BRAIN COMMUNICATIONS

Cerebellar contributions to cognition in corticobasal syndrome and progressive supranuclear palsy

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Mounting evidence suggests an association between cerebellar atrophy and cognitive impairment in the main frontotemporal dementia syndromes. In contrast, whether cerebellar atrophy is present in the motor syndromes associated with frontotemporal lobar degeneration (corticobasal syndrome and progressive supranuclear palsy) and the extent of its contribution to their cognitive profile remain poorly understood. The current study aimed to comprehensively chart profiles of cognitive impairment in relation to cerebellar atrophy in 49 dementia patients (corticobasal syndrome = 33; progressive supranuclear palsy = 16) compared to 33 age-, sex- and education-matched healthy controls. Relative to controls, corticobasal syndrome and progressive supranuclear palsy patients demonstrated characteristic cognitive impairment, spanning the majority of cognitive domains including attention and processing speed, language, working memory, and executive function with relative preservation of verbal and nonverbal memory. Voxel-based morphometry analysis revealed largely overlapping patterns of cerebellar atrophy in corticobasal syndrome and progressive supranuclear palsy relative to controls, primarily involving bilateral Crus II extending into adjacent lobules VIIb and VIIIa. After controlling for overall cerebral atrophy and disease duration, exploratory voxel-wise general linear model analysis revealed distinct cerebellar subregions differentially implicated across cognitive domains in each patient group. In corticobasal syndrome, reduction in grey matter intensity in the left Crus I was significantly correlated with executive dysfunction. In progressive supranuclear palsy, integrity of the vermis and adjacent right lobules I–IV was significantly associated with language performance. These results are consistent with the well-established role of Crus I in executive functions and provide further supporting evidence for vermal involvement in cognitive processing. The current study presents the first detailed exploration of the role of cerebellar atrophy in cognitive deficits in corticobasal syndrome and progressive supranuclear palsy, offering insights into the cerebellum's contribution to cognitive processing even in neurodegenerative syndromes characterized by motor impairment.

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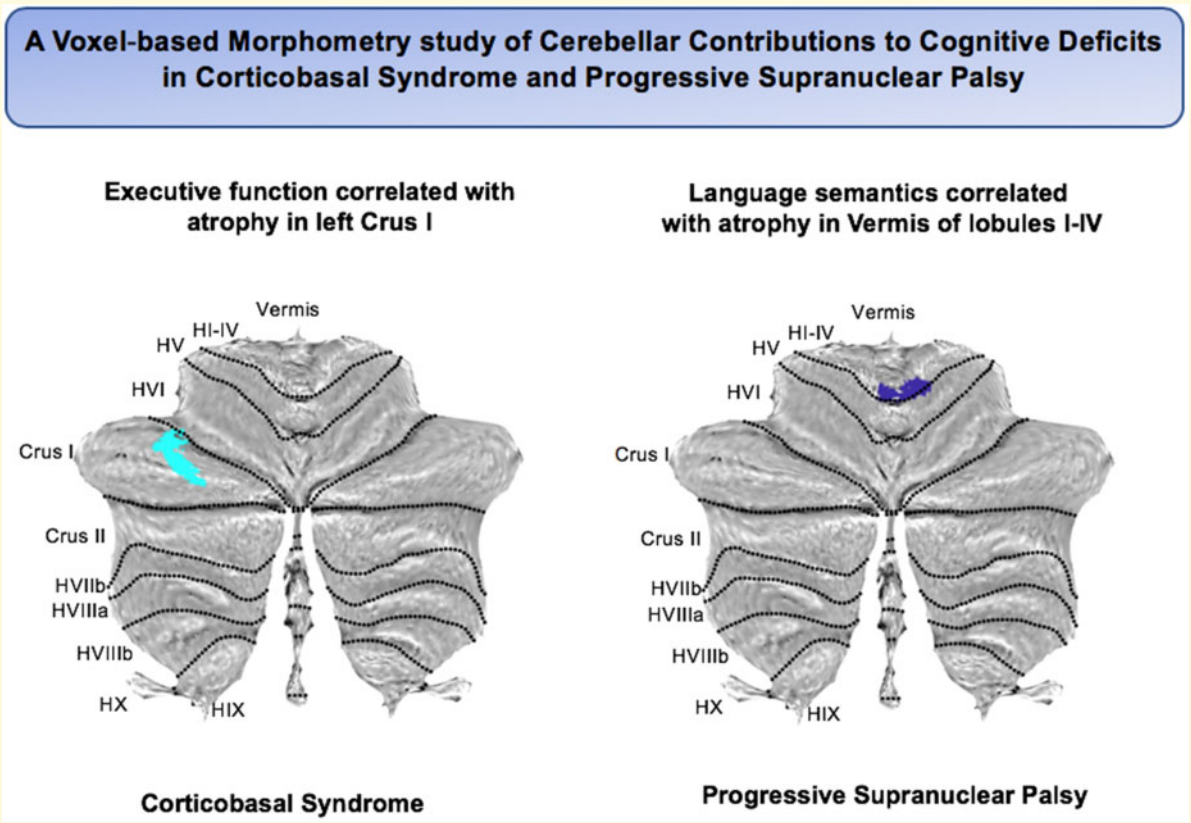
Abbreviations: ACE = Addenbrooke's Cognitive Examination; ACE-III = third edition of the Addenbrooke's Cognitive Examination; ACE-R = revised edition of the Addenbrooke's Cognitive Examination; bvFTD = behavioural-variant frontotemporal dementia; CBS = corticobasal syndrome; FAB = Frontal Assessment Battery; FAST = FMRIB Automatic Segmentation Tool; FRS = Frontotemporal Dementia Rating Scale; FSL = FMRIB Software Library; FTD = frontotemporal dementia; FTD-MND = frontotemporal dementia-motor neuron disease; Glm = general linear model; MNI152 = Montreal Neurological Institute standard space; PSP = progressive supranuclear palsy; RAVLT = Rey Auditory learning test; SYDBAT = Sydney Language Battery; TMT = Trail Making Test; VBM = voxel-based morphometry.

Graphical Abstract



Introduction

The cerebellum has traditionally been regarded as primarily responsible for the coordination and execution of movements (Holmes, 1939); however, mounting evidence reveals its contributions across multiple non-motor domains (see Stoodley and Schmahmann, 2009; Bostan *et al.*, 2013; Buckner, 2013; Van Overwalle *et al.*, 2014 for review). Clinical observations of patients with focal cerebellar lesions have revealed a constellation of cognitive, affective, and personality changes, demonstrating the functional relevance of the cerebellum beyond motor functions (Schmahmann and Sherman, 1998). In parallel, functional magnetic resonance imaging (MRI) and positron emission tomography studies in healthy individuals consistently report activation of the cerebellum during a range of cognitive tasks, including language, verbal working memory, visuospatial and executive function, as well as social cognition and emotional processing (Desmond and Fiez, 1998; Stoodley and Schmahmann, 2009, 2010; Keren-Happuch *et al.*, 2014; Van Overwalle *et al.*, 2014). Inhibitory protocols of repetitive transcranial magnetic stimulation or transcranial direct current stimulation to the cerebellum have been shown to disrupt procedural learning (Torriero *et al.*, 2004), language processing (Lesage *et al.*, 2012), mental flexibility (Arasanz *et al.*, 2012) and changes in response inhibition (Wynn *et al.*, 2019). Collectively, these studies provide converging evidence demonstrating the importance of the cerebellum across a broad array of cognitive and affective processes.

In clinical populations, the cerebellum has been found to be a site of degeneration in many neurodegenerative brain conditions. Meta-analyses of structural MRI studies have shown significant cerebellar grey matter volume loss in Alzheimer's disease (Gellersen *et al.*, 2017; Jacobs *et al.*, 2018), frontotemporal dementia (FTD; Gellersen

et al., 2017; Chen *et al.*, 2019), multiple system atrophy (both cerebellar and parkinsonian subtypes; Gellersen *et al.*, 2017) and progressive supranuclear palsy (PSP; Gellersen *et al.*, 2017; Pan *et al.*, 2017). Despite compelling evidence of cerebellar changes across neurodegenerative disorders, few studies to date have examined the impact of cerebellar atrophy on cognitive function. Cerebellar grey matter reduction has been associated with different profiles of cognitive dysfunction in variants of FTD. Specifically, Chen *et al.* (2018) reported significant association with attention and processing speed, and working memory in behavioural-variant FTD (bvFTD); visuospatial deficit in semantic dementia; and motor aspects of language function in progressive non-fluent aphasia. In a mixed sample of patients with bvFTD and FTD-motor neuron disease (FTD-MND), cerebellar atrophy was significantly associated with decline in memory, language, executive (including working memory) and visuospatial functions (Tan *et al.*, 2015). Importantly, these associations persisted even after controlling for global cerebral atrophy (Chen *et al.*, 2018) or intracranial volume (Tan *et al.*, 2015), indicating an independent role for the cerebellum in the emergence of cognitive deficits in frontotemporal lobar degeneration syndromes.

In contrast, little attention has been given to understanding the nature and impact of cerebellar changes in other clinical syndromes of frontotemporal lobar degeneration, such as PSP and corticobasal syndrome (CBS; MacKenzie *et al.*, 2010; Irwin *et al.*, 2015), despite their prominent motor features. PSP is characterized by early onset of vertical gaze palsy and postural instability (Litvan *et al.*, 1996*a*,*b*), whereas motor deficits including limb rigidity, dystonia, myoclonus, alien limb, parkinsonism and apraxia are observed in CBS (Armstrong *et al.*, 2013). Moreover, it is increasingly appreciated that cognitive dysfunction in the form of executive and language dysfunctions are important features in both CBS and PSP, leading to a revision of the diagnostic criteria (Armstrong *et al.*, 2013; Höglinger *et al.*, 2017).

Studies investigating the neural substrates of cognitive changes in CBS and PSP remain scant, with a focus, to date, on cortical (frontal, parietal, temporal and/or occipital cortex; Cordato *et al.*, 2002, 2005; Josephs *et al.*, 2011) and subcortical (amygdala, thalamus and basal ganglia; Cordato *et al.*, 2002, 2005; or caudate and putamen; Josephs *et al.*, 2011) structures. In PSP, frontal grey matter atrophy (Cordato *et al.*, 2002, 2005), and more specifically, bilateral posterior lateral frontal cortex (Josephs *et al.*, 2011) have been significantly associated with total score on the Frontal Behavioural Inventory, a career-based questionnaire measuring behavioural disturbances. Other significant associations have been identified between letter fluency performance, a measure of executive function, and middle frontal gyrus integrity, bilaterally (Lagarde *et al.*, 2013).

While these frontal correlates of behavioural and executive function are not unexpected, specific cerebellar contributions to cognition remain unclear. Inconsistent findings have been reported in the few studies that have included the cerebellum in their analyses. In CBS, right cerebellar atrophy, together with bilateral frontal and parietal atrophy, were significantly associated with confrontation naming (Grossman *et al.*, 2004). This finding, however, was not replicated in subsequent studies with only frontal and parietal atrophy revealed to be significantly correlated with performance on coherent communication using a spoken narrative task (Gross *et al.*, 2010) and executive functions measured by standardized tests of letter fluency and mental flexibility (Huey *et al.*, 2009). Studies in PSP are similarly characterized by contradictory findings. For example, Giordano *et al.* (2013) reported a significant contribution of cerebellar and frontal atrophy to performance on a screening measure of executive function [the Frontal Assessment Battery (FAB)] and letter fluency in PSP. In contrast, Piattella *et al.* (2015) found no significant association between cerebellar atrophy and FAB results. A longitudinal study of brain atrophy rates in PSP also failed to show an independent contribution of cerebellar atrophy to decline in executive function performance at follow up (Paviour *et al.*, 2006).

Existing studies have tended to use brief questionnaires or screening tools such as the Frontal Behavioural Inventory (Cordato *et al.*, 2002, 2005; Josephs *et al.* 2011), FAB (Piattella *et al.*, 2015) or the Mini Mental State Examination (Cordato *et al.*, 2002, 2005), which are unlikely to be sensitive enough to detect the full extent and nature of cognitive impairment in these syndromes. As such, we are left with an incomplete picture of cerebellar involvement in many cognitive domains relevant to CBS and PSP, particularly, language (Paviour *et al.*, 2006; Giordano *et al.*, 2013; Piattella *et al.*, 2015) and executive functions (Grossman *et al.*, 2004; Gross *et al.*, 2010), also limiting possible comparisons across studies.

The objectives of this study were therefore to (i) comprehensively chart the profile of cognitive deficits in well-characterized cases of CBS and PSP using sensitive neuropsychological measures across a wide range of cognitive domains; (ii) to establish the pattern of grey matter volume reduction in the cerebellum using voxel-based morphometry (VBM) analysis and (iii) to explore the associations between cerebellar atrophy and neuropsychological performance after controlling for global cerebral atrophy and disease duration to establish the unique and independent contribution of cerebellar atrophy to cognitive functioning in CBS and PSP.

Materials and methods

Participants

Forty-one individuals diagnosed with CBS ($n = 33$) or PSP ($n = 16$) were recruited from FRONTIER, the

research clinic specializing in younger-onset dementias at the Brain and Mind Centre, the University of Sydney, Australia. All patients received a comprehensive neuropsychological assessment, a medical and neurological examination, clinical interviews, and a structural brain MRI. Diagnosis was based on clinical presentations and determined by multidisciplinary consensus by a neurologist and neuropsychologist in accordance with the current clinical diagnostic criteria (Litvan *et al.*, 1996*a*,*b*; Armstrong *et al.*, 2013; Höglinger *et al.*, 2017). Thirty-three age-, sex- and education-matched healthy participants were included as controls. All controls scored above the cut-off for normal range (>88/100) on either the revised (ACE-R; Mioshi *et al.*, 2006) or third (ACE-III; Hsieh *et al.*, 2013) edition of the Addenbrooke's Cognitive Examination (ACE), ensuring the absence of significant cognitive impairment. Exclusion criteria for both patients and controls included the presence of other dementia, and/or neurological or psychiatric disorders. This study was approved by the South Eastern Sydney Local Health District and the University of New South Wales ethics committees. All the participants or their person responsible provided written, informed consent in accordance with the Declaration of Helsinki.

Neuropsychological assessment

Neuropsychological assessment was conducted within six months of the MRI acquisition. All participants completed either the ACE-R (prior to September 2014) or the ACE-III, a general cognitive screen comprising a total score as well as scores for the attention, memory, fluency, language and visuospatial subdomains. While both editions have minimal differences, for comparability, all ACE-R total and subdomain scores were transformed into their equivalent ACE-III scores as per published protocol (So *et al.*, 2018). Additional cognitive measures of attention and processing speed [Part A time of the Trail Making Test (TMT; Tombaugh, 2004); and Maximum Forward Digit Span (Wechsler, 1997)], working memory (Maximum Backward Digit Span; Wechsler, 1997), language-motor [Repetition of Sydney Language Battery (SYDBAT; Savage *et al.*, 2013)], language-semantics (Naming and Comprehension of SYDBAT; Savage *et al.*, 2013), verbal memory (Rey Auditory learning test delayed recall percent retention; RAVLT; Rey, 1941), nonverbal memory (Rey Complex Figure recall percent retention; Meyers and Meyers, 1995), and executive functions [Category A and B errors on Hayling Sentence Completion Test (Burgess and Shallice, 1997); Part B time – Part A time of TMT (Tombaugh, 2004); and FAS Letter Fluency test (Controlled oral Word Association Test; Tombaugh *et al.*, 1999)] were also administered. Disease severity was measured using the Frontotemporal Dementia Rating Scale (FRS; Mioshi *et al.*, 2010).

To compare performance across measures, all raw scores were converted into z-scores using Controls' testing results. In order to reduce Type 1 error, only cognitive domains that are characteristic of CBS and PSP, namely, language and executive functions were included in subsequent correlational analysis (Burrell *et al.*, 2014; Höglinger *et al.*, 2017). Therefore, the scores of interest were as follows: z-score of Single-word repetition on the SYDBAT (language-motor), a language-semantics composite derived from averaging the z-scores for naming and comprehension of the SYDBAT, and an executive function composite from averaging the z-scores for the Hayling Sentence Completion Test (Category A and B errors), TMT (Part B time – A time), and FAS Letter Fluency test.

Statistical analyses

Data were analysed using SPSS Statistics, version 24.0 (IBM, Armonk, NY). Demographic variables (i.e. age, education and ACE total score) and neuropsychological performance were compared across groups (CBS, PSP and Controls) using 1-way analysis of variance (ANOVA) followed by Sidak post hoc tests. The assumptions of normality and homogeneity of variances were checked using Shapiro–Wilk test and Levene's test, respectively. In light of the robustness of ANOVA *F*-tests to violation of normality and better control of Type I error over its non-parametric equivalence Kruskal–Wallis test (Blanca *et al.*, 2017; Schmider *et al.*, 2010), *F*-test results were reported. In the case of heterogeneity of variance which is known to have a greater impact on the robustness of *F*-test (Blanca *et al.*, 2017), Welch's *F* was used and followed by Games–Howell post hoc tests (Field, 2013). Categorical variables (i.e. sex) were analysed using chi-squared tests. Other demographic variables specific to patient groups (i.e. disease duration and FRS) were analysed using independent sample *t*-tests (equal variances assumed), as no assumption was violated. The statistical significance level was set at $P < 0.05$ for all analyses unless otherwise specified.

Imaging

Brain imaging acquisition

All participants underwent a whole-brain structural MRI with a 3 T Phillips scanner, fitted with a standard 8-channel head coil using a 3D fast field echo sequence. High resolution T1-weighted image series were acquired using the following protocol: matrix size = 256 × 256, 200 slices, 1mm^2 in-plane resolution, slice thickness = 1 mm, echo time = 2.6 ms, repetition time = 5.8 ms, flip angle = 8°, duration = 5 min and 53 s. Prior to 2014, two T1 scans were routinely acquired. From 2014, to reduce scanning duration, the second T1 sequence was not acquired unless the first acquisition was degraded by movement artefacts. All other parameters remained the same. As a result, 26 of the final 33 CBS and 8 of the 16 PSP participants underwent two T1 scans. For these

cases, only the best sequence was used in the neuroimaging analyses (see below for more details on scan quality control).

Scan quality control. Images were first visually inspected for the presence of any imaging artefacts during image acquisition (e.g. head movements) by the radiographer. The scans were then reviewed by two trained raters who determined the quality of the T1 images according to a standard set of criteria. Each scan was assigned a score of 0 (i.e. images with little to no artefacts with clear distinction of white and grey matter), 1 (i.e. images with mild movement artefact across fewer than 50 slices of the 200 slices and distinct white and grey matter) or 2 (i.e. images with major movement artefact, including mild movements throughout the entire scan and sections of white or grey matter could not be distinguished). Only scans with a rating of 0 or 1 were included for further analyses; as a result, 3 CBS and 1 PSP participants were excluded from the current study due to substantial head movement during scan (i.e. a rating of 2). The final set of 33 CBS, 16 PSP and 33 Control scans were then visually inspected by two investigators (N.Y.T. and Y.C.) to confirm that they were of sufficient quality prior to pre-processing in FSL.

Voxel-based morphometry analysis and clinico-radiological correlations

Pre-processing. Voxel-based morphometry (VBM) analysis was conducted on the T1-weighted images using the FMRIB Software Library (FSL) package, version 6.0.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). In the first instance, brain extraction was conducted using the BET algorithm in FSL (Smith, 2002). Each extracted image was visually checked to ensure that no brain matter was excluded and no non-brain matter (e.g. dura mater, skull) was included. Brain extracted images were then segmented into cerebrospinal fluid, grey matter and white matter using the FMRIB Automatic Segmentation Tool (FAST; Zhang *et al.*, 2001). Next, the grey matter partial volumes were non-linearly registered to the Montreal Neurological Institute standard space (MNI152) using FNIRT with a b-spline representation of the registration warp field (Andersson et al., 2007; Kansal *et al.*, 2017; Chen *et al.*, 2018). An equal number of the registered grey matter images from each group (a total of 48 scans) was used to create a grey matter template specific to this study with nonlinear (nonaffine) registration to minimize potential bias towards any single group's topography (Chen *et al.*, 2018). Each voxel of each registered grey matter image was divided by the Jacobian of the warp field to correct for any contraction/enlargement caused by the non-linear component of the transformation. Smoothing of the segmented and modulated normalized grey matter images were then conducted using a Gaussian kernel of 3 mm.

Analysis. Whole brain VBM analyses were carried out to identify whole brain grey matter intensity differences between each patient group and Controls (i.e. PSP versus controls; CBS versus controls) and to determine the pattern of cerebral atrophy specific to each patient group. Next, binary masks of the significant clusters of cerebral atrophy were created to extract mean intensity values for each patient individually, which were used in subsequent covariate analyses. Following this, in order to compare cerebellar grey matter intensity between patients and Controls, a mask of the cerebellum was created using the Cerebellar Atlas in MNI152 space after normalization with FNIRT, and used in all subsequent covariate analyses to restrict the number of voxels included in the general linear model (GLM) analyses to the cerebellum only.

Comparison of cerebellar grey matter volume between groups was conducted with a voxel-wise GLM. Permutation-based non-parametric testing with 5000 permutations was applied using the voxel-wise method. First, correlations between the intensity of cerebellar grey matter and performance on cognitive domains specific to CBS and PSP including language and executive function, were examined using covariate analyses within each patient group. The language-motor z-scores (Repetition on SYDBAT) and the language-semantics and executive function composite scores were entered as covariates in three separate GLMs. To determine the independent role of cerebellar atrophy in cognition accounting for the effect of cerebral atrophy, subject-level mean intensity values from the significant clusters of cerebral atrophy identified on the group-level whole brain VBM analysis were added as a covariate in the models (Chen *et al.*, 2018). To control for the possible effect of motor impairment on cognitive performance, disease duration, a proxy measure of the severity of motor deficits, was also included as a covariate. Due to the exploratory nature of the study, all analyses were uncorrected for multiple comparisons, however, significance was set at a conservative level of $P < 0.001$ with a cluster extent threshold of 50 contiguous voxels.

Additional exploratory analyses were conducted to examine the potential contribution of related cognitive and demographic variables to cerebellar integrity and cognitive skills. Firstly, all three cognitive variables (language-motor z-scores, and language-semantics and executive function composite scores) were included simultaneously in one combined GLM model within the CBS and PSP group separately. Subsequently, additional demographic variables including age, sex and education years, as well as disease severity (as measured by FRS scores) were included as additional covariates, in addition to the three cognitive variables. A more liberal threshold at $P < 0.01$ (uncorrected) with a cluster threshold of 80 contiguous voxels was used to compensate for the high number of additional covariate variables and their effect on statistical power.

Table 1 Demographic characteristics of study participants

	Controls ($n = 33$)	CBS ($n = 33$)	PSP ($n = 16$)	Test-statistic	*P*	*Post hoc*
Sex (M/F)	14/19	13/20	9/7	1.292[a]	0.524	
Age (years)	66.9 ± 6.5	65.6 ± 7.0	68.2 ± 4.2	0.946[b]	0.392	
Education (years)	12.8 ± 2.2	11.6 ± 3.1	11.8 ± 2.7	1.905[b]	0.156	
Disease duration (months)		49.1 ± 20.5	44.3 ± 37.4	0.577[c]	0.567	
ACE total (/100)	96.0 ± 3.0	70.1 ± 20.8	72.0 ± 8.6	79.879[d]	<0.001	Control> Patients
FRS (Rasch)		0.3 ± 1.6	0.6 ± 2.0	0.574[c]	0.569	

Means ± standard deviation.
[a]Chi-square value.
[b]One-way ANOVA *F* value.
[c]Independent sample *t*-test value.
[d]Welch's *F* value.
ACE = Addenbrooke's Cognitive Examination; CBS = Corticobasal syndrome; FRS = Frontotemporal Dementia Rating Scale; PSP = Progressive supranuclear palsy.

Imaging results were overlaid on surface-based cerebellar flatmaps provided by the SUIT toolbox based on MATLAB, version R2019b (au.mathworks.com/products/matlab.html) and SPM 12 (www.fil.ion.ucl.ac.uk/spm).

Data availability

The data that support the findings of this study are available from the corresponding author on request.

Results

Demographic Characteristics and Neuropsychological Performance

As shown in Table 1, no significant group differences were found in education level, age, or sex distribution across all groups. Patient groups were not found to differ in disease duration or disease severity (all *P*-values > 0.05).

Compared with Controls, both CBS and PSP demonstrated significantly poorer performance on the ACE screening tool across all subdomains (all *P*-values <0.05; Table 2). Further impairments were found in both patient groups compared to Controls across the majority of cognitive domains tested including the attention and processing speed composite ($P < 0.001$) that comprised of Forward Digit Span (CBS, $P < 0.001$; PSP, $P = 0.001$) and TMT-A ($P < 0.001$ for both patient groups); working memory (Backward Digit Span, $P < 0.001$ for both patient groups); and motor aspect of language function [SYDBAT-Repetition, (CBS, $P = 0.003$; PSP, $P = 0.036$)]. While only the CBS group demonstrated a significantly lower language-semantics composite than Controls ($P < 0.001$), both patient groups demonstrated significantly poorer naming compared to Controls (SYDBAT-Naming; CBS, $P < 0.001$; PSP, $P = 0.04$), nonetheless, semantic knowledge (SYDBAT-Comprehension) was only found to be impaired in CBS group ($P < 0.001$). While a significantly lower executive function composite (CBS, $P < 0.001$; PSP, $P = 0.012$) and impairments in mental flexibility (TMT-B-A; CBS, $P = 0.004$; PSP, $P = 0.006$) and letter fluency (FAS letter fluency; $P = < 0.001$ for both groups) were identified in both patient groups relative to Controls, additional circumscribed deficits were only observed in PSP for verbal inhibition (Hayling A + B Errors, $p = 0.011$). No significant differences were found between patient groups and Controls across verbal (RAVLT retention) and non-verbal memory (RCF retention).

Direct comparison of the patient groups further revealed disproportionate deficits in ACE fluency subscale ($P = 0.012$) and executive functions (TMT-B-A, $P = 0.015$ and FAS Fluency, $P = 0.010$) in PSP relative to CBS. No other significant differences were evident between the patient groups (all *P*-values > 0.05).

This pattern of cognitive deficits in attention and processing speed, language and executive function (including fluency and working memory) with relative preservation of verbal and non-verbal memory is consistent with the cognitive profile commonly described in CBS and PSP (Burrell *et al.*, 2014). Further, the significantly poorer fluency and executive function performance in PSP relative to CBS confirmed the prominent executive deficits in PSP previously reported (Litvan *et al.*, 1996*b*; Burrell *et al.*, 2014; Höglinger *et al.*, 2017).

VBM results

Widespread cortical grey matter intensity reduction that are largely consistent with previous reports in the literature was found in both CBS (Whitwell *et al.*, 2010; Burrell *et al.*, 2014) and PSP (Burrell *et al.*, 2014) patient groups when compared to Controls separately (see Supplementary Table 1 and Supplementary Fig. 1).

VBM analyses on the cerebellum grey matter integrity was carried out separately in each patient group against Controls. The CBS group demonstrated significant reduction in grey matter density predominantly in Crus II extending into lobules VIIb and VIIIa, bilaterally, as well as the lateral left Crus I, parts of the vermis and adjacent right lobules V and VI, and lateral right lobule VI (Fig. 1, Table 3). In the PSP group, significant reduction in grey matter density was predominantly found in Crus

Table 2 Neuropsychological test performance in CBS and PSP patients and healthy Controls

Function	Control ($n = 33$)	CBS ($n = 33$)	PSP ($n = 16$)	*F*	*P*	*Post hoc*
ACE						
Attention	17.7 (0.8)	14.7(4.1)	15.2(2.3)	16.316[a]	<0.001	Control>Patients
Memory	24.7 (1.6)	18.7(6.7)	20.9(3.3)	20.221[a]	<0.001	Control>Patients
Fluency	12.5(1.6)	5.6(3.9)	3.0(2.0)	154.106[a]	<0.001	Control>Patients CBS >PSP
Language	25.5(0.8)	20.3(5.1)	20.8(3.7)	28.706[a]	<0.001	Control>Patients
Visuospatial	15.6(0.7)	10.8(4.4)	12.0(2.5)	31.431[a]	<0.001	Control>Patients
Attention and Processing Speed Composite[b]	0.0004(.9)	−3.1(3.6)	−3.7(2.5)	24.875[a]	<0.001	Control>Patients
Forward Digit Span	7.1 (1.2)	5.6(1.6)	5.5(1.1)	12.003	<0.001	Control>Patients
TMT-A (s)	31.3(9.5)	83.5(48.8)	111.8(35.9)	33.751	<0.001	Patients>Control
Working memory						
Backward Digit Span	5.3(1.1)	3.6(1.4)	3.2(0.9)	22.736	<0.001	Control>Patients
Language–Motor						
SYDBAT- Repetition	29.9(0.4)	26.1(5.8)	24.4(6.3)	10.677[a]	0.001	Control>Patients
Language-Semantics Composite[c]	0.002(0.9)	−3.21(2.9)	−2.38(3.1)	20.986[a]	<0.001	Control >CBS
SYDBAT-Naming	27.4(1.9)	20.9(6.0)	22.6(5.8)	19.226[a]	<0.001	Control>Patients
SYDBAT- Comprehension	29.2(1.3)	25.4(4.2)	26.4(4.1)	14.054[a]	<0.001	Control>CBS
Executive Function Composite[d]	−0.0002(.7)	−2.0(1.4)	−5.4(5.0)	28.517[a]	<0.001	Control>Patients
TMT-B-A (s)	37.1(15.2)	99.7(55.7)	253.4(75.3)	26.024[a]	<0.001	Patients>Control PSP>CBS
Hayling A + B errors	2.1(2.8)	3.1(2.3)	5.4(2.8)	4.662	0.013	PSP>Control
FAS Letter Fluency	47.9(11.9)	21.4(11.9)	12(4.6)	99.663[a]	<0.001	Control>Patients CBS>PSP
Non-verbal memory						
RCF 3-min Retention (%)	50.1(15.0)	64.7(61.4)	46.6(23.8)	1.183	0.314	–
Verbal memory						
RAVLT 30-min Retention (%)	83.6(17.8)	80.6(20.3)	69.7(33.2)	1.40	0.255	–

*Values are means (standard deviation) based on raw scores except for composite scores.
[a]Welch's *F* value.
[b]Attention and Processing Speed Composite comprised of averaged z-scores on the Forward Digit Span and Trail Making Test (Part A time).
[c]Language semantics composite comprised of averaged z-scores on the naming and comprehension scores of the Sydney Language Battery.
[d]Executive function composite comprised of averaged z-scores on the Hayling Sentence Completion Test (Category A and B errors), Trail Making Test (Part B time – A time), and FAS Letter Fluency test.
ACE = Addenbrooke's Cognitive Examination; CBS = Corticobasal syndrome; PSP = Progressive supranuclear palsy; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; SYDBAT = Sydney Language Battery; TMT = Trail Making Test.

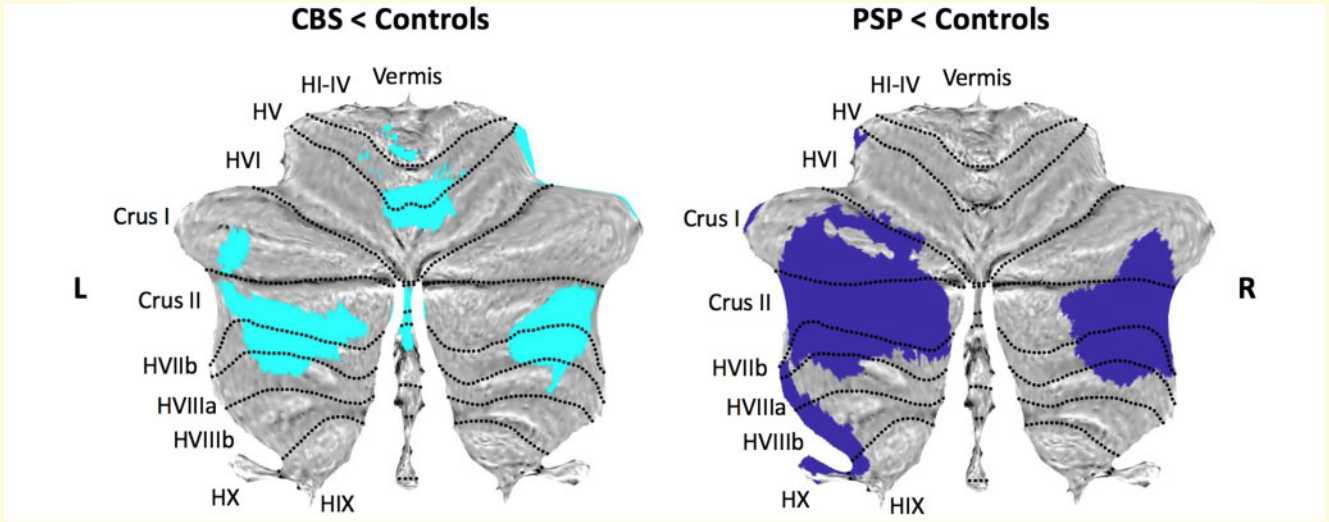


Figure 1 Pattern of cerebellar atrophy in CBS and PSP. Voxel-based morphometry analyses showing significant grey matter intensity reduction in the cerebellum in CBS (left panel, light blue) and PSP (right panel, purple) compared with Controls at the threshold of $P < 0.001$ (uncorrected) with a cluster threshold of 50 contiguous voxels. Figures were generated on surface-based flatmaps provided by the SUIT toolbox. CBS = Corticobasal syndrome; H = hemispheric lobule; L = left; PSP = Progressive supranuclear palsy; R = right.

Table 3 Voxel-based morphometry results of significant cerebellar grey matter intensity reduction in patient groups relative to controls

Contrast	Cluster size, voxels	MNI coordinates			Hemisphere	Regions
		X	Y	Z		
CBS < controls	1092	−32	−66	−62	Left	Crus II extending into lobules VIIb and VIIIa
	650	40	−66	−60	Right	Crus II extending into lobules VIIb and VIIIa
	293	8	−62	−26	Right Vermis	The vermis and adjacent right lobules V and VI
	75	34	−38	−40	Right	Lateral lobules VI
	54	−44	−60	−38	Left	Crus I
PSP < controls	2731	−34	−72	−58	Left	Crus II extending into Crus I, lobules VIIb and VIIIa
	1484	36	−64	−62	Right	Crus II extending into Crus I, lobules VIIb and VIIIa
	175	−16	−40	−52	Left	Lateral lobules VIIIb, X, IX

Significant cerebellar grey matter intensity reduction in CBS and PSP compared to Controls voxelwise at the threshold of $P < 0.001$ (uncorrected) with a cluster threshold of 50 contiguous voxels.
CBS = Corticobasal syndrome; MNI = Montreal Neurological Institute; PSP = Progressive supranuclear palsy.

II extending into Crus I, lobules VIIb and VIIIa bilaterally with smaller clusters identified in lateral left lobules VIIIb, X and IX. Direct comparisons between the two clinical groups revealed no significant difference in cerebellar grey matter integrity.

Neural correlates of neuropsychological performance

Correlation between cerebellar atrophy and neuropsychological performance

Three separate GLMs were run within each patient group to explore associations between cerebellar grey matter integrity and cognitive deficits characteristic of CBS and PSP in terms of language and executive functions, controlling for global cerebral atrophy and disease duration (Fig. 2, Table 4). In CBS, significant correlations were found between the executive function composite score and left Crus I. In PSP, significant correlations emerged between the vermis of lobules I-IV and the language-semantics composite score. No other significant correlation was identified within each patient group. Unthresholded results are freely available via the following link: https://identifiers.org/neurovault.collection : 8616.

When all three cognitive domains were included simultaneously in the same GLM model, the findings of significant association with executive function and language semantics composite scores in CBS and PSP did not survive the original threshold of $P < 0.001$ with a cluster threshold of 50 contiguous voxels. Nonetheless, a smaller cluster (47 voxels) replicating the originally identified region in Crus I emerged again in the CBS group (slightly below the threshold of 50 voxels; see Supplementary Fig. 2 and Supplementary Table 2). More importantly, when demographic (age, sex and education years) and clinical (disease severity) variables were further included as additional covariate variables in addition to the three cognitive variables, using a more lenient threshold of $P < 0.01$ with a cluster extent threshold of 80 contiguous voxels, the regions implicated in executive and language semantic function continued to emerge. Specifically, left Crus I and adjacent lobule VI were found to be significantly associated with executive function performance in CBS group, whereas vermis of the lobules I-IV and adjacent right lobules I–IV were implicated in language semantics performance in the PSP group (see Supplementary Fig. 3 and Supplementary Table 3). Despite the use of a lower threshold, the commonalities in the regions implicated between the original and additional exploratory findings suggest that the additional demographic, clinical and cognitive variables did not alter the overall pattern of findings.

Discussion

Despite the well-documented changes in motor function in the neurodegenerative syndromes of CBS and PSP, studies exploring the integrity of the cerebellum in these disorders are surprisingly scant. Moreover, it remains largely unknown whether cerebellar atrophy might relate to the well-documented cognitive dysfunctions displayed by these patients given the growing evidence of cerebellar involvement in cognitive impairments in many other neurodegenerative brain syndromes. Using a series of targeted neuropsychological tasks in combination with voxel-based morphometry analyses, we present the first comprehensive exploration of the independent contribution of cerebellar atrophy to profiles of cognitive dysfunction in CBS and PSP, providing novel insights and further consolidation of the functional relevance of the cerebellum in cognitive processing in neurodegenerative syndromes characterized by motor impairments.

The most important finding arising from this study is the widespread cerebellar atrophy observed in the syndromes of CBS and PSP, compared to healthy Controls. Relatively consistent patterns of cerebellar atrophy

Table 4 Voxel-based morphometry results of significant cerebellar grey matter intensity reduction that correlates significantly with neuropsychological performance

Contrast	Function	Cluster size, voxels	MNI coordinates			Hemisphere	Regions
			X	Y	Z		
CBS	Executive function composite[a]	60	−40	−74	−22	Left	Crus I
PSP	Language semantics composite[b]	59	12	−48	−10	Vermis	Vermis of the lobules I–IV and adjacent areas in the right lobules I–IV

Cerebral atrophy and disease duration were included as nuisance variables in all contrasts. Results reported voxelwise at $P < 0.001$ (uncorrected) with a cluster extent threshold of 50 contiguous voxels.

[a]Executive Function Composite comprised of averaged z-scores on the Hayling Sentence Completion Test (Category A and B errors), Trail Making Test (Part B time – A time), and FAS Letter Fluency test.

[b]Language Semantics Composite comprised of averaged z-scores on the naming and comprehension scores of the Sydney Language Battery.

CBS = Corticobasal syndrome; MNI = Montreal Neurological Institute; PSP = progressive supranuclear palsy.

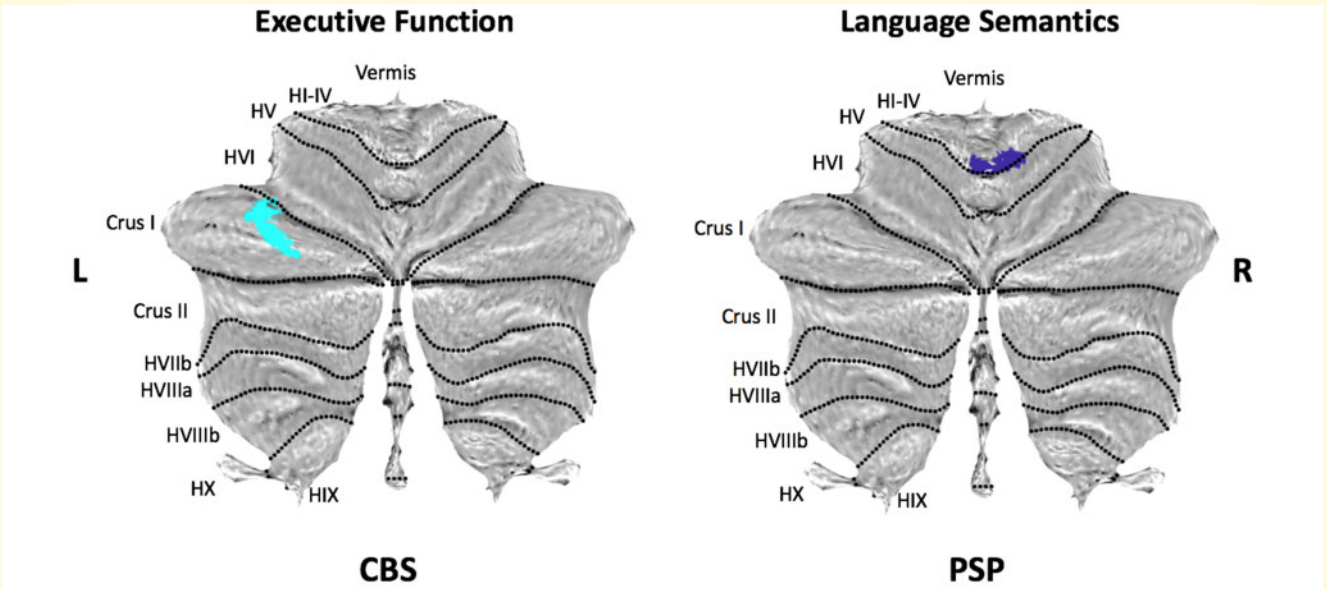


Figure 2 Correlation between cerebellar atrophy and neuropsychological performance. Cerebellar regions that were significantly correlated with neuropsychological performance, controlling for cerebral atrophy and disease duration, using voxel-based morphometry analyses. Clusters were extracted voxelwise using a threshold of $P < 0.001$ (uncorrected) with a cluster extent threshold of 50 contiguous voxels. CBS results displayed in light blue, PSP results displayed in purple. CBS = Corticobasal syndrome; H = hemispheric lobule; L = left; PSP = Progressive supranuclear palsy; R = right.

involving bilateral Crus II extending into adjacent lobules VIIb and VIIIa were present in both patient groups. Cerebellar atrophy in CBS and PSP has been largely overlooked with conflicting results. In PSP, different patterns of atrophy in the left anterior cerebellum (Pan *et al.*, 2017) and primarily left posterior cerebellum were reported in different meta-analyses of structural changes (Gellersen *et al.*, 2017). This posterior involvement, however, appeared to be a characteristic of frontotemporal lobar degeneration syndromes with primarily the Crus and lobule VI regions implicated in a meta-analysis of 53 neuroimaging studies of variants of frontotemporal dementia (FTD; Chen *et al.*, 2019). In CBS, a recent meta-analysis of the only 10 VBM studies available, reported no significant cerebellar atrophy when compared with healthy Controls (Albrecht *et al.*, 2017). This finding, however, may have been confounded by the heterogeneity of underlying pathologies in CBS (Parmera *et al.*, 2016). Specifically, cerebellar involvement appears more likely in the presence of pathological changes associated with frontotemporal lobar degeneration than with Alzheimer's disease (Lee *et al.*, 2011). Future investigations taking into consideration potential confounding effect of underlying pathology are needed to adequately capture cerebellar changes in PSP and CBS with different underlying pathological processes.

Exploring next the relationship between cerebellar atrophy and cognitive dysfunction, discrete patterns of association were evident in each patient group. Importantly, these associations were found to persist even after

controlling for overall level of cerebral atrophy and disease duration. In the CBS group, the executive dysfunction composite, comprising mental flexibility (the Trail Making test), verbal inhibitory control (the Hayling Sentence Completion test) and verbal fluency (the FAS Letter Fluency test), was found to associate with atrophy of the left Crus I. In contrast, the cerebellum was implicated in language-semantics in PSP patients. Specifically, the vermis of lobules I–IV and adjacent right lobules I–IV were found to be significantly associated with poorer language semantic composite.

Our finding of significant association between Crus I and executive function in CBS aligns with functional neuroimaging studies in healthy participants in which Crus I emerges as a consistent site of activation during executive function tasks (Stoodley, 2012; Keren-Happuch *et al.*, 2014) and has been implicated as part of the executive control network in resting state functional connectivity studies (Habas *et al.*, 2009; Stoodley, 2012). Activation of Crus I has been further shown to be unique to executive functioning, persisting when other cognitive contributions are partialled out (Stoodley and Schmahmann, 2009). This is unsurprising as the Crus I is well positioned to support higher order cognitive functions given its anatomical (Kelly and Strick, 2003; Buckner, 2013; Baumann *et al.*, 2015) and functional connections (O'Reilly *et al.*, 2010; Stoodley, 2012; Buckner, 2013) with the prefrontal cortex that are critical for executive functions.

Language deficits have previously been reported in PSP and these changes are of the same magnitude as those typically seen in progressive non-fluent aphasia, a subtype of FTD (Burrell et al., 2018 Snowden *et al.*, 2019; Murley *et al.*, 2020). In the current study, however, reduced semantic performance in the PSP group appeared to have been largely attributable to naming impairment as the only significant difference was found in the naming subtest of the language-semantics composite between PSP patients and Controls. While naming is typically associated with the integrity of the left temporal cortex, a study in Alzheimer's disease, which is characterized by early memory and naming difficulties (McKhann *et al.*, 2011), reported significant correlation between structural changes in a range of cerebellar regions including the vermis and language and attention performance, which, importantly, remained significant after controlling for the temporal lobe volume (Baldaçara *et al.*, 2012). This would be consistent with our finding of the vermal contribution to language function in PSP beyond the effect of global cortical atrophy. In addition, significant activation in the cerebellum, together with frontal, temporal and occipital regions, has been identified in a meta-analysis of functional MRI studies on object naming, even when controlling for speech production and perceptual processing, suggesting that the cerebellar contribution is independent of motor functions (Price *et al.*, 2005). The current findings also resonate well with a growing body of literature demonstrating vermal involvement in cognitive functions in neurodegenerative syndromes. Specifically, vermal atrophy has been implicated in language and memory function across patients with bvFTD and FTD-MND (Tan *et al.*, 2015), and working memory in bvFTD patients (Chen *et al.*, 2018). This vermal involvement in multi-domain cognitive processing is further supported by functional neuroimaging evidence of activation of the vermis during tasks of language, verbal working memory (Desmond and Fiez, 1998), and memory retrieval (Desmond and Fiez, 1998; Chen and Desmond, 2005) in healthy Controls.

Despite the well-established functional relevance of the cerebellum in cognitive functions, the exact mechanism underlying cerebellar contribution to cognitive processing remains largely unclear. Cerebellar-thalamo-cortical and basal ganglia-thalamo-cortical loops, as part of a cerebello-basal ganglia-thalamo-cortical system, are proposed to be essential for effective expression of both motor and non-motor functions including cognitive processing (Caligiore *et al.*, 2017). In other words, it is plausible that the cerebellum contributes to cognitive processing as part of large-scale neural networks subserving cognitive functions. This systems-level framework is supported by the observations of functional and resting state connectivity between the cerebellum and a wide range of cortical regions including the prefrontal and parietal (O'Reilly *et al.*, 2010; Bostan *et al.*, 2013), temporal cortex (O'Reilly *et al.*, 2010), as well as disease-specific pattern of cerebellar circuit disruption in association with interconnected cerebral atrophied regions in different clinical syndromes including Alzheimer's disease and FTD (Guo *et al.*, 2016). As such, degeneration of the left Crus I and/or vermis likely results in disruptions to the distributed cerebellar- cortical and subcortical circuitries, compromising their functional integrity and associated functions (Stoodley and Schmahmann, 2010). Further understanding of the precise cerebellar contributions to cognitive dysfunction in both CBS and PSP will require inclusion of measures of structural connectivity between the cerebellum and the cerebral cortex. This will provide essential convergent evidence regarding the role of the cerebellum in cognitive function from a systems-level view.

While the current study provides the first detailed examination of cerebellar involvement in cognition in CBS and PSP, a number of issues need to be considered. It may be argued that the significant associations between cerebellar atrophy and executive and language dysfunctions identified arose secondary to motor function deficits. The absence of associations between language motor function and cerebellar atrophy, however, suggests that cerebellar contribution to cognitive processing is unrelated to motor skills. This is further supported by clinical observations in patients with focal cerebellar lesions in whom, letter fluency impairments are demonstrated in the absence of significant motor deficits, and conversely, the

subset with the greatest motor deficits demonstrates the best letter fluency performance (Leggio *et al.*, 2000). Furthermore, cognitive deficits following cerebellar stroke has been shown to persist even after full recovery of motor function, suggesting long-term cognitive sequelae of cerebellar damage (Mariën *et al.*, 1996; Fabbro *et al.*, 2000). Nonetheless, future investigations using cognitive measures with minimal motor demands in conjunction with standardized measures of motor function will allow for direct validation of the current findings. Furthermore, future VBM investigations of the contribution of cerebellum to cognition in a large cohort of healthy individuals may also help in eliminating the confounding effect of motor impairment on cognitive performance and to validate findings in clinical populations.

Second, the reported imaging results were exploratory in nature and uncorrected for multiple comparisons. Importantly, however, a conservative P-value of < 0.001 together with a cluster extent threshold of 50 contiguous voxels were applied for all neuroimaging analyses in order to reduce the probability of false positive results. This approach has been shown to be effective in balancing the risk of Type I and Type II errors (Forman *et al.*, 1995). However, it is important that future studies apply correction for multiple comparisons in a larger patient cohort to replicate and confirm the current exploratory findings. Third, the majority of our sample has not yet come to autopsy; therefore, further studies including a larger sample size with post-mortem histopathological confirmation will be needed to confirm the current findings, especially in light of the heterogeneity of the underlying pathology of CBS (Jabbari *et al.*, 2020), which can include Alzheimer's disease, TDP-43 and tau pathology (Shelley *et al.*, 2009; Whitwell *et al.*, 2010).

In addition to cognition, cerebellar involvement in affective processing has been well established. Specifically, the vermis has long been considered to be predominantly involved in affective processing based on the extensive description of pronounced personality changes and emotion dysregulation following focal lesion to the vermis, likely due to its connection to the limbic structures (Schmahmann and Sherman, 1998; Schmahmann, 2004; Stoodley and Schmahmann, 2009; Stoodley *et al.*, 2012). While a recent study of main FTD syndromes failed to identity an association between cerebellar atrophy and emotion processing performance (Chen *et al.*, 2018), measures of emotion processing and behaviour changes should be incorporated in future studies to explore whether the emotional regulation role of the cerebellum applies to CBS and PSP.

Conclusions

Expanding on previous findings in frontotemporal lobar degeneration syndromes, the current study presents the first detailed exploration of the cerebellar contribution to cognitive impairments in CBS and PSP, using comprehensive neuropsychological evaluation together with exploratory structural neuroimaging analysis investigations. Widespread bilateral cerebellar atrophy predominantly concentrated in the regions of Crus II extending into lobules VIIb and VIIIa was observed in both CBS and PSP. Despite the considerable overlap in the atrophy pattern, distinct associations between the left Crus I and executive function, and between the vermis and language function were found in CBS in PSP, respectively. These observations are in line with the well-established role of Crus I in executive function and consolidate the growing evidence of the functional involvement of the vermis in cognitive processing. The current study provides preliminary evidence of the independent contribution of cerebellar atrophy to cognitive impairments in CBS and PSP beyond the effect of cerebral atrophy and disease duration, shedding light on its importance in neurodegenerative conditions characterized by motor dysfunction.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Conflict of interest

The authors report no competing interests.

References

Albrecht F, Bisenius S, Morales Schaack R, Neumann J, Schroeter ML. Disentangling the neural correlates of corticobasal syndrome and corticobasal degeneration with systematic and quantitative ALE meta-analyses. NPJ Parkinson's Dis 2017; 3: 1–7.

Andersson JL, Jenkinson M, Smith S, Non-linear registration aka spatial normalisation FMRIB technial report TR07JA2. FMRIB Analysis Group of the University of Oxford; 2007.

Arasanz CP, Staines WR, Roy EA, Schweizer TA. The cerebellum and its role in word generation: a cTBS study. Cortex 2012; 48: 718–24.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80: 496–503.

Baldaçara L, Borgio JGF, Araújo C, Nery-Fernandes F, Lacerda ALT, Moraes WAS, et al. Relationship between structural abnormalities in the cerebellum and dementia, posttraumatic stress disorder and bipolar disorder. Dement Neuropsychol 2012; 6: 203–11.

Baumann O, Borra RJ, Bower JM, Cullen KE, Habas C, Ivry RB, et al. Consensus paper: the role of the cerebellum in perceptual processes. Cerebellum 2015; 14: 197–220.

Blanca MJ, Alarcón R, Arnau J, Bono R, Bendayan R. Non-normal data: Is ANOVA still a valid option? Psicothema 2017; 29: 552–7.

Bostan AC, Dum RP, Strick PL. Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci 2013; 17: 241–54.

Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 2013; 80: 807–15.

Burgess PW, Shallice T, The hayling and brixton tests test manual. Bury St Edmunds, UK: Thames Valley Test Company; 1997.

Burrell JR, Hodges JR, Rowe JB. Cognition in corticobasal syndrome and progressive supranuclear palsy: a review. Mov Disord 2014; 29: 684–93.

Burrell JR, Ballard KJ, Halliday GM, Hodges JR. Aphasia in progressive supranuclear palsy: as severe as progressive non-fluent aphasia. J Alzheimers Dis 2018; 61: 705–15.

Caligiore D, Pezzulo G, Baldassarre G, Bostan AC, Strick PL, Doya K, et al. Consensus paper: towards a systems-level view of cerebellar function: the interplay between cerebellum, basal ganglia, and cortex. Cerebellum 2017; 16: 203–29.

Chen SA, Desmond JE. Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. Neuropsychologia 2005; 43: 1227–37.

Chen Y, Kumfor F, Landin-Romero R, Irish M, Hodges JR, Piguet O. Cerebellar atrophy and its contribution to cognition in frontotemporal dementias. Ann Neurol 2018; 84: 98–109.

Chen Y, Kumfor F, Landin-Romero R, Irish M, Piguet O. The cerebellum in frontotemporal dementia: a meta-analysis of neuroimaging studies. Neuropsychol Rev 2019; 29: 450–64.

Cordato NJ, Duggins AJ, Halliday GM, Morris JGL, Pantelis C. Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. Brain 2005; 128: 1259–66.

Cordato NJ, Pantelis C, Halliday GM, Velakoulis D, Wood SJ, Stuart GW, et al. Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. Brain 2002; 125: 789–800.

Desmond JE, Fiez JA. Neuroimaging studies of the cerebellum: language, learning and memory. Trends Cogn Sci 1998; 2: 355–62.

Fabbro F, Moretti R, Bava A. Language impairments in patients with cerebellar lesions. J Neurolinguistics 2000; 13: 173–88.

Field A, Discovering statistics using IBM SPSS statistics. Sage; 2013.

Gellersen HM, Guo CC, O'callaghan C, Tan RH, Sami S, Hornberger M. Cerebellar atrophy in neurodegeneration - a meta-analysis. J Neurol Neurosurg Psychiatry 2017; 88: 780–8.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 1995; 33: 636–47.

Giordano A, Tessitore A, Corbo D, Cirillo G, de Micco R, Russo A, et al. Clinical and cognitive correlations of regional gray matter atrophy in progressive supranuclear palsy. Parkinsonism Relat Disord 2013; 19: 590–4.

Gross RG, Ash S, McMillan CT, Gunawardena D, Powers C, Libon DJ, et al. Impaired information integration contributes to communication difficulty in corticobasal syndrome. Cogn Behav Neurol 2010; 23: 1–7.

Grossman M, McMillan C, Moore P, Ding L, Glosser G, Work M, et al. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain 2003; 127: 628–49.

Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain 2016; 139: 1527–38.

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, et al. Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 2009; 29: 8586–94.

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, for the Movement Disorder Society-endorsed PSP Study Group, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017; 32: 853–64.

Holmes G. The cerebellum of man. Brain 1939; 62: 1–30.

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 2013; 36: 242–50.

Huey ED, Goveia EN, Paviol S, Pardini M, Krueger F, Zamboni G, et al. Executive dysfunction in frontotemporal dementia and corticobasal syndrome. Neurology 2009; 72: 453–9.

Irwin DJ, Cairns NJ, Grossman M, McMillan CT, Lee EB, Van Deerlin VM, et al. Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine. Acta Neuropathol 2015; 129: 469–91.

Jabbari E, Holland N, Chelban V, Jones PS, Lamb R, Rawlinson C, et al. Diagnosis across the spectrum of progressive supranuclear palsy and corticobasal syndrome. JAMA Neurol 2020; 77: 377–87.

Jacobs HIL, Hopkins DA, Mayrhofer HC, Bruner E, Van Leeuwen FW, Raaijmakers W, et al. The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline. Brain 2018; 141: 37–47.

Josephs KA, Whitwell JL, Eggers SD, Senjem ML, Jack CR. Gray matter correlates of behavioral severity in progressive supranuclear palsy. Mov Disord 2011; 26: 493–8.

Kansal K, Yang Z, Fishman AM, Sair HI, Ying SH, Jedynak BM, et al. Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration. Brain 2017; 140: 707–20.

Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 2003; 23: 8432–44.

Keren-Happuch E, Chen SHA, Ho MHR, Desmond JE. A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. Hum Brain Mapp 2014; 35: 593–615.

Lagarde J, Valabrègue R, Corvol JC, Pineau F, Le Ber I, Vidailhet M, et al. Are frontal cognitive and atrophy patterns different in PSP and bvFTD? A comparative neuropsychological and VBM study. PLoS One 2013; 8: e80353.

Lee SE, Rabinovici GD, Mayo MC, Wilson SM, Seeley WW, Dearmond SJ, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol 2011; 70: 327–40.

Leggio MG, Silveri MC, Petrosini L, Molinari M. Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. J Neurol Neurosurg Psychiatry 2000; 69: 102–6.

Lesage E, Morgan BE, Olson AC, Meyer AS, Miall RC. Cerebellar rTMS disrupts predictive language processing. Curr Biol 2012; 22: R794–5.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996a; 47: 1–9.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 1996b; 55: 97–105.

MacKenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 2010; 119: 1–4.

Mariën P, Saerens J, Nanhoe R, Moens E, Nagels G, Pickut BA, et al. Cerebellar induced aphasia: case report of cerebellar induced prefrontal aphasic language phenomena supported by SPECT findings. J Neurolog Sci 1996; 144: 34–43.

Meyers JE, Meyers KR, Rey complex figure test and recognition trial (RCFT: Professional manual). Odessa, FL: Psychological Assessment Resources; 1995.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Demen 2011; 7: 263–9.

Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriat Psychiatry 2006; 21: 1078–85.

Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. Neurology 2010; 74: 1591–7.

Murley AG, Coyle-Gilchrist I, Rouse M, Jones PS, Li W, Wiggins J, et al. Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes. Brain 2020; 143: 1555–71.

O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cerebral Cortex 2010; 20: 953–65.

Pan P, Liu Y, Zhang Y, Zhao H, Ye X, Xu Y. Brain gray matter abnormalities in progressive supranuclear palsy revisited. Oncotarget 2017; 8: 80941–55.

Parmera JB, Rodriguez RD, Studart Neto A, Nitrini R, Brucki SMD. Corticobasal syndrome: a diagnostic conundrum. Dement Neuropsychol 2016; 10: 267–75.

Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC. Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy. Brain 2006; 129: 1040–9.

Piattella MC, Upadhyay N, Bologna M, Sbardella E, Tona F, Formica A, et al. Neuroimaging evidence of gray and white matter damage and clinical correlates in progressive supranuclear palsy. J Neurol 2015; 262: 1850–8.

Price CJ, Devlin JT, Moore CJ, Morton C, Laird AR. Meta-analyses of object naming: effect of baseline. Hum Brain Mapp 2005; 25: 70–82.

Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique (Les problems). Archives de Psychologie 1941; 28: 215–85.

Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, Hodges JR. Distinguishing subtypes in primary progressive aphasia: application of the sydney language battery. Dement Geriatr Cogn Disord 2013; 35: 208–18.

Schmahmann JD. An emerging concept: the cerebellar contribution to higher function. Arch Neurol 1991; 48: 1178–87.

Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci 2004; 16: 367–78.

Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561–79.

Schmider E, Ziegler M, Danay E, Beyer L, Bühner M. Is it really robust? Methodology 2010; 6: 147–51.

Shelley BP, Hodges JR, Kipps CM, Xuereb JH, Bak TH. Is the pathology of corticobasal syndrome predictable in life? Mov Disord 2009; 24: 1593–9.

Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002; 17: 143–55.

Snowden JS, Kobylecki C, Jones M, Thompson JC, Richardson AM, Mann DM. Association between semantic dementia and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2019; 90: 115–7.

So M, Foxe D, Kumfor F, Murray C, Hsieh S, Savage G, et al. Addenbrooke's Cognitive Examination III: psychometric characteristics and relations to functional ability in dementia. J Int Neuropsychol Soc 2018; 24: 854–63.

Stoodley CJ. The cerebellum and cognition: evidence from functional imaging studies. Cerebellum 2012; 11: 352–65.

Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. NeuroImage 2009; 44: 489–501.

Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 2010; 46: 831–44.

Tan RH, Devenney E, Kiernan MC, Halliday GM, Hodges JR, Hornberger M. Terra incognita-cerebellar contributions to neuropsychiatric and cognitive dysfunction in behavioral variant frontotemporal dementia. Front Aging Neurosci 2015; 7: 1–9.

Tombaugh TN. Trail making test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 2004; 19: 203–14.

Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol 1999; 14: 167–77.

Torriero S, Oliveri M, Koch G, Caltagirone C, Petrosini L. Interference of left and right cerebellar rTMS with procedural learning. J Cogn Neurosci 2004; 16: 1605–11.

Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M. Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. NeuroImage 2014; 86: 554–72.

Wechsler D, WAIS-III administration and scoring manual. San Antonio, TX: Psychological Corporation; 1997.

Whitwell JL, Jack CR, Boeve BF, Parisi JE, Ahlskog JE, Drubach DA, et al. Imaging correlates of pathology in corticobasal syndrome. Neurology 2010; 75: 1879–87.

Wynn SC, Driessen JMA, Glennon JC, Brazil IA, Schutter DJLG. Cerebellar transcranial direct current stimulation improves reactive response inhibition in healthy volunteers. Cerebellum 2019; 18: 983–8.

Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm IEEE. Ieee Trans Med Imaging 2001; 20: 45–57.