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Volumetric variation in subregions of the cerebellum correlates with working memory performance

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ABSTRACT

We aimed to investigate the relationship between structural variations in the cerebellum and individual differences in working memory performance as assessed by average reaction time (RT) and correction rate (CR) on a 3-back task. High-resolution T1-weighted magnetic resonance images were acquired in 311 healthy young adults. Voxel-based morphometry (VBM) was used to identify cerebellar areas with volumes correlated to working memory performance when controlling for age, gender, years of education and handedness. We found that RT was positively correlated with the grey matter volume (GMV) bilaterally in cerebellar lobules IV/V, VI and VIII, in vermis VII/VIII and in left Crus I; CR was positively correlated with the GMV in the left lobule VI and Crus I. These findings suggest that RT on a working memory task is related to structural variation in both motor and cognitive subregions of the cerebellum, while CR is mainly associated with the cognitive subregions. Our findings provide further evidence that the cerebellum contributes to working memory function.

1. Introduction

Recent studies on the cerebellum have shown that cerebellar function is more complex and diverse than traditionally thought. The conventional view held that the cerebellum is a structure specialized for motor processing [8,17,49]. Motor tasks, especially those involving hand motion, consistently activate cerebellar lobules IV and V, and occasionally lobules VI, VII and VIII [15,23,25,32]. However, converging evidence over the last two decades has also shown the cerebellum to be involved in non-motor functions including cognition, emotion and language [35,37,38,41,45,50].

Working memory, as conceptualized by Baddeley [6,7], is a key area of study in cognitive neuroscience. It is considered to be a short-term memory system with a limited capacity, and it can hold and manipulate information for several seconds in the context of cognitive activity. Previous studies have revealed that patients with cerebellar lesions or disorders show functional deficiencies in working memory [14,30,33]. Neuroimaging studies conducted using positron emission tomography (PET), diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) have implicated the cerebellum in the function of working memory [3,32,46] and have emphasized the contribution of the cerebellar lobules VI–VIII [11,19,44]. This process is mediated by the prefrontal-pontine-cerebellar-thalamic-prefrontal circuit. However, it remains unknown whether structural variations in the cerebellum are correlated with working memory performance.

Many previous studies have revealed that individual differences in working memory capacity are related to structural variations in the brain such as the grey matter volume (GMV) in healthy young adults [48], older individuals [26], subjects receiving working memory training [47], and patients with a variety of disorders [24,40,51]. These findings suggest that working memory capacity in an individual is a reflection of structural variation, which can be determined by either genetic factors or environmental influences such as cognitive training or neurological disorders.

Because the cerebellum is related to both motor coordination [13,31,28] and cognitive function [2,38], we hypothesize that structural volumetric variations in the cerebellum may be correlated with individual performance on a 3-back working memory task as assessed by average reaction time (RT) and correction rate (CR). The CR is generally a reflection of the capacity to recall and manipulate information within working memory, while RT reflects both working memory capacity and motor coordination because it is influenced by the speed of the button press. Therefore, we hypothesize that CR will correlate with GMV in cerebellar regions involved in working memory, while RT will correlate with GMV in cerebellar regions involved in both working memory and motor function.

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2. Materials and methods

A total of 311 right-handed healthy subjects (152 males, 159 females; mean age = 22.6 ± 2.5 years, range 18–31 years) were included in this study (Table 1). Handedness was evaluated using a Chinese questionnaire modified according to the Edinburgh Handedness Inventory [27]. Hand preference was assessed for each subject during performing 10 items, including writing, holding chopsticks, throwing, brushing teeth, using scissors, striking a match, threading a needle, holding a hammer, holding a racket and face washing. When preference was fixed to one hand in all 10 items, the subject was regarded as having strong right- or left-handedness. If a subject preferred using one hand for the first 6 items and the other hand for the last 4 items, these actions indicated either right- or left-handedness. If a subject mixed using the right or left hand for the first 6 items, these actions indicated mixed-handedness. In this situation, preferred writing hand determined handedness tendency. Taken together, handedness was quantitatively scored as a number from 1 to 6, indicating strong right-, right-, mixed right-, mixed left-, left- and strong left-handedness, respectively.

Participants were screened for a history of psychiatric or neurological disorders and any health or safety contraindications prior to MRI scanning. Conventional structural MRI scans were performed in all subjects, with none revealing any visible brain lesions. All subjects signed an informed consent form approved by the local Medical Research Ethics Committee of Tianjin Medical University.

Individual working memory capacity was evaluated with the *n*-back task, which has been widely used in previous studies on working memory [9,29]. This task was presented to individual subjects on a computer in a quiet room outside the MRI scanner. During the task, subjects were instructed to press a button on the right with their middle finger if the letter that appeared on the screen was identical to the one observed either 2 or 3 letters earlier, and otherwise to press the button on the left with their index finger. Every *n*-back block (2-back or 3-back) lasted 60 s with a subsequent rest block of 20 s (R2-back or R3-back). The blocks were presented in a fixed order (2-back R2-back, 3-back R3-back, 2-back R2-back, 3-back R3-back, 2-back R2-back and 3-back R3-back). Each letter stimulus was presented for 200 ms with an inter-stimulus interval of 1800 ms. Thus, there was a time window on RT from 0 to 2000 ms. If a subject could not press the button within 2000 ms, no matter the answer was correct or not, it was recorded “No Response”, and the RT would not be recorded. Before the experiment, participants were verbally instructed and given 3 practice runs of the task. E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA) was used to present the stimuli and collect the mean RT and CR.

MR images were acquired on a Signa HDx 3.0 Tesla MR scanner (GE Medical Systems). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. A high-resolution T1-weighted brain volume (BRAVO) 3D MRI sequence with 176 contiguous sagittal slices was performed (repetition time = 8.1 ms; echo time = 3.1 ms; inversion time = 450 ms; field of view = 256 mm × 256 mm; slice thickness = 1.0 mm; no gap; flip angle = 13°; matrix = 256 × 256).

Table 1
Demographic and behavioral characteristics of 311 healthy subjects.

Characteristics	Mean ± SD	Range
Male/female	152/159	–
Age (years)	22.6 ± 2.5	18–31
Education time (years)	15.6 ± 2.1	9–23
Handedness score[a]	2.4 ± 0.8	1–3
Reaction time (ms)	738.1 ± 138.2	280–1120
Correction rate (%)	81.7 ± 6.5	54.4–95.6

[a] Handedness score ≤ 3 represents right-handedness.

VBM analysis was performed using Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The structural MR images were segmented into grey matter (GM), white matter and cerebrospinal fluid using the standard unified segmentation model in SPM8 [5]. Then, GM population templates were generated from the entire image dataset using the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) technique [4]. After an initial affine registration of the GM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/), non-linear warping of GM images was performed to the DARTEL GM template in MNI space with a 1.5 mm cubic resolution (as recommended for the DARTEL procedure). The GMV at each voxel was obtained through modulation, which was performed by multiplying the GM concentration map by the Jacobian determinants derived from the non-linear spatial normalization step. Finally, the GMV images were smoothed with a FWHM kernel of 8 mm. The analysis of modulated data tests for regional differences in absolute brain volume and removes the confounding effects of variation in individual brain size. After spatial pre-processing, the resulting smoothed, modulated and normalized GMV maps were used for statistical analysis.

Voxel-based partial correlation analyses were carried out to test relationships between GMV and both RT and CR on the working memory task. Age, gender, years of education and handedness score were entered as covariates of no interest. Correction for multiple comparisons was performed using Monte Carlo simulation. We employed a corrected threshold of $P < 0.05$ for each voxel and a cluster size > 333 voxels, which was determined by the AlphaSim program in AFNI software (parameters: single voxel $P = 0.01$, 5000 simulations, FWHM = 8 mm, cluster connection radius = 2.5 mm, with cerebellar grey matter mask, http://afni.nimh.nih.gov/). To avoid interference between the RT and CR measurements, additional correlation analyses were also performed by adding CR as a covariate of no interest when analyzing the correlation between GMV and RT, and vice versa. Only significant differences in the GMV within the cerebellum were investigated because the focus of the present study is the relationship between cerebellar GMV and working memory.

3. Results

The demographic and behavioral data are shown in Table 1. Behavioral results showed that the average RT on the 3-back task was 738.1 ± 138.2 ms (range, 280–1120 ms) and that the average CR was 81.7 ± 6.5% (range, 54.4–95.6%). We have tested the behavioral data using one sample Kolmogorov–Smirnov (K–S) Test provided by Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL, USA) software and found that the data satisfied the Gaussian distribution. Thus, we did not perform any data transformation before the correlation analyses.

The results of the correlation analyses are shown in Table 2 and Fig. 1. After controlling for the effects of age, gender, years of education and handedness score, we found that the RT was positively correlated with the GMV bilaterally in the bilateral cerebellar lobules IV/V, VI, VIII, vermis VII/VIII and left Crus I (Fig. 1A), while the CR was positively correlated with the GMV in the left cerebellar lobule VI and Crus I (Fig. 1B). When further controlling for the RT in the correlation analysis of the CR, or controlling for the CR in the correlation analysis of the RT, the same results were obtained. The results of the 2-back analyses (see Supplementary Material) were similar to the results of the 3-back task with slight differences in the cluster size.

Table 2
Cerebellar subregions in which GMV was correlated with individual performance on working memory (3-back) in healthy young adults.

WM index	Cerebellar areas	Peak *t* values	Peak correlation MNI (*x*, *y*, *z*)	Cluster size (voxels)
RT	L lobules IV/V/VI/Crus I	4.78	−30, −51, −31.5	4325
RT	R lobules IV/V/VI	4.48	28.5, −39, −40.5	2108
RT	B vermis VII/VIII/lobule VIII	3.71	9, −67.5, −31.5	863
CR	L lobules VI/Crus I	4.00	−6, −81, −21	525

Abbreviations: B, bilateral; CR, correction rate; GMV, grey matter volume; L, left; MNI, Montreal Neuroscience Institute; R, right; RT, reaction time; WM, working memory.

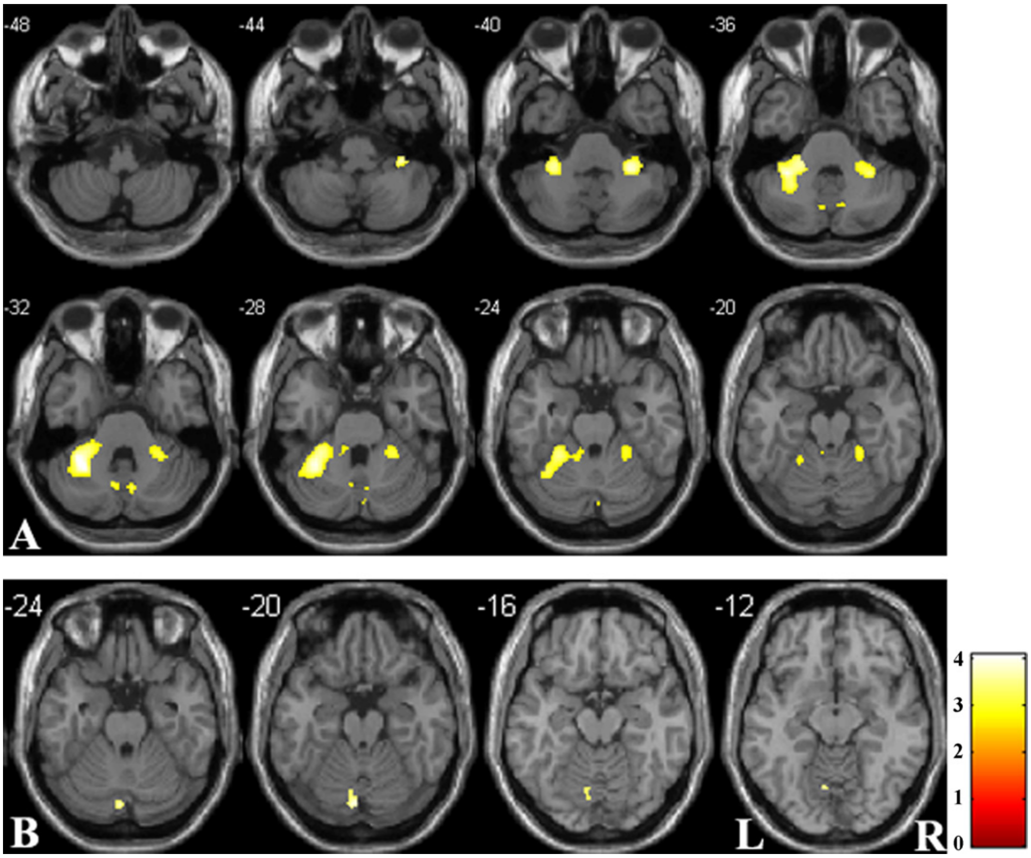

Fig. 1. Cerebellar subregions in which GMV was correlated with the reaction time (A) and correction rate (B) on a 3-back task when controlling for age, gender, years of education and handedness score. L and R represent the left and right hemispheres, respectively.

4. Discussion

In the current study, we aimed to identify the structural basis of cerebellar involvement in working memory processing using a VBM method. We found that volumetric variations in different cerebellar subregions could account for individual differences in aspects of working memory function such as the RT and CR. As predicted, the RT was related to structural variation in cerebellar subregions involved in both motor and cognitive functions, while the CR was only associated with structural variation in cerebellar subregions involved in cognitive function.

The involvement of the cerebellum in working memory has been extensively reported in neuroimaging and lesion studies [3,16,36,39], but the relationship between structural variations and individual working memory performance remains elusive. In the present study we provide evidence of a structural substrate for cerebellar participation in working memory in a large sample of healthy young adults. Moreover, we found that the cerebellar lobules VI–VIII were the main regions associated with working memory processing, which is consistent with a variety of previous studies [11,12,19,44]. In a review by Cabeza and Nyberg [10], the authors discovered that the cerebellum was activated in 10 of 18 verbal working memory tasks including the *n*-back. Task-based functional neuroimaging studies on healthy adults have found that the *n*-back task activates bilateral regions of the posterior cerebellar lobe [11,12], including the superior cerebellum (lobule VI/Crus I) for articulatory control and the inferior cerebellum (lobules VIIB/VIIIA) for phonological storage. A meta-analysis of functional activation patterns within the cerebellum [42] provided converging evidence for activation in the lobules VI and VII during working memory. Stoodley et al. [44] found that the *n*-back task triggered activation in the right lobule VI and Crus I and in the left lobules VIIB and VIIIA. Furthermore, a recent study by Juha Salmi et al. [32] showed that the bilateral Crus I and II, right lobule VIIB and left lobule VIII of the cerebellum were activated in a nonverbal auditory working memory task.

In the *n*-back task, we speculate that RT is an integrated reflection of both finger coordination involved in pressing the button as soon as possible and the capacity of working memory. An individual with better balance and spatial orientation ability should exhibit a faster RT, which may reflect neural processing in motor-related cerebellar subregions. However, if an individual displays increased grey matter volume in cognitive-related areas of the cerebellum, his RT should also be shorter because of faster processing of information; thus, the RT may also reflect the capacity of working memory. Cerebellar regions displaying motor-related correlations were mainly located in the lobules IV/V [20,25,32] and to a lesser extent in the lobules VI and VIII [42–44], while the cognitive-related cerebellar areas were located in the lobules VI/VII/VIII [11,12,19,44]. The significant correlations between the RT and GMV in the cerebellar lobules IV/V/VI/VIII may mainly reflect coordination ability in the motor-related cerebellar areas. However, the significant correlations between the RT and GMV in cerebellar lobules VI/VII/VIII, and especially Crus I and vermis VII, may at least partly reflect working memory capacity in the cognitive-related cerebellar areas.

It is difficult to interpret the finding of a significant positive correlation between RT on the working memory task and the GMV in cerebellar regions (i.e., a larger GMV is associated with a slower reaction time), which conflicts with results obtained in previous fMRI studies [34,52]. These conflicting findings suggest a rather complex relationship between structural variation in the brain and measured behaviors. For example, in patients with Alzheimer's disease (AD), cortical thinning has been extensively reported [21,22] and thinner cortex predicts poorer behavioral performance. However, in patients with amusia, cortical thickening is reported [18]; a thicker cortex predicts poorer behavioral performance. One study outlining alterations in cerebellar-cerebral functional connectivity in patients with geriatric depression also highlights this complex relationship [1], finding both increased and decreased functional connectivity in these patients. The exact relationship between structural variation in the brain and behavioral differences merits further study.

5. Conclusions

In the present study, we used a VBM technique to identify the relationship between volumetric variations in regions of the cerebellum and performance on a working memory task. The RT was positively correlated with the GMV in the bilateral cerebellar lobules IV/V, VI and VIII, vermis VII/VIII and left Crus I, while the CR was positively correlated with the GMV in the left lobule VI and Crus I. Thus, our findings suggest that the RT on a working memory task is related to both motor and cognitive subregions of the cerebellum, while the CR is mainly associated with the cognitive subregions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2011.12.016.

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