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# Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration

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See King *et al.* (doi:10.1093/aww348) for a scientific commentary on this article.

Detailed mapping of clinical dysfunctions to the cerebellar lobules in disease populations is necessary to establish the functional significance of lobules implicated in cognitive and motor functions in normal subjects. This study constitutes the first quantitative examination of the lobular correlates of a broad range of cognitive and motor phenomena in cerebellar disease. We analysed cross-sectional data from 72 cases with cerebellar disease and 36 controls without cerebellar disease. Cerebellar lobule volumes were derived from a graph-cut based segmentation algorithm. Sparse partial least squares, a variable selection approach, was used to identify lobules associated with motor function, language, executive function, memory, verbal learning, perceptual organization and visuomotor coordination. Motor dysfunctions were chiefly associated with the anterior lobe and posterior lobule HVI. Confrontation naming, noun fluency, recognition, and perceptual organization did not have cerebellar associations. Verb and phonemic fluency, working memory, cognitive flexibility, immediate and delayed recall, verbal learning, and visuomotor coordination were variably associated with HVI, Crus I, Crus II, HVII B and/or HIX. Immediate and delayed recall also showed associations with the anterior lobe. These findings provide preliminary anatomical evidence for a functional topography of the cerebellum first defined in task-based functional magnetic resonance imaging studies of normal subjects and support the hypotheses that (i) cerebellar efferents target frontal lobe neurons involved in forming action representations and new search strategies; (ii) there is greater involvement of the cerebellum when immediate recall tasks involve more complex verbal stimuli (e.g. longer words versus digits); and (iii) it is involved in spontaneous retrieval of long-term memory. More generally, they provide an anatomical background for studies that seek the mechanisms by which cognitive and motor dysfunctions arise from cerebellar degeneration. Beyond replicating these findings, future research should employ experimental tasks to probe the integrity of specific functions in cerebellar disease, and new imaging methods to quantitatively map atrophy across the cerebellum.

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**Abbreviations:** ICARS = International Cooperative Ataxia Rating Scale; SCA = spinocerebellar ataxia; SPLS = Sparse Partial Least Squares

# Introduction

In the past three decades, evidence has accumulated that the cerebellum, besides being involved in motor function, is a component of cognitive circuits. Neuronal tracing and electrophysiological studies in animals, and resting state functional MRI studies in humans, have shown its reciprocal connections with motor, premotor, prefrontal and posterior parietal cortices, and with motor and non-motor regions of the basal ganglia (Bostan *et al.*, 2013; Buckner, 2013). These studies show an inverted sensorimotor homunculus largely in the anterior lobe and an upright homunculus largely in lobule HVIII of the posterior lobe. Between these two regions, the cerebellum is connected to association cortices.

Task-based functional MRI studies have shown associations between sensorimotor tasks and activations in the anterior lobe, HVI, HVIII and HIX (Stoodley and Schmahmann, 2009*a*, 2010), and that tests of executive function, working memory, language, visuospatial function, music, and emotion result in activation of lobules HVI, Crus I, Crus II, HVII B and HVIII, and the midline lobule VII (Stoodley and Schmahmann, 2009*a*, 2010; Stoodley *et al.*, 2012; E *et al.*, 2014). These findings buttress the view of a functional topography of the cerebellum. The few structural MRI studies of the cerebellar correlates of function in normal persons show negative association of the anterior lobe with processing speed, and of the posterior cerebellum with sensorimotor performance and spatial working memory (Bernard and Seidler, 2013; Bernard *et al.*, 2015). Regardless, findings from structural studies in normal subjects might be considered inconclusive, as low variability in the data can obscure associations between motor and cognitive functions and cerebellar volumes.

Besides the classical motor syndrome, cognitive and affective syndromes have been described in cerebellar disease populations, highlighting dysfunctions in the executive, visuospatial, memory, and language domains, and alterations in personality (Schmahmann, 2004; Noroozian, 2014). However, detailed mapping of clinical dysfunctions to cerebellar lobules in disease populations has not been achieved. Generally, studies in disease groups showed coarse granularity in their segmentations of the cerebellum or were limited to few functional domains. For instance, patients with cognitive deficits were noted to have a preponderance of posterior lobe lesions, and those with affective or behavioural impairments had lesions in the vermis (Schmahmann and Sherman, 1998; Levisohn *et al.*, 2000). At a finer level, deficits in orientation of spatial attention were quantitatively correlated with lower volumes of vermian lobules VI and VII (Townsend *et al.*, 1999), mobility deficits with lower volumes of posterior lobe regions (lobules HVI, Crus I, HVII B and HVIII) (Jung *et al.*, 2012) and impaired timing of conditioned eyeblink response with lesions in the lateral anterior lobe (Timmann *et al.*, 2010).

In this study, we undertook an exploration of the cerebellar associations of a broad range of clinical dysfunctions in a comparatively large cohort of cerebellar disease subjects, using detailed cognitive and motor characterizations plus cerebellar lobule volumes derived with a novel automated cerebellar segmentation technique (Yang *et al.*, 2016).

# Materials and methods

## Sample

Our 12-year cohort ($n = 353$ in April 2014) of cerebellar syndromes comprises cerebellar disease cases ($n = 217$) and age-matched volunteers not suffering from any cerebellar disease ($n = 136$). Cases were referred from clinics, research programmes or the community, their ascertainment based on a specialist diagnosis (genetic or clinical) of cerebellar disorder reported by the referral source. We selected for this cross-sectional study those who had an MRI within 6 months of a clinical assessment (i.e. $n = 113$; 77 cases and 36 controls). We then excluded three cases whose cerebellar disease was not primary, and two more who had cerebellar neoplasm and an arachnoid cyst.

The final sample size was 108. Among the 72 cases were 45 with spinocerebellar ataxia (SCA), comprising five with SCA2, seven with SCA3, 24 with SCA6, two with SCA8, one with both SCA6 and SCA8, one with SCA15, and five with SCA of unknown type (two had negative tests and three were not tested). Eighteen genetic diagnoses were made in the Natural History Study on spinocerebellar ataxias (https://clinicaltrials.gov/ct2/show/NCT01060371), 20 in a commercial laboratory, and two were close relatives of known mutation carriers. We also included 22 subjects who had cerebellar ataxias of unknown type. Ten of these were members of one family that had negative genetic testing—as did six of the other 12 subjects. Another case had Friedrich's ataxia, and four had the cerebellar subtype of multiple system atrophy.

Information on non-cerebellar co-morbidities was collected through self-reported questionnaires, available for 102 of the 108 subjects. One subject had a seizure in childhood with no recurrence, and another had an olfactory epithelial tumour that was excised 3 days after our assessment. Thirteen per cent (10% of cases and 15% of controls) had a history of remote head trauma, typically due to falls or sport injuries. Head trauma was complicated by skull fracture in one case, and concussion in two cases and one control; as there were no indications of enduring neurological sequelae, these subjects were not excluded from this study. No subjects reported a

history of stroke. About 43% had a history of depression/anxiety (44% of cases and 39% of controls). One case had also been treated for obsessive-compulsive disorder and another had an equivocal history of post-traumatic stress disorder. There was one case of bipolar disorder. Forty-six per cent of cases and 18% of controls reported alcohol consumption, typically with dinner or in social settings. Two cases had heavy drinking in the past, and one control reported drinking three times daily. There were six current smokers (five cases, with one exceeding a pack per day), whereas 24% of cases and a similar proportion of controls were ex-smokers. Four subjects (three cases and one control) had used cocaine, one case also had used LSD and mushrooms. Another case had a history of opiate use. The lifetime severity of recreational drug use in these subjects was undocumented.

We conducted clinical interviews, physical examinations, detailed neurological examinations with structured assessments of cerebellar functions, and psychometric assessments of cognition, psychological and psychosocial states, and day-to-day function. The motor assessment consisted of the Functional Staging For Ataxia (FSFA; Subramony *et al.*, 2005), a subset of the Unified Ataxia Disorders Rating Scale assessing overall mobility, and the International Cooperative Ataxia Rating Scale (ICARS), a standard tool for semi-quantitative assessment of the motor dysfunctions associated with primary cerebellar syndromes (Trouillas *et al.*, 1997; Storey *et al.*, 2004). Following convention, we condensed the 19 ICARS items into four subscales denoting abnormal posture and stance (items 1–7), abnormal limb kinesis (items 8–14), dysarthria (items 15 and 16), and oculomotor dysfunction (items 17–19). The cognitive assessment consisted of tests of object naming (Boston naming Task, BNT); semantic and phonemic fluency (Noun and Verb fluency tasks, and Controlled Oral Word Association, COWA); immediate recall and working memory (Digit Span forward and backward); verbal learning and recall (Rey Auditory Verbal Learning Test, RAVLT); perceptual organization (Hooper Visual Organization Test); visual scanning, cognitive flexibility and complex tracking (Trail Making Test, TMT parts A and B); cognitive and motor speed (Grooved Pegboard).

## Image processing

$T_1$-weighted magnetization prepared rapid gradient-echo images of the subjects were acquired with a 3 T Philips Integra scanner. The imaging parameters were: 132 slices, axial orientation, 1.1 mm slice thickness, 8° flip angle, echo time = 3.9 ms, repetition time = 8.43 ms, field of view 21.2 × 21.2 cm, matrix 256 × 256 (resolution: 0.828125 × 0.828125 × 1.1 mm). We used a graph theoretical approach for automated segmentation of the cerebellar lobules and estimation of their volumes (Yang *et al.*, 2016), the code for which is available at http://iacl.ece.jhu.edu/Resources. Briefly, we used FreeSurfer version 5.3.0 to transform each original MRI scan into MNI space, generate a skull-stripped and intensity-normalized image, and create a classification of the cerebellum into grey and white matter. For each subject, we carried out an initial segmentation by registering and fusing lobular labels from multiple atlases (15 manually delineated training subjects). This segmentation was refined with a graph-cut based segmentation that combined the multi-atlas label-fusion result and tissue and boundary classifications. Specifically, we used a machine-learning algorithm to label voxels as cerebellar versus non-cerebellar and a second classifier to detect boundary voxels. These classifications were then used to modify the graph-cut energy function, so that the optimal subject-level lobular segmentation occurred along subject-specific cerebellar fissures. As reported (Yang *et al.*, 2016), this method out-performs both a multi-atlas labelling approach based on the non-local STAPLE method (Asman and Landman, 2013), and ACCLAIM (Bogovic *et al.*, 2013), which in turn outperforms SUIT atlas-based labelling (Diedrichsen *et al.*, 2009). This is especially true where cerebellar atrophy is marked.

## Statistical analyses

We analysed the anterior lobe (lobules I–V), HVI, Crus I, Crus II, HVII B, HVIII, HIX, posterior lobe vermis (vermian lobules VI, VII, VIII and IX) and the flocculonodular lobe (hemispheric and vermian lobules X). The difference between the sum of these volumes and the whole brain volume (rest of brain volume = whole brain volume − sum of cerebellar lobule volumes) was included in the models to account for between-subject differences in extra-cerebellar regions (primarily the cortex) that contribute to function. Volumes were normalized to the intracranial volume derived using FreeSurfer (http://www.freesurfer.net/fswiki/eTIV). For clinical tests and cerebellar volumes, left and right-sided values were combined to limit collinearity. The posterior lobe vermis was analysed as a single volume because the small size of each vermian lobule increases the risk for measurement error during cerebellar segmentation. In addition, a categorical variable for musculoskeletal conditions was incorporated in the models where the tests involved movement of the limbs.

Group comparisons used the Mann-Whitney U-test for age, education and raw test scores, and the chi-squared test for sex. For ease of interpretation of all other analyses, the signs of the test scores were inverted as necessary so that high scores reflected good performance. Correlation matrices of test scores and regional volumes were based on the Pearson correlation coefficients. Volumes and test scores were then scaled by dividing by their respective standard deviations in controls, and centred by subtracting the mean of the total sample (ICARS speech was not scaled because the standard deviation was zero in controls). Using 'spls' version 2.2-1 (Chung *et al.*, 2012, 2013; http://cran.r-project.org/package=spls) in R (version 3.1.0), we created a Sparse Partial Least Squares (SPLS) model for each test score to select predictors and compute coefficients. SPLS is a modification of Partial Least Squares (PLS) regression. PLS entails finding unit direction vectors that maximize the inner products of the test score with the latent components, i.e. the projections of predictor variables onto the direction vectors (Chun and Keleş, 2009). The inner product is proportional to the covariance when the predictor variables and test scores are mean-centred. Regression coefficients of the latent components are used to obtain coefficients for the original predictors. SPLS uses an L1 penalization on the direction vectors to enforce sparsity in the number of predictors that combine linearly to form latent components (Chun and Keleş, 2010), as detailed in the Supplementary material. The L1 parameter and number of latent components were selected using 10-fold cross-validated mean squared prediction errors. For each test, SPLS selected a subset of lobules

and provided coefficients. One thousand bootstraps were conducted with random sampling with replacement (regardless of disease status). PLS regression performed on each bootstrapped sample, using only the lobules selected in the original SPLS model, yielded a distribution of coefficients for deriving the 95% confidence interval for each selected lobule. For greater parsimony, coefficients of variables with confidence intervals that contained zero were set to zero. The musculoskeletal variable was not selected in any models. Therefore, the SPLS procedure was repeated without the musculoskeletal variable, and this was taken as the final variable selection result. The robustness of this selection was indexed using 1000 bootstraps in which all lobular volumes were included as predictors.

A variable selection approach and sparsity constraints are justified by evidence from animal, task-functional MRI and lesion studies, that different subregions of the cerebellum are involved in different functions and networks (as described in the 'Introduction' section). SPLS has been shown to have comparable or superior variable selection performance in the presence of collinearity in comparison to other approaches such as Lasso, Elastic net and Supervised Principal Components (Chun and Keleş, 2010; Acharjee *et al.*, 2013).

Group comparisons, correlations and SPLS analyses were also conducted on residuals derived from linear regressions of specific combinations of raw test scores. For correlation and SPLS analyses, the signs of these residuals were inverted as necessary so high values reflect good performance. In each linear regression, the dependent variable (i.e. a test) tapped several functional domains (e.g. A, B and C), of which one was of interest (e.g. A). The independent variables tapped the extraneous domains (B and C), and the residuals were taken to specifically reflect performance in the domain of interest (A) and entered into analyses. Considering two or more related tests together has been used to isolate a cognitive domain when interpreting neuropsychological test scores that depend on more than one domain (Leggio *et al.*, 2000; Van der Werf *et al.*, 2000; Gerton *et al.*, 2004; Sánchez-Cubillo *et al.*, 2009). In this study, this entailed adjusting: (i) TMT B scores for TMT A scores to isolate correlates of cognitive flexibility and complex tracking; (ii) Grooved Pegboard scores for the ICARS kinetic and oculomotor scores to isolate the component for visuomotor coordination; (iii) noun fluency, verb fluency and COWA scores for ICARS speech score to address effects of dysarthria; (iv) Digit Span backward scores for Digit Span forward scores to examine correlates of working memory beyond simple immediate recall and the demands of verbal production; (v) RAVLT trial I scores for Digit Span forward scores to find regions associated with encoding and storage of complicated stimuli (words versus digits); (vi) RAVLT trial V scores for RAVLT trial I scores to disentangle effects of attention and effects of verbal learning; and (vii) RAVLT delayed recall scores for RAVLT recognition scores to assess spontaneous retrieval of memory.

# Results

## Descriptive statistics

The characteristics of the study subjects are described in Table 1, which reports demographics, raw test scores, and residuals (i.e. adjusted test scores). There were no group differences in age, sex, and years of education. Cases performed worse than controls in all motor and mixed tasks, and in most cognitive tasks (unadjusted $P < 0.05$)—except BNT, Digit Span forward, RAVLT trial I, and Hooper test. Cases and controls also differed on Digit Span backward adjusted for Digit Span forward and RAVLT trial V adjusted for RAVLT trial I. Most scores differing between cases and controls had positive correlations with whole cerebellar volume (except RAVLT trial I, RAVLT recognition, Hooper, RAVLT trial I adjusted for Digit Span forward, and RAVLT trial V adjusted for RAVLT trial I). These results are shown in Fig. 1 (see Supplementary Figs 1 and 2 for results for the left and right hemispheres). Correlations between motor and mixed test scores and cerebellar volumes were higher than those for the cognitive test scores. None of the cognitive tests had a correlation with HVIII and just one (COWA) had a significant correlation with HIX. High correlations were observed between the cerebellar volumes, between all pairings of motor and mixed tasks, between the verbal fluency tasks, and between the RAVLT trials. High correlations were also observed between the residuals and their dependent variables.

## Sparse Partial Least Squares models

Table 2 and Fig. 2 show coefficients of the cerebellar volumes in SPLS models of motor, mixed and cognitive test scores. The bootstrap frequencies of these associations, which index the robustness of each association, are shown in Supplementary Table 1. Table 3 and Fig. 3 show the coefficients from SPLS models of the residuals described earlier, and Supplementary Table 2 shows the bootstrap frequencies that index these associations. Generally, the volume coefficients were higher for the motor and mixed tests than for the cognitive tests and residuals.

### Motor tests

Positive associations were observed between (i) ICARS posture and kinetic scores and the anterior lobe, HVI, and Crus I volumes; (ii) posture scores and Crus II; (iii) speech scores and HVI; (iv) oculomotor scores and anterior lobe; and (v) FSFA and anterior lobe and HVI. There were inverse associations between (i) kinetic scores and HVIII and HIX volumes; (ii) speech scores and HIX; and (iii) FSFA and HVIII.

### Mixed motor and cognitive tests

Positive associations were observed between TMT A, TMT B and Grooved Pegboard on the one hand, and the anterior lobe, Crus I and HVII B volumes on the other. Additionally, the Grooved Pegboard test had positive associations with HVI, TMT B with HIX, TMT B adjusted for TMT A with Crus I and HIX, and Grooved Pegboard test adjusted for ICARS kinetic and oculomotor scores with

**Table 1 Demographic and clinical characteristics of the study sample**

| Variable | Median (MAD), cases | Mean (SD), cases | Median (MAD), controls | Mean (SD), controls | Effect size[a] | *P*-value | Adjusted *P*-value[b] |
|---|---|---|---|---|---|---|---|
| Age | 55 (10.38) | 53.42 (13.40) | 53.5 (16.31) | 50.75 (16.19) | 2.00 | 0.358 | |
| Education | 16 (2.97) | 15.90 (2.92) | 16 (2.97) | 16.97 (3.09) | −1.00 | 0.142 | |
| Sex (male: female) | 31: 41 | | 17: 19 | | | 0.837 | |
| **Motor** | | | | | | | |
| FSFA | 3 (1.48) | 2.60 (1.32) | 0 (0.00) | 0.29 (0.59) | 2.00 | 0.000 | 0.000 |
| ICARS posture | 9 (7.41) | 11.50 (9.37) | 1 (1.48) | 1.50 (1.36) | 8.00 | 0.000 | 0.000 |
| ICARS kinetic | 6.5 (5.37) | 6.55 (4.22) | 1 (1.48) | 1.16 (1.18) | 5.00 | 0.000 | 0.000 |
| ICARS speech | 2 (2.97) | 2.06 (1.73) | 0 (0.00) | 0.00 (0.00) | 2.00 | 0.000 | 0.000 |
| ICARS oculomotor | 4 (1.48) | 3.45 (1.79) | 0.5 (0.74) | 0.76 (0.87) | 3.00 | 0.000 | 0.000 |
| **Mixed** | | | | | | | |
| TMT A | 41.89 (16.15) | 48.40 (24.13) | 27 (11.86) | 30.97 (16.68) | 14.00 | 0.000 | 0.000 |
| TMT B | 94 (50.41) | 105.66 (54.53) | 54.5 (21.50) | 64.30 (34.09) | 37.08 | 0.000 | 0.000 |
| GP | 131.71 (75.32) | 176.10 (127.37) | 72.25 (15.20) | 79.63 (23.74) | 55.73 | 0.000 | 0.000 |
| **Cognitive** | | | | | | | |
| BNT | 57 (4.45) | 56.53 (3.47) | 58 (2.97) | 56.94 (3.93) | 0.00 | 0.357 | 1 |
| Noun fluency | 38.5 (11.12) | 38.33 (10.28) | 42 (11.86) | 44.08 (10.46) | −6.00 | 0.013 | 0.343 |
| Verb fluency | 13.5 (6.67) | 14.24 (5.82) | 19 (5.93) | 19.86 (7.00) | −5.00 | 0.000 | 0.003 |
| COWA | 36 (10.38) | 36.04 (11.39) | 48 (12.60) | 48.78 (12.92) | −12.00 | 0.000 | 0.000 |
| DS forward | 10 (2.97) | 10.50 (2.14) | 11.5 (3.71) | 10.92 (2.55) | 0.00 | 0.463 | 1 |
| DS backward | 6 (2.97) | 6.49 (2.19) | 8 (2.97) | 7.86 (2.39) | −1.00 | 0.006 | 0.166 |
| RAVLT I | 5 (1.48) | 5.04 (2.11) | 6 (2.97) | 6.08 (2.53) | −1.00 | 0.117 | 1 |
| RAVLT delayed recall | 9 (3.71) | 8.12 (3.98) | 11.5 (2.22) | 10.50 (3.26) | −2.00 | 0.002 | 0.043 |
| RAVLT recognition | 12 (2.97) | 10.94 (3.60) | 13 (1.48) | 12.75 (2.43) | −1.00 | 0.008 | 0.211 |
| Hooper | 15 (0.00) | 14.29 (1.10) | 15 (0.00) | 14.56 (0.91) | 0.00 | 0.083 | 1 |
| **Residuals[c]** | | | | | | | |
| TMT B ~ TMT A | −0.8 (20.15) | 3.45 (33.76) | −7.56 (10.92) | −6.80 (21.63) | 7.19 | 0.132 | 1 |
| GP ~ ICARS kinetic + ICARS oculomotor | −5.63 (57.52) | 1.58 (88.73) | −2.5 (27.66) | −4.23 (25.40) | −4.65 | 0.673 | 1 |
| Noun fluency ~ ICARS speech | 1.26 (8.58) | −0.08 (9.13) | −2.02 (11.86) | 0.21 (11.10) | 0.00 | 0.987 | 1 |
| Verb fluency ~ ICARS speech | −0.18 (5.07) | −0.07 (4.52) | −1.18 (2.97) | 0.20 (5.12) | −0.68 | 0.787 | 1 |
| COWA ~ ICARS speech | −1.24 (9.09) | −0.67 (8.90) | 2.06 (11.86) | 1.82 (11.46) | −2.73 | 0.295 | 1 |
| DS backward ~ DS forward | −0.7 (2.22) | −0.40 (2.06) | 0.99 (1.94) | 0.81 (2.19) | −1.23 | 0.006 | 0.172 |
| RAVLT I ~ DS forward | −0.27 (2.04) | −0.32 (2.08) | 0.14 (1.90) | 0.64 (2.50) | −0.63 | 0.171 | 1 |
| RAVLT V ~ RAVLT I | −0.17 (2.43) | −0.43 (2.52) | 1.33 (2.22) | 0.86 (2.18) | −1.28 | 0.006 | 0.165 |

BNT = Boston Naming Test; DS = Digit Span; FSFA = Functional Staging For Ataxia; GP = Grooved Pegboard MAD = median absolute deviation; SD = standard deviation.
[a]Effect size is computed as the median of differences between all pairs of cases and controls.
[b]Adjustment for multiple comparisons using Holm-Bonferroni method.
[c]In each model used to derive residuals (i.e. adjusted scores), the dependent variable tapped several functional domains (e.g. A, B and C), of which one was of interest (e.g. A). The independent variables tapped domains B and C, and the residuals were taken to reflect performance in A. The dependent variables in the models are denoted on the left of '~', while the independent variables are on the right.

HVII B and HIX. The flocculonodular lobe was inversely associated with TMT A and B, and the posterior lobe vermis with the Grooved Pegboard adjusted for ICARS kinetic and oculomotor scores.

### Cognitive tests

The BNT, noun fluency with and without adjustment for ICARS speech, RAVLT recognition, and Hooper Test had no cerebellar associations. Positive associations were observed between (i) unadjusted verb fluency and COWA and HVI and Crus II; (ii) verb fluency and COWA adjusted for ICARS speech and Crus II; (iii) Digit Span forward and HVII B; (vi) Digit Span backward with and without adjustment for Digit Span forward and Crus I; (v) RAVLT I with and without adjustment for Digit Span forward and all anterior and posterior lobe volumes (except HIX); (vi) RAVLT V adjusted for RAVLT I and all posterior lobe volumes except HVIII and posterior lobe vermis; (vii) unadjusted RAVLT delayed recall and all the volumes; and (viii) RAVLT delayed recall adjusted for RAVLT recognition and anterior lobe. Unadjusted verb fluency was inversely associated with posterior lobe vermis, while verb fluency adjusted for ICARS speech was inversely associated with HVIII.

## Discussion

This study represents the first detailed structural cerebellar mapping of cognitive and motor dysfunctions in cerebellar

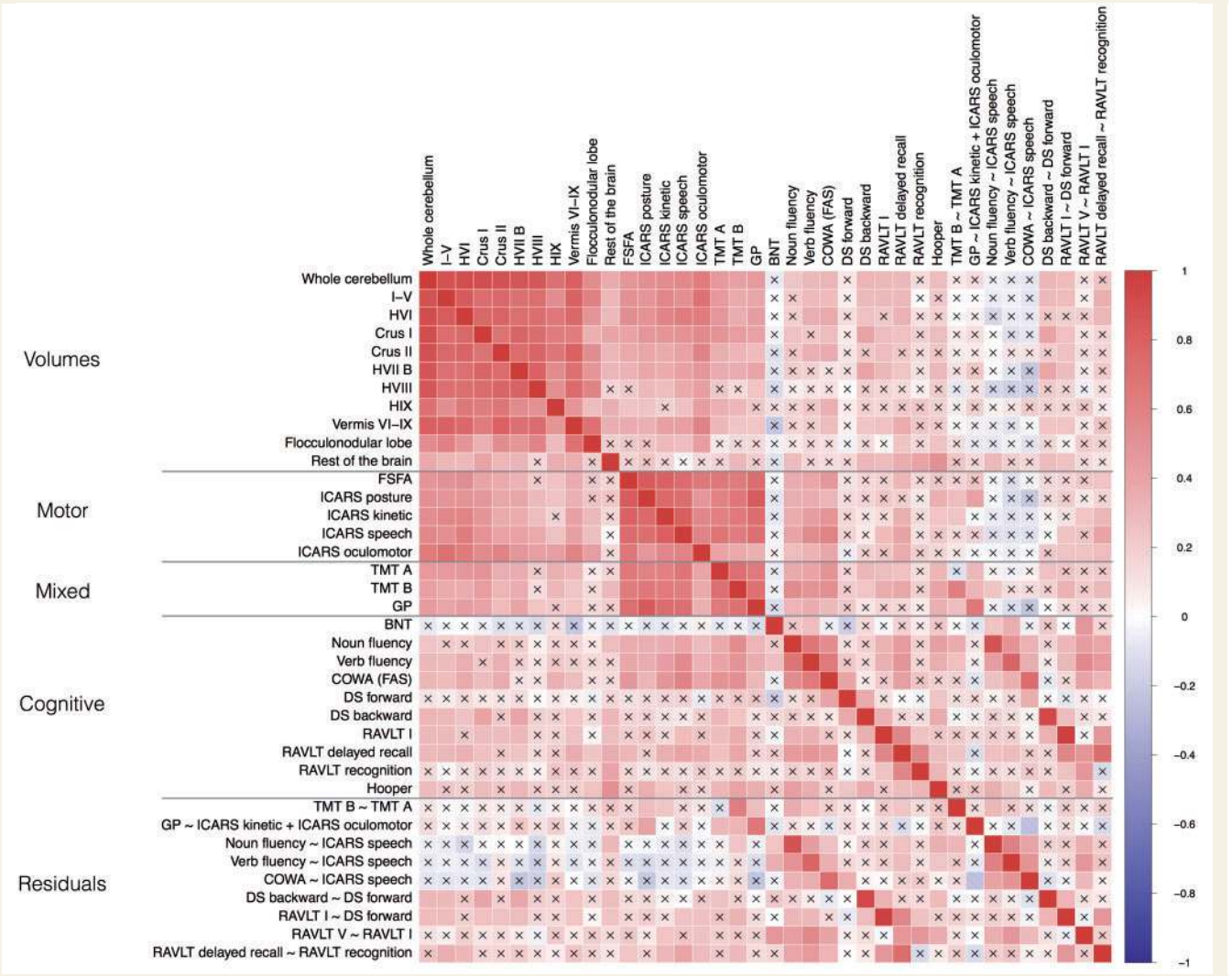


**Figure 1 Pearson correlations between cerebellar volumes and motor and cognitive test scores.** The colours of the squares denote strength and direction of correlations, and crosses mark the correlations that did not attain statistical significance ($P < 0.05$). The signs of motor and mixed tests were inverted so that high scores corresponded to good performance. This held true by default for all the cognitive tests.

disease, examining associations of lobule volumes with test scores in a relatively large cohort of patients and control subjects. The inclusion of different cerebellar disease types, and controls, facilitated the dissociation of atrophy patterns corresponding to discrete tasks, as findings were not dictated by the specific characteristics of a particular cerebellar disease. We used automated parcellation of the cerebellum alongside variable selection to map test scores to cerebellar lobules. Based on the variables selected, the main findings were associations of (i) anterior lobe with motor and mixed tasks, except ICARS speech, and with immediate and delayed recall; and (ii) posterior lobules with verb and phonemic fluency, working memory, immediate and delayed recall, and all mixed and motor (except ICARS oculomotor) tests. We found no associations between the flocculonodular lobe and most tasks. Generally, cerebellar volumes had greater influence on motor functions than on cognitive functions, as reflected in the SPLS (and Pearson correlation) coefficients. These findings dovetail with the current understanding of cerebellar function and functional topography, as discussed below.

## Motor tasks

Our results, broadly indicating a linkage of the anterior lobe and HVI with motor tasks, are consistent with anatomical and resting state functional MRI data demonstrating reciprocal connections between the motor cortex and these cerebellar regions and HVIII (Kelly and Strick, 2003; Buckner *et al.*, 2011). Anterior lobe, HVI and HVIII also receive the spinal and trigeminal inputs to the cerebellum (Stoodley and Schmahmann, 2010). Furthermore, sensorimotor functional MRI tasks result in activations in the (ipsilateral) anterior lobe, HVI and HVIII (Stoodley and Schmahmann, 2009*a*, 2010). We also observed paradoxically inverse associations between some motor tasks (FSFA, ICARS kinetic, and ICARS

**Table 2 Sparse partial least squares coefficients of cerebellar volumes for motor and cognitive test scores**

| Test | I-V | HVI | Crus I | Crus II | HVII B | HVIII | HIX | Vermis VI–IX | FNL | RBV |
|---|---|---|---|---|---|---|---|---|---|---|
| **Motor** | | | | | | | | | | |
| FSFA | 0.879 | 0.810 | 0 | 0 | 0 | −0.638 | 0 | 0 | 0 | 0 |
| ICARS posture | 0.785 | 0.779 | 0.714 | 0.720 | 0 | 0 | 0 | 0 | 0 | 0 |
| ICARS kinetic | 0.872 | 1.619 | 1.109 | 0 | 0 | −1.330 | −1.652 | 0 | 0 | 0 |
| ICARS speech[a] | 0 | 0.805 | 0 | 0 | 0 | 0 | −0.606 | 0 | 0 | 0 |
| ICARS oculomotor | 1.003 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Mixed** | | | | | | | | | | |
| TMT A | 0.179 | 0 | 0.231 | 0 | 0.168 | 0 | 0 | 0 | −0.233 | 0.239 |
| TMT B | 0.226 | 0 | 0.287 | 0 | 0.178 | 0 | 0.171 | 0 | −0.228 | 0.368 |
| Grooved Pegboard | 0.673 | 0.674 | 0.619 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Cognitive** | | | | | | | | | | |
| BNT | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Noun fluency | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.266 |
| Verb fluency | 0 | 0.237 | 0 | 0.247 | 0 | 0 | 0 | −0.302 | 0 | 0 |
| COWA | 0 | 0.177 | 0 | 0.178 | 0 | 0 | 0 | 0 | 0 | 0 |
| DS forward | 0 | 0 | 0 | 0 | 0.019 | 0 | 0 | 0 | 0 | 0.019 |
| DS backward | 0 | 0 | 0.267 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RAVLT I | 0.036 | 0.034 | 0.032 | 0.032 | 0.034 | 0.030 | 0 | 0.031 | 0 | 0.024 |
| RAVLT delayed recall | 0.048 | 0.045 | 0.046 | 0.041 | 0.045 | 0.036 | 0.024 | 0.042 | 0.026 | 0.031 |
| RAVLT recognition | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.501 |
| Hooper | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.500 |

BNT = Boston Naming Test; DS = Digit Span; FNL = flocculonodular lobe; FSFA = Functional Staging For Ataxia; I–V = anterior lobe; RBV = rest of brain volume.
Zeroes denote variables that were not selected by the models.
The significance value of the coefficients is $<0.05$ for all the selected variables in all the models.
The signs of all motor and mixed test scores were inverted, so that high scores corresponded to good performance. This held true by default for all cognitive scores.
[a]All model variables were scaled by dividing by the respective standard deviations in control subjects, except for ICARS speech (the standard deviation in control subjects was zero).

speech) and lobules HVIII and/or HIX. These are likely to be statistical artefacts as there were no inverse Pearson correlations. We also showed associations between Crus I and II and posture/gait and limb coordination, which fits with data linking complex movements to the medial aspects of the posterior lobules HVI and Crus I (Schlerf *et al.*, 2010). The recruitment of HVI and Crus I in the motor tasks was proposed to reflect higher-order motor planning, rather than attentional processes that cause more lateral activations (Schlerf *et al.*, 2010).

We expected oculomotor movements to be associated with the posterior lobe vermis (specifically lobules VI, VII, and IX), Crus I, Crus II, HIX, and the flocculonodular lobe, as other work (Glasauer, 2003; Voogd *et al.*, 2012) show these areas to participate in oculomotor control, including smooth pursuit, gaze-holding (mainly the flocculus), and saccadic eye movements (mainly vermian lobules VI and VII, Crus I and Crus II). Only the anterior lobe, which had the highest correlation, was selected in our SPLS model, although the ICARS oculomotor score showed significant correlations with all cerebellar volumes. This lack of associations with other cerebellar regions may stem partly from signal attenuation due to using a composite variable combining scores for abnormalities of smooth pursuit, gaze-evoked nystagmus, and dysmetria of saccades. Indeed, in *post hoc* analyses that considered these scores separately, we found associations between (i) anterior lobe, HVI, and posterior lobe vermis and smooth pursuit movements; (ii) the anterior lobe and gaze-evoked nystagmus; and (iii) anterior lobe, HVI, HVII (Crus I and II, and HVII B), and posterior lobe vermis and dysmetria of saccades.

## Language tasks

We did not observe differences in confrontation naming between cases and controls, or correlations between confrontation naming and cerebellar volumes, and earlier research has indicated that anomia is absent or mild in cerebellar diseases (Schmahmann and Sherman, 1998; Schweizer *et al.*, 2010). On the other hand, the associations between phonemic and verb fluency (but not noun fluency) and HVI and Crus II are consistent with an earlier observation that phonemic fluency is impaired more than noun fluency in subjects with right cerebellar lesions (Schweizer *et al.*, 2010). Furthermore, activations with strong right lateralization have been observed in HVI, Crus I, HVII B, and HVIII in normal subjects performing verb-for-noun generation tasks (Frings *et al.*, 2006; Stoodley *et al.*, 2012). This activation is independent of the articulation and motor imagery associated with speaking verbs (Silveri and Misciagna, 2000; Frings *et al.*, 2006), especially in HVI and Crus I (Frings *et al.*, 2006). Dysarthria-adjusted phonemic fluency has also been observed to be impaired in cerebellar disease patients (Leggio *et al.*, 2000), and

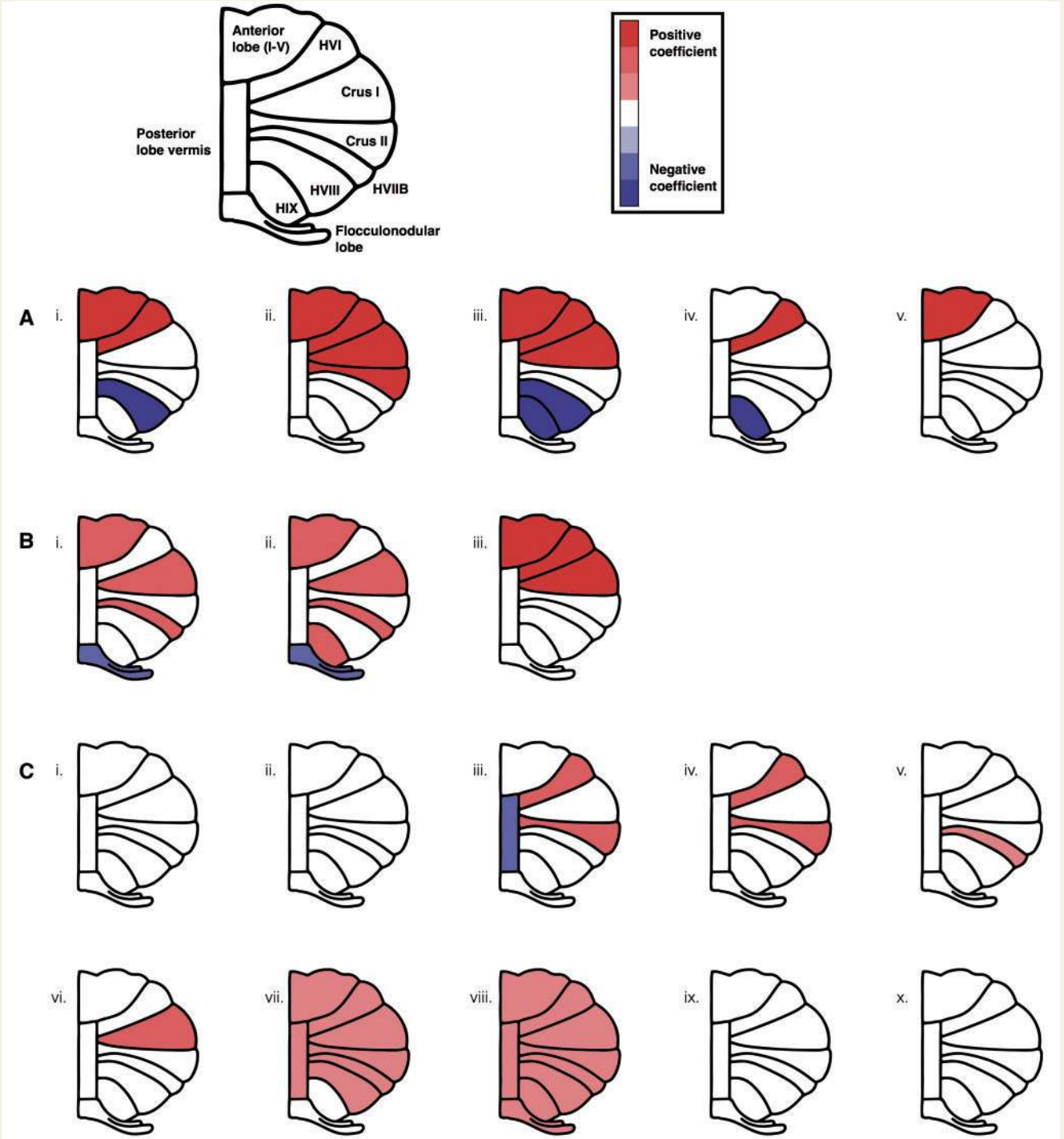


**Figure 2 Associations between cerebellar volumes and motor and cognitive test scores.** Associations were derived with the sparse partial least squares approach. Colours illustrate the direction and size of the coefficients (Table 2). (**A**) Motor tests: (**i**) Functional Staging for Ataxia; (**ii**) ICARS posture; (**iii**) ICARS kinetic; (**iv**) ICARS speech; (**v**) ICARS oculomotor. (**B**) Mixed tests: (**i**) TMT A; (**ii**) TMT B; (**iii**) Grooved Pegboard. (**C**) Cognitive tests: (**i**) Boston Naming Test; (**ii**) Noun fluency; (**iii**) Verb fluency; (**iv**) COWA (F, A and S); (**v**) Digit Span forward; (**vi**) Digit Span backward; (**vii**) RAVLT I; (**viii**) RAVLT delayed recall; (**ix**) RAVLT recognition; (**x**) Hooper Visual Organization.

associations with phonemic and verb fluency in our study were seen after adjustment for dysarthria. The apparently paradoxical association between verb fluency and HVIII may be explained, in part, by a putative association between HVIII and speech production (Bohland and Guenther, 2006; Ghosh *et al.*, 2008).

The apparent lack of cerebellar involvement in noun fluency, relative to phonemic and verb fluency, is in line

**Table 3 SPLS coefficients of cerebellar volumes for residuals obtained from linear regressions of combinations of clinical test scores**

| Linear regression models for residuals[a] | I-V | HVI | Crus I | Crus II | HVII B | HVIII | HIX | Vermis VI-IX | FNL | RBV |
|---|---|---|---|---|---|---|---|---|---|---|
| TMT B ~ TMT A | 0 | 0 | 0.040 | 0 | 0 | 0 | 0.030 | 0 | 0 | 0.037 |
| Grooved Pegboard ~ ICARS kinetic + ICARS oculomotor | 0 | 0 | 0 | 0 | 0.714 | 0 | 0.518 | −0.589 | 0 | 0 |
| Noun fluency ~ ICARS speech | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.358 |
| Verb fluency ~ ICARS speech | 0 | 0 | 0 | 0.314 | 0 | −0.229 | 0 | 0 | 0 | 0 |
| COWA ~ ICARS speech | 0 | 0 | 0 | 0.113 | 0 | 0 | 0 | 0 | 0 | 0 |
| DS backward ~ DS forward | 0 | 0 | 0.266 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RAVLT I ~ DS forward | 0.034 | 0.031 | 0.030 | 0.029 | 0.031 | 0.029 | 0 | 0.030 | 0 | 0.021 |
| RAVLT V ~ RAVLT I | 0 | 0.033 | 0.032 | 0.029 | 0.029 | 0 | 0.022 | 0 | 0 | 0.022 |
| RAVLT delayed recall ~ RAVLT recognition | 0.179 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]In each model used to derive residuals, the dependent variable tapped several functional domains (e.g. A, B and C), of which one was of interest (e.g. A). The independent variables tapped domains B and C, and the residuals were taken to reflect performance in A.

BNT = Boston Naming Test; DS = Digit Span; FNL = flocculonodular lobe; FSFA = Functional Staging For Ataxia; I–V = anterior lobe; ICARS = International Cooperative Ataxia Rating Scale; RBV = rest of brain volume.

Zeroes denote variables that were not selected by the models.

The significance value of the coefficients is $<0.05$ for all the selected variables in all the models.

The signs of all motor and mixed test scores were inverted, so that high scores corresponded to good performance. This held true by default for all cognitive scores.

All model variables were scaled by dividing by the respective standard deviations in control subjects.

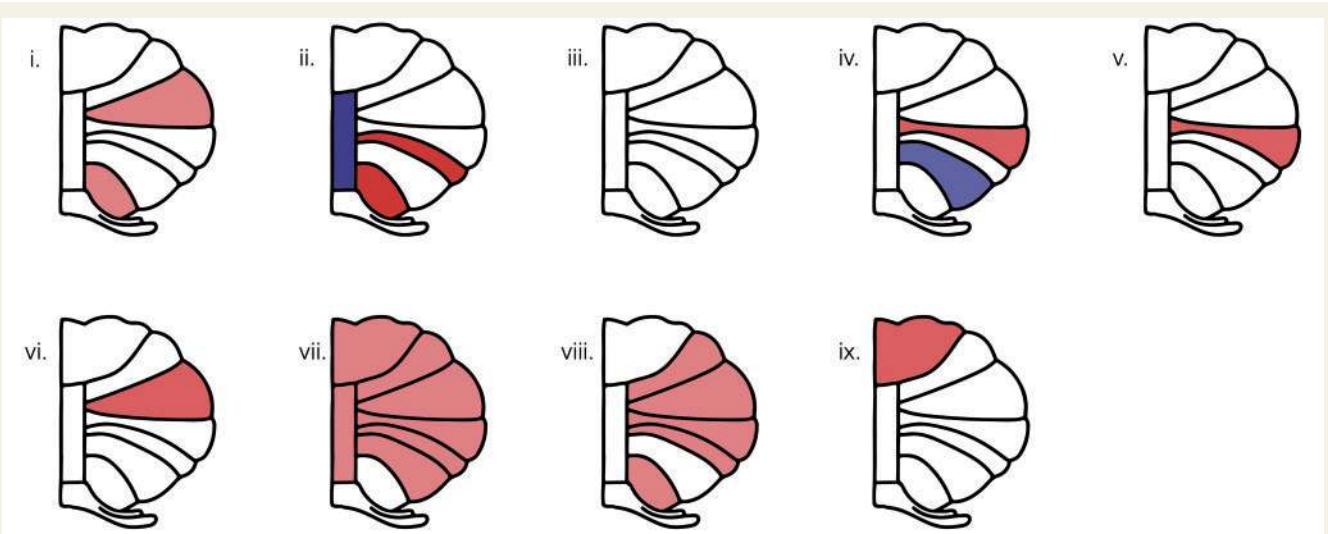


**Figure 3 Associations between cerebellar volumes and residuals obtained from linear regressions of combinations of motor and cognitive test scores.** Associations were derived with the sparse partial least squares approach. Colours illustrate the direction and size of the coefficients (shown in Table 3). **(i)** TMT B adjusted for TMT A; **(ii)** Grooved Pegboard adjusted for ICARS speech and ICARS oculomotor; **(iii)** Noun fluency adjusted for ICARS speech; **(iv)** Verb fluency adjusted for ICARS speech; **(v)** COWA adjusted for ICARS speech; **(vi)** Digit Span backward adjusted for Digit Span forward; **(vii)** RAVLT I adjusted for Digit Span forward; **(viii)** RAVLT V adjusted for RAVLT I; **(ix)** RAVLT delayed recall adjusted for RAVLT recognition.

with earlier work in subjects with cerebellar disease (Leggio *et al.*, 2000; Neau *et al.*, 2000; de Nóbrega *et al.*, 2007; Stoodley and Schmahmann, 2009*b*), although not a consistent finding (Gottwald *et al.*, 2004). This pattern of performance in fluency tasks is not well understood. Phonemic and verb fluency have been proposed to reflect frontal lobe dysfunction due to cerebro-cerebellar diaschisis (Silveri and Misciagna, 2000), consistent with the connectivity between the posterior lobe of the cerebellum and the prefrontal association cortices (Buckner *et al.*, 2011). However, noun fluency is associated with activation in the left prefrontal cortex (Gourovitch *et al.*, 2000; Birn *et al.*, 2010) and is as impaired as phonemic fluency in patients with frontal lesions (Henry and

Crawford, 2004). This suggests that cerebellar efferents selectively target neurons involved in phonemic and verb fluency tasks. It has been proposed that phonemic fluency tasks require non-semantic word searching strategies (rather than the more natural semantic strategy), so that selective impairment of phonemic fluency (compared to noun fluency) in cerebellar disease reflects the role of the cerebellum in strategy formation (Leggio *et al.*, 2000). Low verb fluency may be explained by the proposal that verb retrieval depends on the efficiency of action representation, which involves the frontal lobe and the cerebellum (Silveri and Misciagna, 2000). An alternative is that the cerebellum has a role in inner speech production, which may be required for lexical search during verb generation (Frings *et al.*, 2006); this would be an incomplete explanation that does not account for the relative preservation of noun fluency.

## Immediate recall

Tests of immediate recall are believed to involve the phonological loop, a slave system for short-term maintenance of verbal information in Baddeley and Hitch's working memory model (Baddeley, 2003*b*). The loop has two subsystems, a phonological store and an articulatory rehearsal process similar to sub-vocal speech. We observed immediate recall of digits (Digit Span forward) and words (RAVLT I) to be associated with HVII B, and recall of words also with the anterior lobe and posterior lobules HVI, Crus I, Crus II, HVIII, and posterior lobe vermis, observations consistent with the current view linking the phonological loop with the posterior lobules. It is believed that lobules VI and Crus I support preparation of complex motor programs and covert speech during articulatory rehearsal, while lobules VIIB and VIII support phonological storage when information is maintained across a delay (Marvel and Desmond, 2010).

Word length appears to have an inverse relationship with immediate memory span as the time-related decay of phonological memory is sensitive to the time required for overt recall of longer words and their covert rehearsal (Cowan *et al.*, 1992; Baddeley, 2003*a*). Selection of more regions in our model for immediate recall of words than that for immediate recall of digits suggests higher demands on the integrity of the sub-vocal rehearsal system and phonological store during tasks involving recall of words rather than digits, since a slower rehearsal process may be prone to interference and the phonological memory of words is more susceptible to decay. In short, higher processing demands may entail larger-scale recruitment of the cerebellum. The small coefficients corresponding to Digit Span forward can be explained from the zero effect size (Table 1) and the small and non-significant correlations of Digit Span forward with the cerebellar lobules (Fig. 1). The small magnitudes of the SPLS coefficients for RAVLT I relative to the other cognitive tests raise the suspicion that owing to collinearity, the true association of RAVLT I to a specific region was distributed to other cerebellar volumes in the modelling process. Regardless, the cerebellar coefficients for RAVLT I together outweigh that for Digit Span forward, suggesting word length is a relevant factor. This hypothesis contradicts an earlier report (Ravizza *et al.*, 2006) describing similar effects of word length on immediate recall in cerebellar patients ($n = 8$) as in normal controls ($n = 8$), and a case study (Silveri *et al.*, 1998) that described slightly better recall of longer words in a subject with a right cerebellar lesion.

## Working memory

The association of working memory with Crus I is consistent with previously observed associations with the left and right lobules IV, V, VI, Crus I, VII B, and VIII in normal subjects (Stoodley and Schmahmann, 2009*a*; Marvel and Desmond, 2010; Stoodley *et al.*, 2012; E *et al.*, 2014). Furthermore, working memory deficits have been observed in earlier studies of cerebellar disorders (Schmahmann and Sherman, 1998; Gottwald *et al.*, 2004; Ravizza *et al.*, 2006; Marvel and Desmond, 2010). Working memory involves the temporary storage of information and its manipulation. The core component is considered to be the 'central executive', which functions as a supervisory and attention-controlling system (Baddeley, 2003*b*; Bellebaum and Daum, 2007). The ventral dentate nucleus has been shown to be activated during scenarios of online manipulation of information (Marvel and Desmond, 2010) and is linked to prefrontal executive regions including the dorsolateral prefrontal cortex (Middleton and Strick, 2000; Dum and Strick, 2003), which suggests interactions between the cerebellum and the central executive.

## Cognitive flexibility

Cognitive flexibility and complex tracking (TMT B after adjustment for TMT A) appeared to involve Crus I and HIX in this study. The SPLS coefficients were small compared to the motor, mixed and several cognitive tasks, suggesting the cerebellum has a smaller impact on cognitive flexibility. Studies in cerebellar disease showing impaired shifting of attention between two kinds of stimuli, particularly for rapid shifts (Akshoomoff and Courchesne, 1992, 1994; Ravizza and Ivry, 2001), suggest the cerebellum mediates cognitive flexibility. Ravizza and Ivry (2001) noted significant improvement in task performance when motor demands were reduced, particularly for rapid attention shifts, though still not matching that of the controls. The explanation put forward was that there was interaction between the demands of rapid motor responses and cognitive requirements. This fits well with the absence of impairments in set shifting in the Wisconsin Card Sorting Test (which does not require rapid motor responses) in the majority of cerebellar disease subjects (Fehrenbach *et al.*, 1984; Schmahmann and Sherman, 1998), and in another study of shifting attention that used a task with lower

motor demands (Helmuth *et al.*, 1997). Furthermore, a functional MRI study (Bischoff-Grethe *et al.*, 2002) using the low motor demand version of Ravizza and colleagues' (2001) task did not find cerebellar activation beyond that seen in the focused attention task, whereas the higher motor demand version resulted in activations in the vermian lobule IV, HIV, and HVI. Another study (Le *et al.*, 1998) found activation in Crus I in the latter paradigm, which matches our finding.

## Memory

The association of delayed recall of words, but not recognition, with cerebellar volumes implies the cerebellum participates in the spontaneous retrieval of learned information. Our results agree in part with PET and functional MRI studies in healthy subjects that suggest activation in the left lateral posterior cerebellum during free or cued recall, or recognition, of words, faces or autobiographical information (Desmond and Fiez, 1998). The absence of associations for recognition may be due to a conservative approach to variable selection. It is also possible cerebellar dysfunction can be compensated for by cortical regions during the less effortful recognition trial. One PET study (Cabeza *et al.*, 1997) found left cerebellar activation during recall of word pairs, beyond that during recognition and reading, which is not inconsistent with the anterior lobe association we found.

## Verbal learning

The association between verbal learning and the posterior lobe is supported by earlier work positing a role for the cerebellum in learning during verb generation tasks with repeated trials using the same set of nouns. One patient with a right cerebellar infarct did not show a significant reduction in reaction time for verb generation with practice, unlike controls (Fiez *et al.*, 1992). In another study, the right cerebellar activations associated with a verb generation task decreased with practice in normal subjects (Raichle *et al.*, 1994).

## Perceptual organization

The Hooper test, which involves mental rotation, spatial attention, object identification, and name retrieval, did not differ in scores between cases and controls, and had no associations with cerebellar volumes. This conflicts with studies of spatial manipulation and spatial attention in cerebellar disease subjects (Fehrenbach *et al.*, 1984; Wallesch and Horn, 1990; Townsend *et al.*, 1999; Levisohn *et al.*, 2000). A few of these show impairments in 3D tasks including mental folding and rotation (Fehrenbach *et al.*, 1984; Wallesch and Horn, 1990), which are more difficult than the 2D Hooper test, which appears to have ceiling effects. Moreover, it has been suggested that in Friedrich's ataxia impairment may arise, in part, from lack of training in adolescence due to motor/somatosensory handicaps (Fehrenbach *et al.*, 1984). Also, slowed orientation of spatial attention has been observed in subjects with cerebellar lesions (Townsend *et al.*, 1999). Since the Hooper test is not timed, it is insensitive to slowed orientation of spatial attention, unlike the Block Design Test that has been used to measure visuospatial function in patients with cerebellar disease (Levisohn *et al.*, 2000; Gottwald *et al.*, 2004).

## Visuomotor coordination

The associations with HVII B and HIX are in agreement with earlier work in patients that suggested involvement of the cerebellum in visuomotor coordination (Brown *et al.*, 1993). However, a functional MRI study has shown activation of Crus I, Crus II, HVIII, and the posterior lobe vermis, but not HVII B or HIX, during visuomotor tasks (Miall *et al.*, 2000). Our results also showed a paradoxical association between visuomotor coordination and posterior lobe vermis that might be attributed to a putative association between oculomotor function and posterior lobe vermis (Voogd *et al.*, 2012).

## Comments and caveats

The associations between motor and cognitive dysfunctions and cerebellar atrophy are largely in accord with findings from task-based functional MRI studies, but there are caveats. The SPLS approach can provide good predictive accuracy and variable selection in the presence of collinearity (Chun and Keleş, 2010; Acharjee *et al.*, 2013). However, sparse regression solutions on highly collinear regression problems can also produce arbitrary associations—and the bootstraps of the full SPLS models plus the variable selection (Supplementary Tables 1 and 2) showed disparity in the robustness of the associations. Thus replication of our findings will be important. As the preciseness of SPLS is in estimating the separate coefficients has not been examined, we emphasized the presence or absence of associations rather than their magnitudes—an approach that also made interpretations more robust by minimizing the influence of errors in the magnitudes of the coefficients (possibly arising due to unobserved variables). As the sample was not extremely large and correlations between volumes were strong, it is unlikely any statistical approach, including SPLS, could eliminate entirely the risk for variable selection errors arising from collinearity of cerebellar volumes. It is also possible the strong correlations among the motor and mixed test scores (Fig. 1) affected the accuracy of the discrete cerebellar associations, though the findings are still valid when considered collectively for the overall group of motor and mixed tests since the cognitive variables generally did not show strong correlations with other tests. The problem of collinearity also precluded separate consideration of left and right cerebellar hemispheres, and we acknowledge the evidence for lateralization of

function (Buckner, 2013). Another issue is that paradoxical inverse associations are probably statistical artefacts and, in principle, variable selection approaches that provide non-negative coefficients could yield more biologically plausible solutions. However, to our knowledge, such variable selection methods do not exist. Using residuals as proxies of unobserved neuropsychological domains can lead to interpretation error when one or more of the tests has a low ceiling (such as RAVLT V adjusted for RAVLT I) owing to non-linear relationships. Future work should utilize tests that directly tap each neuropsychological domain of interest. It is also to be noted that our sample included some subjects with concurrent neurological or psychiatric conditions, because they did not appear to have motor or cognitive manifestations. However, secondary analyses excluding subjects with a history of skull fracture or concussion yielded results largely similar to the findings we have reported. We acknowledge that the relatedness of some subjects to one another, and the unequal representation of cerebellar disease types in our sample, potentially affected the results. However, this was an exploratory design, the inclusion of different types of cerebellar disease was a significant strength (as noted earlier), and the sample was not large enough for clustering methods. Finally, while we have emphasized the lobular organization of the cerebellum, the mediolateral organization is also important with respect to functional specification (Timmann *et al.*, 2010; Diedrichsen and Zotow, 2015). Therefore, more specific anatomical associates of clinical dysfunctions may be discovered if future analyses are not constrained by lobular demarcations while examining correlations.

# Conclusions

In summary, we report a detailed cerebellar mapping of cognitive and motor dysfunctions in cerebellar disease. The main findings were associations of the anterior lobe with motor tasks, and measures of immediate and delayed recall, and associations of posterior lobules with verb and phonemic fluency, working memory, immediate and delayed recall, and with motor tasks.

These observations are approximately in agreement with several studies and inform some of the existing proposals regarding cerebellar contributions to cognition. For example, our findings suggest that frontal lobe neurons involved in designing phonological search strategies and representing actions receive inputs from the cerebellum. We also provide evidence for greater involvement of the cerebellum when immediate recall tasks involve more complex verbal stimuli (e.g. longer words versus digits), although this finding contradicts some earlier work and requires replication. With respect to long-term memory, we propose that free recall of learned information employs the cerebellum to a greater degree than does recognition recall.

We provide a structural validation, in disease subjects, of a functional topography of the cerebellum defined on the basis of functional MRI data from healthy subjects. One of the key goals of MRI-behaviour studies is to find cause-and-effect relationships between brain regions and behaviour, for which demonstration of associations between loss of functions and anatomic defects is valuable. In this sense, this study is important as it provides the first detailed examination of the correlations of clinical dysfunctions with cerebellar atrophy. The findings will provide a preliminary anatomical background for studies seeking the mechanisms by which cognitive and motor dysfunctions arise from cerebellar degeneration. Future research should seek to replicate the findings, use experimental tasks to probe the integrity of specific functions in cerebellar disease, and use new imaging methods to quantitatively describe distributions of cerebellar atrophy. Our group has begun to study how changes in cerebellar shape relate to clinical profiles of dysfunction, an approach that frees analyses from the constraints of lobular boundaries and takes into account differing degrees of atrophy across the cerebellum.

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# Supplementary material

Supplementary material is available at *Brain* online.

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