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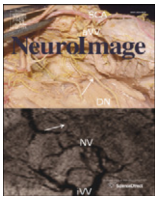

Manual dexterity correlating with right lobule VI volume in right-handed 14-year-olds

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ABSTRACT

Background: Dexterity is a fundamental skill in our everyday life. Particularly, the fine-tuning of reaching for objects is of high relevance and crucially coordinated by the cerebellum. Although neuronal cerebellar structures mediate dexterity, classical whole brain voxel-based morphometry (VBM) has not identified structural correlates of dexterity in the cerebellum.
Methods: Clusters of gray matter (GM) volume associated with the Purdue Pegboard Dexterity Test, a test of fine motor skills and complex upper limb movements, were identified in a cerebellum-optimized VBM analysis using the Spatially Unbiased Infratentorial (SUIT) toolbox in 65 healthy, right-handed 14-year-olds. For comparison, classical whole brain VBM was performed.
Results: The cerebellum-optimized VBM indicated a significant positive correlation between manual dexterity and GM volume in the right cerebellum Lobule VI, corrected for multiple comparisons and non-stationary smoothness. The classical whole brain VBM revealed positive associations (uncorrected) between dexterity performance and GM volume in the left SMA (BA 6), right fusiform gyrus (BA 20) and left cuneus (BA 18), but not cerebellar structures.

Abbreviations: BA, Brodman area; CT, Cortical thickness; FDR, false discovery rate; fMRI, Functional magnetic resonance imaging; GM, Gray matter; rCBF, regional cerebral blood flow; ROI, region of interest; SMA, supplementary motor area; SUIT, Spatially Unbiased Infratentorial (SUIT) toolbox; VBM, Voxel based morphometry.

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Conclusions: The results indicate that cerebellar GM volumes in the right Lobule VI predict manual dexterity in healthy untrained humans when cerebellum-optimized VBM is employed. Although conventional VBM identified brain motor network areas it failed to detect cerebellar structures. Thus, previous studies might have underestimated the importance of cerebellum in manual dexterity.

Introduction

Manual dexterity is a complex primate attribute with reaching and grasping for objects being one of the most frequent daily actions. Human manual skills constitute the fundament of tool use and cultural development whilst its disturbances can cause severe impairment in daily life. In order to execute goal-directed movements, the brain must specify the position of the target in an egocentric frame of reference by integrating external signals (e.g. visual and auditory stimuli) with intrinsic signals (proprioceptive, vestibular, motor) related to body, arm, head and eye position. Dexterity depends on a continuous flow of information from the cerebral cortex to the spinal cord and provides a precise, dynamic representation of the external world. Previous electrophysiological investigations in nonhuman primates as well as functional neuroimaging studies in humans have defined a broad range of cortical areas being active during goal-directed grasping. In particular, several frontal cortical motor areas involved in hand control were identified in nonhuman primates (He et al., 1993; Hepp-Reymond et al., 1994; Muakkassa and Strick, 1979). Cerebellar involvement in prehensile movements has been shown by Smith et al. (1993) in their neurophysiological work. Furthermore, functional imaging reach-to-grasp studies have reported cerebellar activation (Begliomini et al., 2007; Chapman et al., 2002; Grafton et al., 1996a,b; Rizzolatti et al., 1988, 1996). Additionally, Miall and Christensen (2004) has shown increased movement times in pegboard task induced by repetitive transcranial magnetic stimulation over the right cerebellum. In general, the involvement of the cerebellum in sensorimotor control, balance and motor speech is well investigated, yet primarily based on observation of deficits resulting from cerebellar lesions (Flourens, 1824; Holmes, 1939; Luciani, 1891). In particular, several abnormalities of all components of prehensile movements, such as increased path curvatures, corrective movements, variable wrist velocity profiles and a general lower velocity of movement execution were observed in cerebellar patients (Bastian and Thach, 1995; Haggard et al., 1994; Timmann et al., 1999, 2001; Zackowski et al., 2002). A number of previous studies on object manipulation have reported, that patients with cerebellar degeneration exhibit higher grip forces compared to controls (Babin-Ratte et al., 1999; Rost et al., 2005; Serrien and Wiesendanger, 1999).

However, up to now no systematic structural brain imaging investigation (e.g. voxel-based morphometry (VBM)) in healthy untrained subjects has focused on cerebellar gray matter correlates underlying the complex performance of manual dexterity.

We chose the performance score of the pegboard dexterity test assessing the coordination of goal-directed precise movements, a measure associated with a well replicated relationship between behavioral performance and cerebellar function (Haggard et al., 1994; Johnson-Greene et al., 1997; Maltz and Goldberg, 1982). This test involves unilateral and bilateral hand movements guided and coordinated by visual stimuli under time pressure. We predicted that pegboard task performance involves brain regions associated with complex grasping and reaching movements rather than regions required for simpler tasks such as finger tapping (Desmond et al., 1997). Both cortical and subcortical regions have been found to be involved in completing similar tasks in functional neuroimaging (Begliomini et al., 2007; Chapman et al., 2002; Grafton et al., 1996a,b; Rizzolatti et al., 1996; Shibasaki et al., 1993). In those experiments increased activation of primary sensorimotor cortex, premotor cortices as well as of the caudal part of supplementary motor area (SMA) , the right posterior cerebellum and occipital visual cortices was observed. In particular, Desmond et al. (1997) have reported cerebellar activation in lobule IV, V and VI during finger taping in functional magnetic resonance imaging (fMRI). In line with those functional findings, we expected corresponding structural gray matter correlates in these lobules in our study. VBM studies have reported distinct structural correlates in the cerebellum only in highly trained typists (Cannonieri et al., 2007) and musicians (Gaser, 2003), but not golfers (Jäncke et al., 2009). Draganski et al. (2004) have reported no GM changes induced by juggling training in the cerebellum in their VBM studies. To the knowledge of the authors, no previous study has demonstrated an association between manual dexterity and cerebellar morphometry in samples not restricted to specific as well as highly trained participants in a large sample.

The specific anatomy of the cerebellum including thinner striations of gray and white matter as well as less obvious demarcations compared to cortical structures pose a particular methodological challenge to ordinary whole brain VBM. Thus, in order to provide an optimized analysis of structural correlates in the cerebellum we applied an optimized normalization by using the Spatially Unbiased Infratentorial (SUIT) toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm, Diedrichsen, 2006).

Material and methods

Participants

Sixty five 14-year-olds (*M* 14.4 years; *SD* 0.32 years; 44 females) volunteered for this study within the scope of the IMAGEN project (Schumann et al., 2010). Written informed consent was obtained from all participants as well as from their legal guardians. The adolescents were recruited from secondary schools in Berlin, Germany. The assessment was approved by the assigned ethics committee. Participants with a medical condition such as a tumor, neurological disorders such as epilepsy or mental-health problems like affective disorders were excluded. All participating students were screened by means of both a self rating and two external ratings (parents; psychiatrists specialized in pediatrics) as part of a scale tailored to adolescents and based on ICD-10 as well as DSM-IV (The Development and Well-Being Assessment Interview; Goodman et al., 2000). All participants included were right-handed.

Manual dexterity measure

As part of the behavioral assessment within the IMAGEN study the participants were asked to perform the Purdue Pegboard Dexterity Test to assess hand dexterity as well as fine motor skills and complex upper limb movements (Gardner and Broman, 1979). After explanation as well as demonstration of the task and some practice trials prior to all three conditions, participants were asked to place as many pins into the holes of the perforated board as possible within 30 s of each trial. Three trials per condition were administered, starting with the dominant (right) hand, subsequently using the non-dominant hand and finally using both hands simultaneously. By averaging the number of pins placed correctly over the trials per condition, three scores were computed with higher values signifying more dexterity.

Scanning procedure

Structural MRI was performed on a General Electric SIGNA EXCITE 3 T scanner (Milwaukee WI, USA) with a standard 8 channel head coil. High-resolution anatomical magnetic resonance images were obtained using a 3D T1-weighted gradient-echo sequence based on the ADNI protocol (Jack et al., 2008) (sequence version = adni14m4; www.adni-info.org), modified to give isotropic voxels with sagital slice plane (repetition time = 7.16 ms; echo time = 3.02 ms; flip angle = 8°; 256 × 256 × 166 matrix, 1.1 × 1.1 × 1.1 mm voxel size).

Image and data analysis

Firstly, we created study-specific templates to compensate scanner specific contrast differences and non-uniformities as well as demographic differences of our adolescent population from those used to build the standard Montreal Neurological Institute (MNI) templates to optimize the VBM procedure.

Whole brain VBM

A whole brain VBM analysis was computed with gray matter (GM) maps based on the VBM procedure. This procedure spatially normalizes GM-segmented images to a standard space by matching images to their GM template (Good et al., 2001). For the whole-brain VBM we used a commonly applied smoothing kernel of 8 mm full-width at half maximum (FWHM) and a lenient threshold of $p<0.001$ uncorrected. The results were corrected for non-stationary smoothness (Hayasaka et al., 2004) with the VBM8 Toolbox by Gaser (http://dbm.neuro.uni-jena.de/vbm/).

Cerebellum VBM

Using the Isolate function within the Spatially Unbiased Infratentorial (SUIT) toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm, Diedrichsen, 2006) we ensured that infratentorial structures, namely cerebellum and brainstem, were isolated from the surrounding tissue. This preliminary segmentation obtained by a first iteration served as a weight map for an affine alignment to the new infra-tentorial template, such that only the tissue that has been identified as being part of the cerebellum or brainstem influenced the alignment. Then, during a second iteration, a new prior defined in the SUIT template space was used. The segmented GM images were then normalized to the SUIT template. A modulation of the segmented GM probability map was undertaken to compensate for volume changes during the spatial normalization by multiplying the intensity value in each voxel with the Jacobian determinants. Finally, all resulting GM probability images were smoothed with a 4-mm FWHM smoothing kernel in SPM5 to satisfy the Gaussian distribution assumption for statistical analysis to test regional differences. The use of the small 4 mm smoothing kernel is in line with previous publications that focussed on cerebellum VBM by means of the SUIT toolbox (D'Agata et al., 2011; Fan et al., 2010). All images were visually inspected to ensure that the pre-processing steps were successful and that the quality of each image was acceptable for subsequent analysis. Anatomical localizations (i.e. cerebellar lobules) were determined by the probabilistic MRI atlas of the human cerebellum developed by Diedrichsen et al. (2009). Cluster criteria were a voxel threshold of $p<0.001$. Those results were corrected for the non-stationary smoothness with the VBM8 Toolbox by Gaser (http://dbm.neuro.uni-jena.de/vbm/non-stationary-cluster-extent-correction/).

Standardized regression coefficients and t values are reported for the maximum voxel within the resulting brain region.

Results

Descriptive data on dexterity measurements results

Participants placed on average 15.7 (SD = 1.8) pins with their right hand, 14.4 (SD = 1.5) with their left hand and 12.2 (SD = 1.5) with both hands. As expected based on the self-reported right-handedness participants performed significantly better using their dominant right hand ($t(64) = 6.86$, $p<0.001$) (Fig. 1).

Cerebellar morphometry — correlation between GM thickness and manual dexterity

In the cerebellar VBM we found a positive correlation between pegboard performance and GM volume in right cerebellum Lobule VI (−30, −50, −33, cluster size 373 voxels). This result survived correction for non-stationary smoothness in VBM8 toolbox.

Pegboard performance of the non-dominant left hand also correlated positively with GM volume in right cerebellum Lobule VI extending into Crus I (36, −52, −35, cluster size 115 voxels). This result did not survive the correction for non-stationary smoothness in VBM8 toolbox. The clusters found for right-hand and left-hand performance are displayed in Fig. 2. The bilateral pegboard performance revealed no significant structural correlate in the cerebellum.

Whole brain morphometry — correlation between GM thickness and manual dexterity

In the whole brain VBM analysis with 8 mm smoothing kernels we found that pegboard performance with the dominant right hand was positively correlated with GM volume in the left SMA (BA 6) (0, 0, 56, cluster size 98 voxels), right fusiform gyrus (BA 20) (52, −28, 30, cluster size 129 voxels) and left cuneus (BA 18) (0, −80, −4, cluster size 118 voxels). All results are uncorrected and did not survive the correction for non-stationary smoothness (Fig. 3). There was no significant cerebral GM correlation with pegboard performance of the non-dominant left hand. The bilateral pegboard performance correlated positively with GM volume in the right fusiform gyrus (54, −32, −28, cluster size 72 voxels). The whole brain VBM analysis with both smoothing kernels 4 mm and 8 mm revealed no significant structural correlates for the cerebellum.

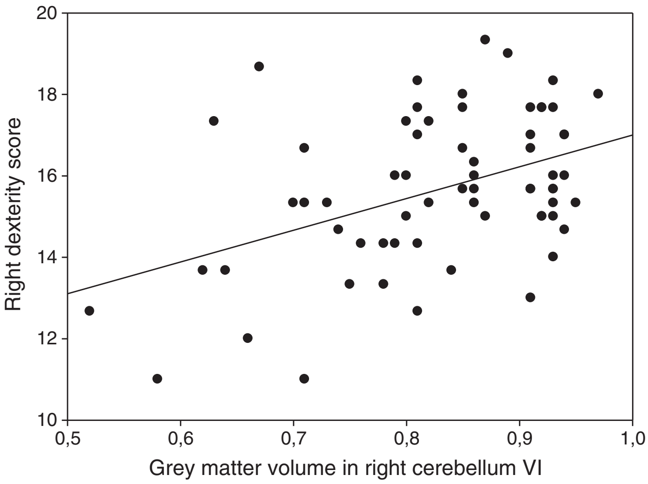

Fig. 1. Positive correlation between cerebellar gray matter volume and right hand pegboard performance ($r(65) = .430$, $p<0.001$).

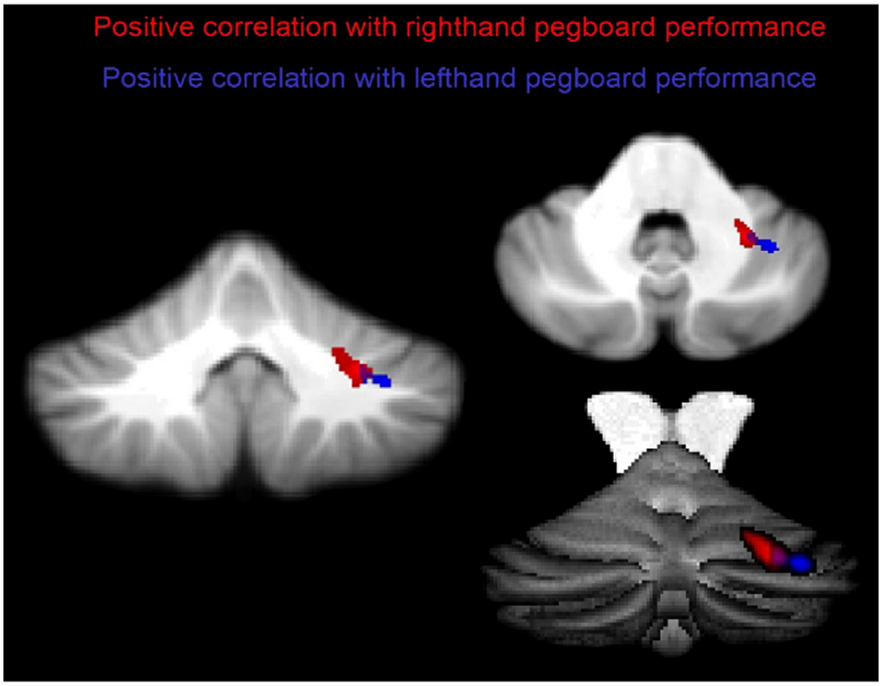

Fig. 2. Positive correlation between cerebellar gray matter volume and right (red) non-stationary smoothness corrected and left (blue) hand pegboard performance (N = 65).

Discussion

A whole brain VBM analysis was performed and a VBM analysis focussing on the cerebellum using the SUIT toolbox (Diedrichsen, 2006) in order to identify morphological correlates of the dexterity test performance in the brain with special focus on the cerebellum.

In the whole brain VBM we found positive GM volume correlations with pegboard scores for SMA, fusiform gyrus and cuneus. Although this result did not survive correction for non-stationary smoothness, we decided to discuss this association against the background of consistent previous findings on motor skills required to perform the pegboard task. Those skills comprise highly precise, spatially and temporarily well coordinated and visually controlled hand movements. Further, they involve grasping with according hand shaping and prior object recognition (Jeannerod, 1984). The latter aspect might suggest an association with the fusiform gyrus as found in our study. The role of SMA in precise movements has been shown in a number of studies (Binkofski et al., 1999; Ehrsson et al., 2002; Rijntjes et al., 1999a,b; Roland and Zilles, 1996; Roland et al., 1980; Sadato et al., 1996). In particular, Fox et al. (1985a,b) using positron emission tomography (PET) have reported an association between finger movements and regional cerebral blood flow (rCBF) changes within the sensorimotor hand areas, the supplementary motor area and the cerebellum. According to Damasio and Van Hoesen (1980) the right SMA is concerned with activation of the motor output and the left SMA is less involved with motor activation but is more concerned with sequencing of primary motor routines. The SMA and the posterior parietal cortex might be interconnected with the cerebellar hemisphere (lobule VI; Schmahmann and Pandya, 1995). Additional support for this interconnection has been described by Ehrsson et al. (2002) reporting the involvement of SMA and the lateral cerebellum in the control of nonsynergistic skilful movement of the digits, whereby lobule VI of cerebellum was found to be active. Congruent with this notion, lobule VI has been shown to play a central role in movement preparation (Hulsmann et al., 2003). These findings suggest a functional interconnection between the cerebellar lobule IV and SMA, which might be reflected in our results. In line with the assumption, that the posterior cerebellum

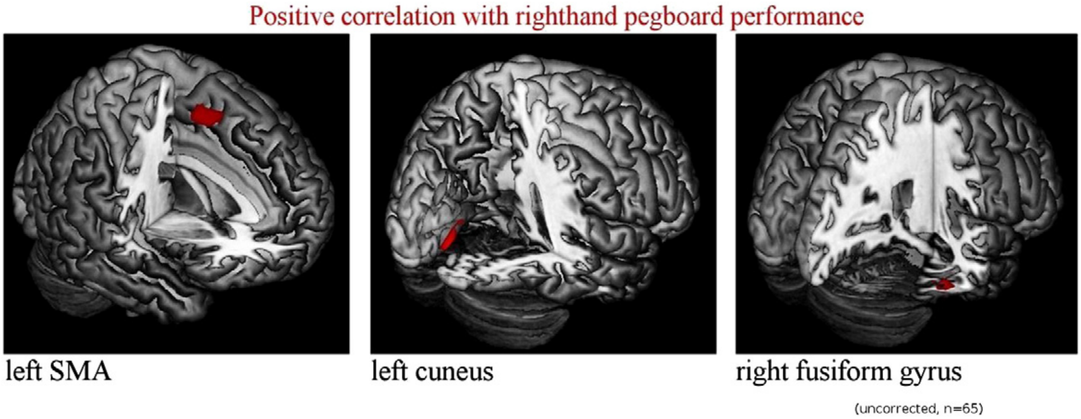

Fig. 3. Positive correlation between cerebral gray matter volume and right hand pegboard performance. Whole brain analysis covaried for total gray matter, age and gender; ($p<.005$ Monte Carlo Simulation corrected; N = 65).

may also be involved in the inhibition of movement execution during imagination, differential activation in the cerebellum was found by Lotze et al. (1999) as well as Lacourse et al. (2005) during executed and imagined movements in accordance. Finally, our results are in line with those of Diedrichsen et al. (2009), who reported bilateral activation in lobule VI using fMRI experiments with a robotic manipulandum and arm reaching movements. Using fMRI Rijntjes et al. (1999a,b) have confirmed the existence of somatotopy in the human posterior cerebellar lobe and found separate peaks of activation for finger and toe movement in three ipsilateral cerebellar regions. In accordance with the results of previous studies showing impairments in the coordination of skilful finger, hand and arm movements in human subjects as well as in monkeys with damage to the posterior and lateral cerebellum (Dow, 1938; Holmes, 1939; Muller and Dichgans, 1994; Thach et al., 1992), we found correlates exclusively in the posterior lobe of the cerebellum. No associations in the phylogenetically older anterior lobe, usually active during simple movement control, were identified in our study. The GM volume correlates found in our study are in line with previous findings and emphasize the role of the posterior lobe of the cerebellum in controlling the performance in complex motor tasks.

Neither in our whole brain VBM analysis, nor in any previous study using classical VBM any cerebellar GM clusters correlated with dexterity in untrained subjects have been identified. This could suggest that whole brain VBM may not be sufficiently sensitive for detecting small local cerebral structural differences. Although the cortical areas detected by means of whole brain VBM are involved in control of the grasping, the results did not survive the correction for non-stationary smoothness. Our whole-brain data with negative findings in the cerebellum for both smoothing kernel sizes (4 and 8 mm) show that this negative results cannot be explained by the differences in the smoothing kernel alone. This emphasizes the need for specialized procedures to investigate the cerebellum due to its specific anatomy (Diedrichsen, 2006; Diedrichsen et al., 2010). The cerebellum consists of a number of clearly defined lobules and sublobules. Yet, these structures show substantial interindividual variance of their shape. Hence, superimposing individual cerebella in group space is difficult. For instance, in standard spatial normalization procedures the location of the primary fissure (boundary between V and VI) spreads over 1–2 cm. Applying the SUIT toolbox improves the overlap of individual lobules by nearly 8% over both FSL and unified segmentation in SPM (Diedrichsen et al., 2009).

The somatotopy of activation within the cerebellum has previously been explored by means of electrophysiological and neuroimaging methods in animals (Adrian, 1943; Snider and Stowell, 1944; Welker et al., 1988) and fMRI or PET in humans (Allen et al., 1997; Catalan et al., 1998; Desmond et al., 1997; Fox et al., 1985a; Hanakawa et al., 2003; Lutz et al., 2000; Riecker et al., 2003). However, studies on structural correlates of motor skills in cerebellum are rare. For instance, Good et al. (2001) have detected focal handedness dependent asymmetry in medial cerebellum and lateral cerebellum. In a study comparing musicians (Gaser and Schlaug, 2003) vs. control subjects small localized differences (in Lobe V and IV) have been found in a whole brain VBM analysis. Further, Park et al. (2010) have reported an enlargement of declive, folium and tuber in a region of interest (ROI) analysis of the absolute volume of the vermian lobules in basketball players. Draganski et al. (2004) and Driemeyer et al. (2008) have not reported any anatomical changes in the cerebellum in their VBM studies of GM changes induced by juggling. In contrast, Cannonieri et al. (2007) have shown a positive correlation between the duration of typing practice and GM volume in the SMA, the prefrontal cortex and the cerebellum (lobule VIII). Yet, so far none of the studies has demonstrated an association between the superior dexterity of certain body parts and morphological changes in the cerebellum in untrained subjects. Unlike the work discussed above, the present study was not restricted to a specific sample of highly trained participants. To our knowledge, this is the first VBM study indicating distinct cerebellar correlates of manual dexterity in healthy adolescents.

Clinical relevance, translational implications and conclusions

A volumetric study in pre-term infants has shown a direct association between cerebellar tissue damage and development of the contralateral cerebral volumes (Limperopoulos et al., 2005). That finding supports the idea that cortical and cerebellar GM volume may be interdependent. Those results have further been supported by a study by Allin et al. (2001) reporting significantly reduced cerebellar volume in pre-term-born subjects compared to term-born controls. The cerebellar and cerebral structures identified in our study seem to play a crucial role in children with developmental coordination disorder (Zwicker et al., 2010). In those minors, compared to healthy children, decreased blood-oxygen-level-dependent signal has been shown in a network of brain regions associated with skilled motor practice: bilateral inferior parietal lobules (BA 40), right lingual gyrus (BA 18), right middle frontal gyrus (BA 9), left fusiform gyrus, right cerebellar Crus I, left cerebellar lobule VI and left cerebellar lobule IX. Moreover, Pangelinan et al. (2011) have reported relationships between general cognitive ability (IQ) and the volume of subcortical brain structures (cerebellum and caudate) as well as spatial working memory and the putamen in their ROI VBM study in children of 6 to 13 years of age. Interestingly, on the behavioral level, general cognitive ability has also been found to be related to visuomotor ability (pegboard) and executive function (spatial working memory). These results support the notion that motor skills and cognition may be fundamentally interrelated at both levels of behavior and brain structure.

The recent volumetric study by Balsters et al. (2010), comparing the volumes of cerebellar lobules in structural MRI scans in capuchins, chimpanzees and humans has demonstrated some evidence suggesting that functionally related structures in the cortico-cerebellar system evolve in concert with each other. The evolutionary expansion of these prefrontal-projecting cerebellar territories might contribute to the development of higher cognitive functions in humans.

Limitations

The focus on 14-year-old subjects in the current study may have an impact on the generalisability of the results. For instance, Tiemeier et al. (2010) have reported in his VBM study on cerebellum development a cerebellum volume peak at age 11.8 years for females and 15.5 years for males. This could mean that the male subjects in our sample have not achieved their maximal cerebellar volumes yet. Furthermore, brain imaging studies have shown that skill acquisition is accompanied by neuroplastic changes associated with a shift in cortical–subcortical interaction (Debaere et al., 2004; Doyon et al., 2003; Jueptner et al., 1997; van Mier et al., 1998), which may be a confound of the present results. However the precise nature of these shifts in neural activation is assumed to have several reasons and depends on the type of tasks studied, the amount of practice provided, etc. In our study we cannot differentiate between the capability to learn quickly new skillfull movements and individual ability to perform precise and complex tasks without prior training, yet in our setting short term learning effects are improbable. It has to be stated that the role of cerebellum in the manual dexterity has a complex and heterogeneous nature and involves coordination and timing of movements as well as learning processes.

In order to avoid confounding effects of handedness, we chose a homogenous sample of right-handed subjects. Another aspect not addressed in our study is the impact of handedness on the reported cerebellar correlates of manual dexterity. In contrast to cerebellum the cortical anatomical correlates of handedness in primary motor cortex are well established (see Hammond, 2002 for a review). Recently Begliomini et al. (2007) have shown distinct cerebellar activation patterns in anterior intraparietal sulcus area (AIP) and right lobule 6 of the cerebellum depending on handedness in reaching and grasping movements, whereby the activation in right lobule 6 mirrored that found for AIP. Further studies on left handed subject should follow. As described in the Results section, clusters identified in the whole brain VBM part of the study failed to survive the correction for non-stationary smoothness. This may reflect a weakness of whole brain VBM in detecting such subtle morphological differences in the present healthy sample. Larger sample size will be needed. The lack of finding in basal ganglia (striatum) that play an important role in the motor system may speak for those limitations.

Conclusion

To our knowledge, the present study is the first in a large sample of healthy 14-year-old adolescents using a cerebellum optimized VBM procedure that shows cerebellar correlates of human manual dexterity in untrained subjects. The results correspond with previous findings on cortical and subcortical structures involved in completing complex manual tasks. The use of cerebellum optimized VBM (SUIT) revealed substantial results, which have not been detected by classical VBM procedures. Furthermore, those VBM results did not survive the correction for non-stationary smoothness. The data strongly suggests that future research on morphological correlates of higher cognitive functions might benefit from considering both cortical as well as cerebellar structures.

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