerebellum was imaged in our previous functional study [Della-Maggiore and McIntosh, 2005], we cannot rule out the possibility that more posterior cerebellar areas may also take part in adaptation. The location of the posterior cluster identified here is more consistent with the results from the visuomotor functional studies by Imamizu et al. and Krakauer et al. although ipsilateral to the active hand.

The lesion literature is also controversial; small cerebellar lesions tend to yield no deficit whereas lesions or brain damage over large cortical areas tend to impair adaptation dramatically [Thach et al., 1992]. A few studies carried out in nonhuman primates suggest that the lateral cerebellar cortex, which projects to the dentate nucleus, is critical for adaptation. Inactivation of the somatosensory representation of this area (Lobules III, IV, and V and lateral within Crus I) slows the rate of visuomotor adaptation but does not affect the level of performance [Keating and Thach, 1990, 1995]. Reduced learning rate has also been observed in a patient with stroke of the ipsilateral superior cerebellar artery when performing the same task [Keating and Thach, 1990]. Yet, a different study from the same laboratory has shown that the rate of adaptation to reversed prisms is impaired in patients with stroke of the posterior cerebellar artery, which supplies the posterior cerebellar cortex and the inferior cerebellar peduncle, but not in patients with stroke of the superior cerebellar artery, which supplies the SCP, the dentate nucleus, and the anterior cerebellar cortex. Recent findings by Rabe et al. [2009] indicate that the topography of the lesion may affect differently force-field and visuomotor adaptation. Cerebellar atrophy affecting more significantly the anterior

cerebellum interferes with adaptation to a proprioceptive perturbation but not as much with adaptation to a visual perturbation. The opposite pattern is observed for lesions affecting more significantly the posterior cerebellum. The posterior cerebellar cluster identified in our study is consistent with the results from the last two patient studies [Martin et al., 1996; Rabe et al., 2009] whereas the SCP cluster is inconsistent with the findings from Martin et al. but is in agreement with those from Keating and Thach [1990]. Differences in the motor demands associated with each task (optical rotation when moving a cursor likely requires less coordinated control than adapting while throwing a ball with the arm) may account for the differences in functional topography.

What aspects of cerebellar processing could relate to the structural properties of these cerebellar clusters? The neural mechanism through which the cerebellum mediates adaptation remains unknown. It has been postulated that information about the motor plan conveyed by mossy fibers is contrasted with sensory feedback information conveyed by climbing fibers [Gilbert and Thach, 1977; Watanabe, 1984]. This error could be used to update the forward model so that predictions of the sensory consequences of movement based on an efferent copy of the motor command are accurate (forward learning, [Martin et al., 1996; Mazzoni and Krakauer, 2006; Miall et al., 2007; Tseng et al., 2007], or could be transformed into motor corrections that act as teaching signals for the brain (feedback learning [Kawato, 1996; Thoroughman and Shadmehr, 1999]). As mentioned previously, most efferent fibers passing through the SCP originate in the dentate nucleus. On the other hand, the posterior cerebellar cluster identified in this study is located in the lateral cerebellum, which in turn projects to the dentate nucleus. Higher FA may reflect, among other things, higher thickness of the myelin sheath [Beaulieu, 2002], which can influence conduction velocity [Gillespie and Stein, 1983]. Given that the dentate nucleus appears to be involved early in movement production, we can speculate that faster transduction of nervous signals might be beneficial to forward learning by increasing the likelihood of synaptic plasticity. For example faster conduction of cerebral signals to lateral cerebellar cortex could contribute to more effective synaptic plasticity at the parallel fiber-Purkinje synapse. This would lead to a progressive reduction in error and may explain the contribution of the posterior cluster. Likewise for the SCP, faster conduction speed of output signals from the cerebellum may be essential for synaptic plasticity at the level of the motor cortex, which may also contribute to faster learning. Further examination using a longitudinal design may help elucidate the role of these cerebellar regions in adaptation.

ACKNOWLEDGMENTS

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