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Cerebellar atrophy in Parkinson's disease and its implication for network connectivity

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Pathophysiological and atrophic changes in the cerebellum are documented in Parkinson's disease. Without compensatory activity, such abnormalities could potentially have more widespread effects on both motor and non-motor symptoms. We examined how atrophic change in the cerebellum impacts functional connectivity patterns within the cerebellum and between cerebellar-cortical networks in 42 patients with Parkinson's disease and 29 control subjects. Voxel-based morphometry confirmed grey matter loss across the motor and cognitive cerebellar territories in the patient cohort. The extent of cerebellar atrophy correlated with decreased resting-state connectivity between the cerebellum and large-scale cortical networks, including the sensorimotor, dorsal attention and default networks, but with increased connectivity between the cerebellum and frontoparietal networks. The severity of patients' motor impairment was predicted by a combination of cerebellar atrophy and decreased cerebellar-sensorimotor connectivity. These findings demonstrate that cerebellar atrophy is related to both increases and decreases in cerebellar-cortical connectivity in Parkinson's disease, identifying potential cerebellar driven functional changes associated with sensorimotor deficits. A *post hoc* analysis exploring the effect of atrophy in the subthalamic nucleus, a cerebellar input source, confirmed that a significant negative relationship between grey matter volume and intrinsic cerebellar connectivity seen in controls was absent in the patients. This suggests that the modulatory relationship of the subthalamic nucleus on intracerebellar connectivity is lost in Parkinson's disease, which may contribute to pathological activation within the cerebellum. The results confirm significant changes in cerebellar network activity in Parkinson's disease and reveal that such changes occur in association with atrophy of the cerebellum.

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Abbreviations: CBMc = cognitive cerebellum comprising bilateral Crus I and Crus II; CBMm = motor module comprising bilateral lobules V, VI, VIIb, VIIIa and VIIIb; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

Parkinson's disease is classically synonymous with basal ganglia dysfunction, which is secondary to the dopaminergic denervation that follows the loss of nigrostriatal dopamine neurons (Dickson *et al.*, 2009), but also impacts on cerebellar function (Wu and Hallett, 2013). The cerebellum exerts a far-reaching influence on behaviour, given its anatomical and functional interconnections with the basal ganglia and much of the cortical mantle (Bostan *et al.*, 2013) and is known to be involved in motor planning and execution, as well as a range of higher-order cognitive and emotional functions (Ito, 2006; Ramnani, 2006; Schmahmann, 2010; Balsters and Ramnani, 2011; Buckner, 2013; Koziol *et al.*, 2014; Shine and Shine, 2014; Leggio and Molinari, 2015).

Connectivity studies confirm that reciprocal cerebellar-cortical loops run poly-synaptically to the thalamus via the topographically arranged dentate nucleus, before targeting multiple neocortical regions, with anatomically distinct cerebellar subregions projecting to unique cortical targets (Middleton and Strick, 2000, 2001; Kelly and Strick, 2003). These functional distinctions support the existence of a 'motor' cerebellum comprising lobules V, VI, VIIb and VIII projecting to motor regions (pre- and post-central gyrus), and a 'cognitive' cerebellum comprising Crus I and II and projecting to prefrontal and parietal cortices (Hoover and Strick, 1999; Kelly and Strick, 2003; O'Reilly *et al.*, 2010; Balsters *et al.*, 2014). Similar striato-cerebellar loops have been identified. The motor and cognitive cerebellar regions output (via the dentate) to topographically distinct regions in the sensorimotor and associative striatum, respectively; the subthalamic nucleus of the basal ganglia then projects via a disynaptic connection to the cerebellar cortex, maintaining a functional topographic arrangement (Hoshi *et al.*, 2005; Bostan *et al.*, 2010). Projections from associative, limbic and motor territories of the subthalamic nucleus terminate in motor and non-motor cerebellar regions, highlighting this as a critical pathway for integrating basal ganglia and cerebellar function across a range of behavioural modalities (Bostan *et al.*, 2013).

From a networks perspective, cerebellar motor subregions show preferential coupling with the cortical sensorimotor network, while cognitive subregions are associated with large-scale cortical networks involved in cognitive and limbic function, including the cognitive control, salience and default networks (Habas *et al.*, 2009; Buckner *et al.*, 2011). Although cerebellar architecture is arguably more complex than two distinct subsystems (Buckner *et al.*, 2011), the division into motor and cognitive cerebellar territories reflects the underlying structural connectivity with the cortex and it subsumes the more detailed modules described in functional parcellation schemes. Therefore, focusing on the functional cerebellar subsystems provides an important framework for understanding how alterations in the cerebellum's structure and function may manifest behaviourally in disease states.

In Parkinson's disease, alterations to the cerebellum and its cortical connections have been implicated in an array of motor and non-motor symptoms (Wu and Hallett, 2013). Direct pathological change in the cerebellum includes atrophy (Benninger *et al.*, 2009; Borghammer *et al.*, 2010) and denervation of cerebellar dopamine receptors (Hurley *et al.*, 2003). Yet, both at rest and during the execution and planning of motor tasks, hyper-activation of the cerebellum can be apparent (Mentis *et al.*, 2003; Wu and Hallett, 2005; Lewis *et al.*, 2007; Yu *et al.*, 2007; Ballanger *et al.*, 2008; Bédard and Sanes, 2009; Palmer *et al.*, 2009, 2010; Wu *et al.*, 2009*a*, 2011; Sen *et al.*, 2010; Festini *et al.*, 2015; Ham *et al.*, 2015). In the context of the hypoactive cortico-striatal motor circuitry typically seen in Parkinson's disease, the increased activation of cortico-cerebellar motor circuitry is thought to exert a compensatory effect in an attempt to circumvent the dysfunctional basal ganglia and normalize motor behaviour. Alternatively, increased cerebellar activation may result from a pathological increase in outflow from a dysfunctional subthalamic nucleus (Wu and Hallett, 2013). A modulatory relationship between the subthalamic nucleus and cerebellum is supported by evidence of normalized cerebellar activity post-deep brain stimulation to the subthalamic nucleus (Payoux *et al.*, 2004; Geday *et al.*, 2009). To date, much of the focus on pathological versus compensatory cerebellar engagement in Parkinson's disease has centred on the role of dopaminergic depletion as a precipitating factor. The manner in which local grey matter change in the cerebellum, or in a major input structure (the subthalamic nucleus), might influence cerebellar activity has not been investigated. This is particularly relevant, as the cerebellum's ability to exert a positive compensatory effect likely depends on its internal integrity as well as the integrity of its input structures.

Establishing the relationship between local grey matter atrophy and both local and distal functional connectivity changes has received considerable interest recently in ageing and disease states. Grey matter loss has been identified as a critical factor that drives both changes in task-based activation (Brassen *et al.*, 2009; Nyberg *et al.*, 2010; Kalpouzos *et al.*, 2012; Salami *et al.*, 2012) and network functional connectivity (Meunier *et al.*, 2014; Ward *et al.*, 2015). However, across these studies, the functional consequences of grey matter loss are not uniform. Patterns of over- and under-activity, as well as increased and decreased connectivity, both appear to be driven by local grey matter loss. Similar to the conclusion drawn in Parkinson's disease, incidences of hyper-activation and hyper-connectivity in healthy ageing are equated with functional compensation, in the context of age-related structural and molecular deterioration (Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009). Yet, the bidirectional findings highlight that while grey matter loss may spark compensatory changes, it can also lead to less beneficial effects such as neural inefficiency and dedifferentiation that result in

decreases in functional activity (Cabeza *et al.*, 2002; Grady, 2012; Maillet and Rajah, 2013; Reuter-Lorenz and Park, 2014).

In this study we sought to determine whether local atrophy in the cerebellum was associated with alterations in intrinsic cerebellar resting state connectivity and in connectivity between the cerebellum and large-scale cortical networks. We hypothesized that the extent of grey matter loss would be associated with alterations in intracerebellar and cerebellar-cortical resting state connectivity. Importantly, we expected to see bidirectional relationships, such that atrophy would be associated with both increases and decreases in resting state connectivity, reflecting that local atrophy in the cerebellum is an important driving factor in both compensatory and pathological functional changes. Finally, a *post hoc* analysis was conducted to determine the relationship between subthalamic nucleus atrophy and cerebellar intraconnectivity, to identify whether atrophic change in a cerebellar input source might influence cerebellar connectivity patterns.

Materials and methods

Case selection

A total of 78 patients were recruited from the Parkinson's Disease Research Clinic at the Brain and Mind Research Institute, University of Sydney, Australia. All patients satisfied the United Kingdom Parkinson's Disease Society Brain Bank criteria and were not demented (Martinez-Martin *et al.*, 2011). Patients were assessed on the Hoehn and Yahr Scale and the motor section of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS part III). The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were administered as measures of general cognition. All clinical and neuropsychological assessments (described below), as well as neuroimaging, were performed with patients in the ON state, having taken their regular dopaminergic medications. Dopaminergic dose equivalence scores were also calculated for each patient. Specifically, 15 patients were on L-DOPA monotherapy; 21 were on L-DOPA plus a dopaminergic agonist; a further 21 were on L-DOPA plus adjuvant therapy (rasagaline, entacapone or a monoamine oxidase inhibitor); 14 were on a combination of L-DOPA, dopaminergic agonist and adjuvant therapy; one patient was on dopaminergic agonist monotherapy, and two were on an agonist plus adjuvant therapy; three were on monoamine oxidase inhibitor monotherapy and one was unmedicated. No patients in the cohort were taking antipsychotic medication or cholinesterase inhibitors. Due to issues with imaging acquisition and motion artefacts, we did not include patients with dyskinesia as identified by a positive response to the dyskinesia items in Part IV of the MDS-UPDRS. A total of 51 healthy controls were recruited from a volunteer panel to participate in the study. Control participants were screened for a history of neurological or psychiatric disorders, as well as the concurrent use of any psychoactive medications. Patients and controls were matched for age and education level. The study was approved by the local Ethics Committees and all participants provided informed consent in accordance with the Declaration of Helsinki. See Table 1 for demographic details and clinical characteristics.

Behavioural and neuropsychological assessment

Mood was assessed via a self-report questionnaire, the Beck Depression Inventory-II (BDI-II; Beck *et al.*, 1996). Basic attention and working memory were assessed via a digit span task, with digits repeated in the original order (forward) and in the reverse order (backwards) (Wechsler, 1997). To assess attentional set-shifting, the Trail Making Test (Strauss *et al.*, 2006) was administered and the time score of Part B − Part A was calculated. Results from these measures are also shown in Table 1.

Imaging acquisition

Imaging was conducted on a General Electric 3 T MRI. Whole-brain 3D T_1-weighted sequences were acquired as follows: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm^2 in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8 ms. T_2*-weighted echo planar functional images were acquired in interleaved order with repetition time = 3 s, echo time = 32 ms, flip angle 90°, 32 axial slices covering the whole brain, field of view = 220 mm, interslice gap = 0.4 mm, and raw voxel size = 3.9 mm × 3.9 mm × 4 mm thick. Each resting state scan lasted 7 min (140 repetition times). During the resting state scan, patients were instructed to lie awake with their eyes closed and to let their minds wander freely.

Voxel-based morphometry analysis

The total sample of 78 patients with Parkinson's disease and 51 control subjects underwent the structural neuroimaging

Table 1 Demographics and patient clinical characteristics

Parameter	Control	Parkinson's disease	*P*-values
n	51	78	-
Sex (M:F)	14:37	53:25	-
Age	65.9 (7.7)	66.9 (8.3)	n.s.
Education	13.5 (2.8)	13.5 (3.0)	n.s.
MMSE (max. 30)	29.0 (1.2)	28.3 (2.1)	<0.05
MoCA (max. 30)	-	26.1 (2.9)	-
Duration (years diagnosed)	-	5.8 (4.2)	-
DDE (mg/day)	-	673.7 (444.9)	-
Hoehn and Yahr stage	-	2.2 (.6)	-
UPDRS III		32.0 (14.9)	
BDI-II		11.1 (8.1)	
TMT B − A (s)		80.3 (62.6)	
Digit span forward		10.2 (2.1)	
Digit span backward		6.4 (2.0)	

Values are mean (standard deviation).
n.s. = non-significant.
BDI-II = Beck Depression Inventory-II; DDE = dopaminergic dose equivalence; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; TMT B-A = Trail Making Test part B − part A.

protocol. Voxel-based morphometry (VBM) was performed on the 3D T_1-weighted scans, using the FSL-VBM toolbox in the FMRIB software library package (http://www.fmrib.ox.ac.uk/fsl/). Preprocessing of the scans firstly involved extracting the brain from all scans using the BET algorithm in FSL, using a fractional intensity threshold of 0.22 (Smith, 2002). Each scan was visually checked after brain extraction to ensure that no brain matter was excluded and no non-brain matter was included (e.g. skull, optic nerve, dura mater). A grey matter template, specific to this study, was then built from canvassing the maximum equal amounts from both groups (i.e. the entire sample of 51 control scans and a randomly selected 51 from the pool of patient scans). Including an equal amount of scans from the two groups ensures equal representation and thus avoids potential bias toward one group's topography during registration. Template scans were then registered to the Montreal Neurological Institute Standard space (MNI 152) using non-linear b-spline representation of the registration warp field, resulting in study-specific grey matter template at 26 262 mm^3 resolution in standard space. Simultaneously, the brain-extracted scans were also processed with the FMRIB's Automatic Segmentation Tool (FAST v4.0) (Zhang *et al.*, 2001) to achieve tissue segmentation into CSF, grey matter and white matter. Specifically this was achieved via a hidden Markov random field model and an associated Expectation-Maximization algorithm. The FAST algorithm also corrected for spatial intensity variations such as bias field or radio-frequency inhomogeneities in the scans, resulting in partial volume maps of the scans. In the next step, grey matter partial volume maps were non-linearly registered to the study-specific template via non-linear b-spline representation of the registration warp. These maps were then modulated by dividing by the Jacobian of the warp field, to correct for any contraction/enlargement caused by the non-linear component of the transformation (Andersson *et al.*, 2007). After normalization and modulation, smoothing the grey matter maps occurred using an isotropic Gaussian kernel (standard deviation = 3 mm; full-width half-maximum = 8 mm).

To compare cerebellar grey matter intensity between patients and controls, a region of interest mask encompassing the entire cerebellum was created. The cerebellum was defined using a validated probabilistic atlas of the human cerebellum (Diedrichsen *et al.*, 2009) available in the SUIT toolbox for FSL. Statistical analysis was performed with a voxel-wise general linear model (GLM). Significant clusters were formed by employing threshold-free cluster enhancement (TFCE), a cluster-based thresholding method that does not require the setting of an arbitrary statistical threshold. Instead, it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then converted into voxel-wise *P*-values via 5000 permutations (Nichols and Holmes, 2002). The group comparison included age and MMSE scores as covariates, to control for possible effects of global cognition and age across the range of patients and controls. The patient-control group comparison was tested for significance at $P < 0.01$, corrected for multiple comparisons via family-wise error (FWE) correction across space.

In a final step, to extract regional grey matter intensity measurements that would be contrasted with resting state patterns, motor and cognitive cerebellum regions of interest were created using cerebellar subregions from the probabilistic atlas referenced above (CBMm and CBMc, respectively). The CBMm was defined as bilateral lobules V, VI, VIIb, VIIIa and VIIIb and the CBMc was defined as the bilateral Crus I and Crus II (Balsters *et al.*, 2014). The mean grey matter intensity value of non-zero voxels within the regions of interest was then extracted for each subject and then averaged to create a value that represented the extent of cerebellar atrophy for each individual in the study. A similar analysis was also performed to extract grey matter intensity values from the subthalamic nucleus; this region was defined using a published atlas of the subthalamic nucleus based on a middle aged-elderly dataset (Keuken *et al.*, 2013).

Resting state functional connectivity analysis

A subsample of individuals from the study (42 patients and 29 controls) underwent resting state functional connectivity analysis. Preprocessing and analyses of resting state data were conducted using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/). Images were preprocessed according to a standard pipeline, as described previously (Shine *et al.*, 2013). Scans were first slice-time corrected to the median slice in each repetition time, then realigned to create a mean realigned image, with measures of 6° of rigid head movements calculated for later use in the correction of minor head movements. For quality assurance, each trial was analysed using ArtRepair (Mazaika *et al.*, 2009) and trials with a large amount of global drift or scan-to-scan head movements > 1 mm were corrected using interpolation. None of the subjects included in this study demonstrated scan-to-scan head movements > 3 mm (less than one voxels' breadth). Images were normalized to the Echo Planar Image template, resampled to 3 mm isotropic voxels and then subsequently smoothed using a 4 mm full-width at half-maximum isotropic Gaussian kernel.

Regions of interest reflecting key nodes within putative resting state networks were identified using peaks of activation ($Z > 3.0$) from group-level spatial independent component analysis using GIFT software in SPM8 (Calhoun *et al.*, 2001). Twenty independent components were initially extracted from the data using the Infomax algorithm; however, as we were principally interested in exploring the consequences of Parkinson's disease on commonly reported large-scale networks, our study specifically targeted five large-scale networks of interest (Laird *et al.*, 2011): the default network, frontoparietal network, the ventral attention network, the dorsal attention network and the sensorimotor network. To identify network nodes, we spatially sorted components from a group-level independent components analysis using a series of seeds known to comprise important regions within each network. Specifically, we used a posterior cingulate cortex seed (a sphere of 8 mm radius centred on 0 – 52 35) to extract the default network; a right-lateralized dorsolateral prefrontal cortex masks (45 11 34) to extract a bilateral frontoparietal network; a superior parietal mask (28 – 42 60) to extract the dorsal attention network; a right anterior insula mask (32 20 – 2) to extract the ventral attention network; a midline precentral gyrus mask (0 – 31 67) to extract the sensorimotor network. In the case of multiple correlates components, the independent component (IC) with the best correlation to the seed region was selected. Each of these large-scale network components was then subjected to a random effects analysis across the entire cohort, after which a stringent statistical

threshold of $P < 0.001$ [false discovery rate (FDR): $P < 0.05$, cluster size > 50] was applied to strictly define the spatial topography of each network component. Regions of interest were subsequently defined, five per network, such that they recapitulated key regions within each network component as previously reported in the literature (Laird *et al.*, 2011). Spherical regions of interest of radius 4 mm were centred on each of these coordinates (see Supplementary Table 1 for MNI coordinates).

Smoothed images were imported into the Functional Connectivity toolbox (www.nitrc.org/projects/conn) in SPM12. A temporal band pass filter was applied retaining frequencies between 0.009–0.08 Hz. Spurious variance was reduced by regression of nuisance waveforms derived from six variable head motion parameters (and their first temporal derivative), mean whole brain signal, and the signal extracted from 4 mm radius masks placed in the white matter (27 − 21 28) and CSF (−21 −36 20). The blood oxygen level-dependent time course was extracted from each of the nuisance-corrected source regions of interest and then Pearson's correlation coefficients were calculated for each pair-wise connection across the network regions of interest. These values were then normalized using a Fisher's r-to-Z transformation and then compared between controls and patients with Parkinson's disease using the Bonferroni-Holm correction for multiple comparisons (Holm, 1979).

Relationship between cerebellar grey matter intensity and resting state functional connectivity

To establish the relationship between cerebellar grey matter volume and patterns of within-network resting state connectivity, we correlated the average cerebellar atrophy score against the average resting state connectivity separately between each cerebellar module (CBMm and CBMc) and each of the five resting state cortical networks defined above, for both the patients and controls. Using the correlation between cerebellar module atrophy and cerebello-cortical connectivity in controls as a baseline, we then determined whether the patterns were significantly different in patients by creating a difference score between the *Z*-score for patients by directly comparing their scores to the control sample. In doing so, negative differences between patients and controls implied a relative loss of functional cerebello-cortical connectivity as a function of cerebellar atrophy, whereas positive differences implied a relative increase in connectivity as a function of cerebellar atrophy, possibly reflecting a compensatory mechanism.

The relationship between subthalamic nucleus integrity and intracerebellar functional connectivity

To determine whether the amount of grey matter within the subthalamic nucleus was associated with the alterations in intracerebellar functional connectivity observed in the patient cohort, we ran a separate analysis in which we correlated the mean grey matter intensity of the subthalamic nucleus (averaged across hemispheres) with the resting state functional connectivity observed between the two cerebellar modules for both controls and patients. The correlation coefficients of each cohort were then compared using the Dunn-Clark statistic (Dunn and Clark, 1969).

Relationship between motor severity, connectivity and atrophy

To determine whether a relationship existed between motor severity, atrophy and impaired connectivity between the cerebellar modules and the cortical networks, we correlated a composite connectivity/atrophy score [created by multiplying the functional connectivity for each cerebellar module to each cortical network by the inverse value of the percentage of atrophy in the cerebellum (such that increased amounts of atrophy penalized impaired connectivity and vice versa)] with the severity of motor symptoms of Parkinson's disease (UPDRS III) using a Pearson's correlation. We reasoned that an inverse relationship between these two variables would suggest that worse atrophy and connectivity between cerebellum and cortex would be responsible for the manifestation of more impaired motor symptomatology.

Results

Voxel-based morphometry analysis

Comparison of cerebellar atrophy in patients versus controls

Atrophy in cerebellar subregions was apparent in the Parkinson's disease patients relative to controls. Specifically, one large, contiguous cluster was identified (voxel size: 57 720; peak MNI co-ordinates: $x = -24$, $y = -64$, $z = -63$). The cluster included cerebellar subregions bilateral lobules I–IV, VI, VII (Crus I), VII (Crus II), VIIb, VIIIa, VIIIb, right-sided lobule V, and the vermis. See Fig. 1 for illustration of the overlap with this atrophy cluster and the motor and cognitive cerebellar territories. Comparisons between overall mean grey matter intensity for patients relative to controls revealed an overall volume loss of 5% in the CBMc and 4% in the CBMm.

Resting state functional connectivity analysis

Within the cerebellum, patients with Parkinson's disease displayed increased connectivity between the two subsystems (intermodular correlation mean $r = 0.71 \pm 0.02$) when compared to controls (mean $r = 0.59 \pm 0.03$; $t = 2.3$; $P = 0.025$). This contrasted with a relative preservation of broader cortical network connectivity when comparing patients with controls and correcting for multiple comparisons. These analyses revealed only an increase in negative connectivity between the dorsal attention network and default network in patients versus controls ($t = 3.02$, $P = 0.004$). Assessing the patterns of resting state cortico-cerebellar connectivity revealed a significant loss of connectivity between the CBMc and the sensorimotor network in patients (controls: average $r = 0.61$; patients: average $r = 0.00$; $t = 3.21$, $P = 0.003$). There were no significant differences between controls and patients with respect to head motion ($P > 0.500$).

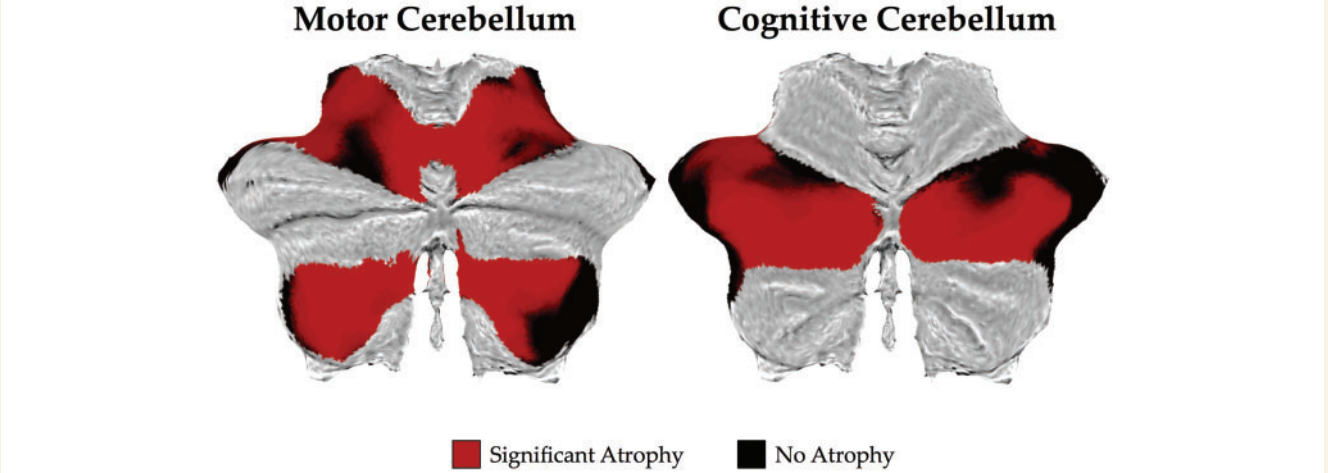

Figure 1 Voxel-based morphometry showing grey matter loss in the motor and cognitive cerebellar territories for Parkinson's disease patients in comparison to controls. Areas of significant grey matter loss (red) in the motor and cognitive cerebellar territories, for patients with Parkinson's disease versus control subjects. Results reported at $P < 0.01$, corrected for multiple comparisons (FWE).

Structure–function relationships

There was no significant relationship for either controls (mean $r = -0.143 \pm 0.02$) or patients (mean $r = -0.065 \pm 0.05$) when comparing cerebellar atrophy with the increases in intracerebellar connectivity. However, the extent of atrophy within the cerebellum was differentially correlated with specific impairments in resting state connectivity between the cerebellar modules and the resting state networks in patients, when compared with controls. Specifically, after Bonferroni-Holm correction, the extent of cerebellar atrophy was associated with a relative loss of connectivity between the CBMm and the default network ($Z = -5.4$, $P < 0.001$), the sensorimotor network ($Z = -4.4$, $P < 0.001$), and the dorsal attention network ($Z = -15.4$, $P < 0.001$). In contrast, cerebellar atrophy was associated with an increase in connectivity between the CBMm and the frontoparietal network ($Z = 7.5$, $P < 0.001$) relative to controls, suggesting a potential compensatory role. In regards to the CBMc network, cerebellar atrophy was related to a significant loss of connectivity between the CBMc and the sensorimotor network ($Z = -11.5$, $P < 0.001$) (Fig. 2).

As a *post hoc* investigation to determine the influence of atrophy in a cerebellar input nucleus, for the subthalamic nucleus in controls we observed a negative correlation ($r = -0.310$, $P < 0.05$) between the extent of subthalamic nucleus grey matter intensity and inter-modular cerebellar connectivity (Supplementary Fig. 1). This relationship was not apparent in the patient group ($r = 0.091$, $P > 0.200$). The difference between these two correlation coefficients was also significant ($Z = 1.8$, $P < 0.05$), suggesting that the patients had lost a modulatory relationship between subthalamic nucleus integrity and cerebellar function that is present in healthy control subjects.

To explore the potential effect of dopamine medication, we ran an additional correlational analysis to determine whether patients' dopamine dose equivalence (DDE) scores correlated with the relationships between cerebellar atrophy and functional connectivity between the cerebellum and cortical networks. Only two structure-function relationships were significantly correlated with DDE: the extent to which cerebellar atrophy modulated both reduced connectivity between the CBMc and ventral attention network ($r = -0.310$, $P = 0.046$) and between the CBMm and ventral attention network ($r = -0.392$, $P = 0.010$), although these results did not survive correction for multiple comparisons.

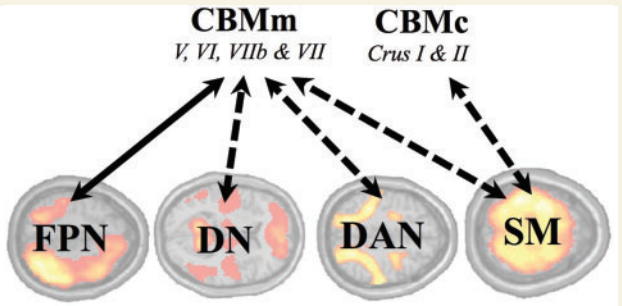

Figure 2 Cerebellar to cortical networks structure-functional relationships. Relationships between cerebellar atrophy and resting state connectivity between the cerebellar modules and large-scale cortical networks, where dashed lines denote a loss of connectivity and solid lines an increase in connectivity. FPN = frontoparietal network; DN = default network; SM = sensorimotor network; DAN = dorsal attention network.

Relationship between motor severity, connectivity and cerebellar atrophy

We observed an inverse correlation between the UPDRS III subscore and the extent of cerebellar atrophy and impaired

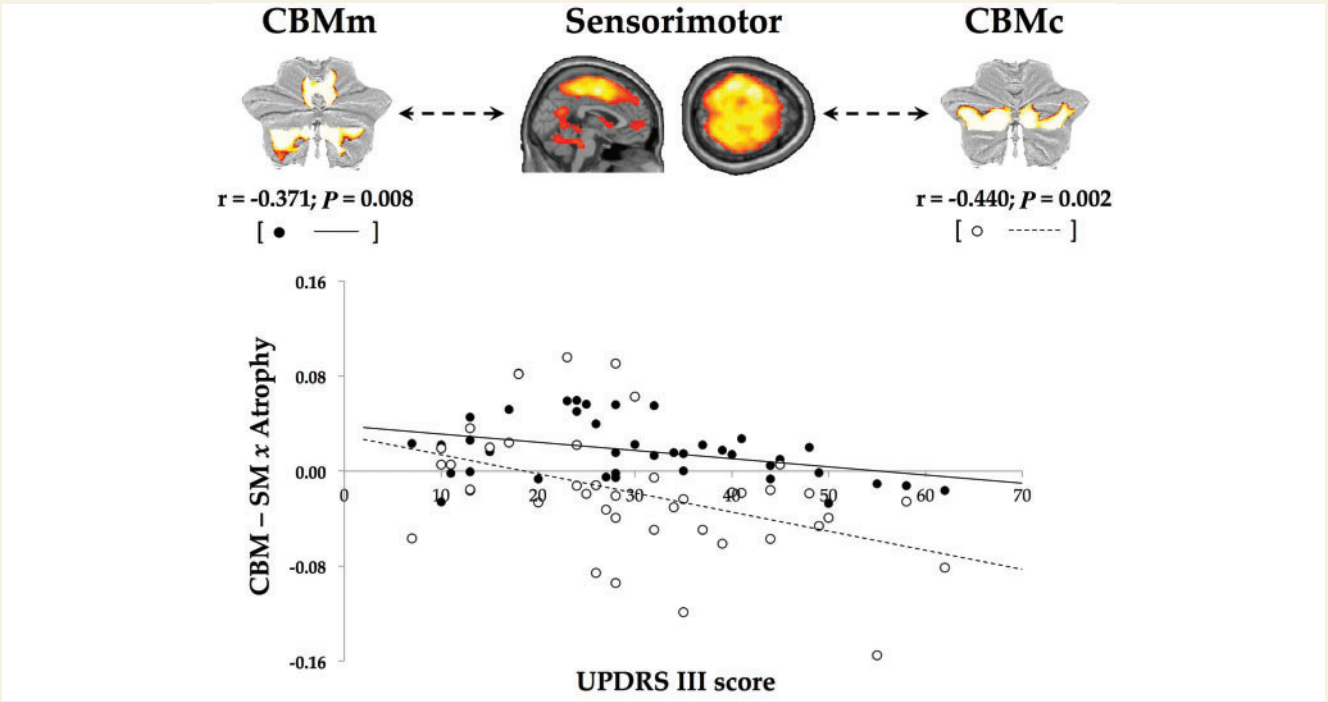

Figure 3 Relationship between motor severity, connectivity and atrophy. Relationships between cerebellar atrophy, resting state connectivity between the cerebellar modules and large-scale cortical networks and motor severity. We observed a negative correlation between the extent of atrophy and impaired connectivity between the motor and cognitive cerebellum and the sensorimotor network and the extent of motor severity, as measured by section III of the UPDRS. CBMm-SM: black circles and full lines; CBMc-SM: white circles and dashed lines.

connectivity between the CBMm and sensorimotor network ($r = -0.371$, $P = 0.008$) as well as between the CBMc and sensorimotor network ($r = -0.441$, $P = 0.002$; Fig. 3). No other relationships between cerebellar atrophy and connectivity were significantly correlated with UPDRS III scores, suggesting a selective relationship between motor severity and impaired communication between the cerebellum and the sensorimotor network.c

Discussion

The findings described here reveal a combination of structural and functional cerebellar abnormalities in Parkinson's disease. Although we demonstrate atrophic change across the cerebellum, the changes were accompanied by increased connectivity between the two functional subsystems. Our findings suggest that the integrity of the subthalamic nucleus may be contributing to alterations in cerebellar intrinsic connectivity, along with the changes in dopaminergic function previously described (Wu and Hallett, 2013). Furthermore, we show that connectivity between the cerebellar subsystems and large-scale cortical networks undergoes bidirectional changes, as may be expected due to changes in cortical network activity with basal ganglia dysfunction. However, we also show that abnormalities in these cortical networks correlated with the extent of local cerebellar atrophy, suggesting a greater role for intrinsic structural changes in the cerebellum in Parkinson's disease.

Our data on resting state cerebellar activity in Parkinson's disease are consistent with numerous studies showing its hyper-activation and associated functional gains to achieve performances at the level of controls (Yu *et al.*, 2007; Palmer *et al.*, 2009; Wu *et al.*, 2015), with previous studies also suggesting the possibility that cerebellar overactivity is pathological rather than compensatory (Turner *et al.*, 2003; Grafton *et al.*, 2006; Wu *et al.*, 2011; Wu and Hallett, 2013). The novelty of our study was to explore the effects of cerebellar grey matter loss on functional connectivity patterns within the cerebellum and between cerebellar–cortical networks. Importantly, the extent of increased intracerebellar connectivity in our patient sample was not associated with the extent of cerebellar atrophy. The resilience of intracerebellar connectivity suggests that local synaptic circuits remain intact despite cerebellar atrophy and that more likely there is a loss of external synaptic input to the cerebellum. This is consistent with our results showing a loss of the relationship between subthalamic nucleus integrity and intra-cerebellar connectivity in patients with Parkinson's disease. Interpreting morphological changes in the Parkinson's disease subthalamic nucleus are not straightforward, as both grey matter increases (Camlidag *et al.*, 2014) and decreases (Colpan and Slavin, 2010) have been documented. Our results highlight that disease-related alterations to subthalamic nucleus

integrity may result in a loss of modulatory input over cerebellar activity, suggesting that increased resting state connectivity within the Parkinson's disease cerebellum could be at least partly due to an additional pathological input disturbance, apart from potential dopaminergic denervation (Wu and Hallett, 2013). This is in keeping with previous suggestions that increased intracerebellar connectivity may reflect pathological, as opposed to compensatory, activity.

In contrast to the lack of relationship between local cerebellar atrophy and cerebellar intrinsic connectivity, our results show that cerebellar atrophy may be an important determinant of alterations in the connectivity between the cerebellum and large-scale cortical networks. Local cerebellar atrophy in the patients was associated with a loss of connectivity between the cognitive cerebellum and sensorimotor network, and between the cerebellar motor subsystem with the default, sensorimotor and dorsal attention networks. In addition, atrophy in the cerebellum was uniquely associated with increased connectivity between the motor cerebellum and frontoparietal network, and importantly related to motor symptoms (Fig. 3). This result underscores a more causative role for impaired cerebello-cortical connectivity in the pathophysiology of Parkinson disease motor symptoms (Wu and Hallett, 2013). As our sample was evaluated for motor symptoms in the ON state, it will be important for future studies to replicate this finding using OFF state measures, which can potentially provide a more accurate description of motor severity. In addition, our sample did not contain patients with dyskinesia. Levodopa-induced dyskinesia in Parkinson's disease has been related to reduced modulation of cortical motor areas by the cerebellum (Kishore and Popa, 2014), a prediction to be answered in future work would be whether dyskinetic patients show an even greater degree of cerebellar-sensorimotor connectivity reductions.

The influence of cerebellar atrophy was most prominent with respect to connectivity between the motor subsystem and large-scale cortical networks. This prominence suggests that the motor cerebellum may be particularly involved in adaptive changes that occur in Parkinson's disease in response to local atrophic change. These findings dovetail with studies in healthy ageing and other disease states showing that local cerebellar atrophy can drive both decreases and increases in functional connectivity patterns (Kalpouzos *et al.*, 2012; Maillet and Rajah, 2013). Whether increased connectivity between the motor cerebellum and the frontoparietal network is associated with compensatory behavioural gains remains an open question; however, it would be in keeping with a heavier reliance on attentional resources to guide motor behaviour in an effort to circumvent dysfunctional motor circuits and normalize movement. Indeed, further proof is needed to better clarify whether examples of increased cortico-cerebellar activity in Parkinson's disease do represent a compensatory neural response to other primary pathological changes. Continued comparisons between cortico-cerebellar changes and motor or non-motor symptoms will also reveal the extent to which increases in connectivity are associated with preservation of function.

Our results also show that atrophy of the Parkinson's disease cerebellum is associated with fundamentally distinct changes in other cerebello-cortical functional connectivity. Cerebellar atrophy in Parkinson's disease has previously been associated with cognitive deficits and markers of disease severity (Pereira *et al.*, 2009; Nishio *et al.*, 2010; Chou *et al.*, 2015). Our findings suggest that cerebellar atrophy may also contribute to changes in cognition and behaviour in Parkinson's disease due to a pathological loss of connectivity with large-scale cortical networks. However, it is unlikely that the cerebellar atrophy modulates all changes in cortical network activity in Parkinson's disease. Changes in basal ganglia connectivity are significant, and the correlations between cerebellar motor or cognitive territories and cortical networks occur in networks with no direct anatomical connections (including the motor cerebellum with frontoparietal, dorsal attention and default networks; and the cognitive cerebellum with the sensorimotor network). This suggests that some of the correlations are driven by effects at the cortical level, whereby long-term compensatory rewiring in a chronic condition like Parkinson's disease results in networks that are no longer effectively segregated from each other (Stam, 2014). Importantly, we show that dopamine medication levels were not a significant predictor of the structure-function changes identified in our analysis. Dopamine medication correlated only with the relationship between cerebellar atrophy and loss of connectivity between both cerebellar modules and the ventral attention network, although this did not survive strict correction for multiple comparisons. The cerebellum is reciprocally connected with the ventral tegmental area (Perciavalle *et al.*, 1989; Ikai *et al.*, 1992), as part of the mesolimbic dopaminergic system supplying limbic brain regions (Mittleman *et al.*, 2008; Rogers *et al.*, 2011, 2013). An interaction with dopamine medication levels might be expected for cerebellar-ventral attention network connectivity, as this network encompasses ventral-medial limbic regions, including anterior cingulate and anterior insula. A speculative interpretation of our finding is that increased dopamine medication, in the context of cerebellar atrophy, may impair this aspect of cerebello-cortical connectivity due to dopaminergic overdose of this system.

Reduced cerebellar modulation of cortical function is hypothesized to have generalized effects upon the ability to smoothly coordinate and sequence both movement and cognition (Schmahmann, 1991; Andreasen *et al.*, 1999; Andreasen and Pierson, 2008). The cerebellum is also a crucial source of the brain's predictive capacity, as well-learnt behavioural patterns stored in the cerebellum can be engaged to anticipate the consequences of current behavioural options (Ito, 2008; Koziol *et al.*, 2014; Leggio and Molinari, 2015). Thus, increased cerebellar atrophy and the concomitant loss of cerebellar-cortico connectivity is likely to be a key contributor in a wide range of motor

and non-motor deficits that can emerge with the progression of Parkinson's disease. The precise mechanism by which atrophy would affect the cerebellum's widespread modulatory role remains speculative (Koziol *et al.*, 2014). However, output signals from the deep cerebellar nuclei are governed by a delicate balance of excitatory and inhibitory tone arising from the granule and Purkinje cell layers of the cerebellar cortex (Ramnani, 2006). Atrophic changes in the cerebellar cortex are likely to interfere with the precision of cerebellar output signals, impairing its modulation of the cerebral cortex (Andreasen and Pierson, 2008), as we have shown in the selective reductions in cerebello-cortical functional connectivity.

Our results confirm that increased intracerebellar connectivity can persist in the ON state. This contrasts with previous reports of OFF medication increases in cerebellar regional connectivity that are normalized in the ON state (Wu *et al.*, 2009*a*, *b*) or even over-corrected (Festini *et al.*, 2015). Interpretations of these previous findings were that restoration of basal ganglia dopamine levels meant that compensatory drive from the cerebellum was no longer necessary. However, we have demonstrated that integrity of the subthalamic nucleus is also likely to play a modulatory role on intrinsic cerebellar connectivity. Compared to those previous studies, our patient cohort had a longer disease duration and increased disease severity, which would be consistent with more extensive subthalamic nucleus abnormalities in our patients. Taken together, these findings emphasize that a combination of global dopamine levels and a loss of cerebellar input contribute to cerebellar connectivity patterns. It is possible that, with disease progression, long term hyper-excitation of the cerebellum from the subthalamic nucleus causes synaptic reconfiguration that effectively 'locks' the cerebellum in a hyper-active state, such that normalizing basal ganglia dopamine with medication no longer ameliorates the overactive cerebellum (Kishore *et al.*, 2014). Indeed, many of the cortico-striatal resting state abnormalities in Parkinson's disease that are present in the OFF state can be normalized in the ON state (Wu *et al.*, 2009*a*, *b*). Nevertheless, with medication, resting state hypo-connectivity in the OFF state is sometimes only improved to a level that is still below controls (Bell *et al.*, 2015) or in the case of hyper-activations, these can be overcorrected with medication (i.e. decreased relative to controls) (Kwak *et al.*, 2010). The variable impact of dopamine medication on resting state activity doubtless reflects differences in the regional baseline levels of endogenous dopamine, however an important determinant of levels of endogenous dopamine, particularly with disease progression, are also structural factors including synaptic availability and white matter connectivity. Following on from this, there is increasing evidence that structural changes to the grey and white matter in Parkinson's disease are markers for motor and non-motor symptoms (Duncan *et al.*, 2013; O'Callaghan *et al.*, 2013*a*, *b*, 2014; Rosenberg-Katz *et al.*, 2013). In this way, the capacity for cerebellar-cortico functional compensation, as well as pathological changes in cerebellar-cortico connectivity, are likely to be mediated by both fluctuations in dopamine levels and also by underlying structural changes in the cerebellum and its input structures. Future studies incorporating both measures of structural integrity and ON/OFF states will be needed to disentangle their relative effects on cerebellar functional versus pathologic change across the disease course.

Our findings reveal the prominent functional and atrophic changes within the Parkinson's disease cerebellum. Furthermore, we show that changes within the cerebellum have ramifications for the integrity of large-scale cortical networks, highlighting the fact that cerebellar abnormalities in Parkinson's disease are likely to have far-reaching effects particularly on movement, but also on cognition. With the growing recognition that the cerebellum is imperative to successful adaptive behaviour, across all domains, continued understanding of its role in Parkinson's disease remains an important goal in unravelling the complex, multisystem nature of this disorder.

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Supplementary material

Supplementary material is available at *Brain* online.

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