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Cerebellar correlates of visual hallucinations in Parkinson's disease and Charles Bonnet Syndrome

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ABSTRACT

Hallucinations, percepts in the absence of external stimuli, are a shared feature of eye-disease (Charles Bonnet Syndrome, CBS) and Parkinson's disease (PD) thought to arise through pathophysiologically distinct mechanisms: deafferentation and attentional network dysfunction respectively. Recent studies have found an association between visual hallucinations and structural changes in the cerebellum without obvious link to either mechanism.

Here, we employed Voxel Based Morphometry (VBM), optimised for the cerebellum using the Spatially Unbiased Infratentorial Template (SUIT), to characterise similarities and differences in cerebellar structure associated with visual hallucinations in PD and CBS. Grey and white matter volume (GMV & WMV) from patients with eye-disease (n = 12 hallucinators; n = 9 non-hallucinators) and PD (n = 7 hallucinators; n = 9 non-hallucinators) was examined in a 2-way ANOVA controlling for age, sex, and intracranial volume.

Comparing hallucinators to controls across both groups, lower GMV was found bilaterally within cerebellar lobule VIII extending to IX/VII. GMV reductions were also found in Crus 1, greater in PD than eye-disease. Predominantly within PD, hallucination-related lower WMV was found in the medulla. No regions of increased GMV or WMV were found. A correlation was observed between brainstem WMV and lobule VIIIb GMV suggesting a functional association.

Lobule VIII comprises a functional node within the Dorsal Attention Network (DAN), linking these findings to current attentional theories of hallucinations, while Crus 1 is linked to cortical visual processing. These findings provide preliminary evidence of a cerebellar contribution to hallucinations that transcends clinical conditions.

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1. Introduction

Hallucinations, percepts in the absence of cognate external stimuli, are a shared feature of several clinically distinct conditions. In eye-disease or damage to visual pathways leading to visual loss, for example following stroke, visual hallucinations (VH) are referred to as Charles Bonnet syndrome (CBS). Depending on the degree of visual impairment, CBS affects 10–60% of patients (ffytche, 2009). In Parkinson's disease (PD) VH are part of a spectrum of symptoms referred to collectively as PD psychosis (ffytche et al., 2017) and occurs in up to 60% of patients as the disease progresses (Forsaa et al., 2010). Hallucinations can also occur in neurodegenerative diseases such as Alzheimer's disease and Dementia with Lewy bodies (DLB), in schizophrenia (where they are typically auditory-verbal, not visual), following bereavement, and may also be present in 10–15% of the general population without clearly identifiable cause (Badcock et al., 2008; Barrett & Etheridge, 1992; Castelnovo et al., 2015; Paulik et al., 2006; Romme et al., 1998; Sommer et al., 2010).

There are overlaps in phenomenological features of hallucinations in different conditions. In PD and eye-disease, for example, some hallucination categories are characteristic of one or other condition: passage hallucinations where a figure or animal passes by in the visual periphery or presence hallucinations where someone is felt to be nearby without an associated visual, tactile or auditory experience are characteristic of PD while simple hallucinations of dots, colours and shapes are characteristic of CBS (ffytche, 2007). However, many of the hallucinations in CBS and PD are common to both conditions. Patients with CBS or PD report hallucinations of people, animals and objects, for example. Despite such similarities in content, current theories of the underlying pathophysiology of hallucinations in the two conditions are entirely distinct. In CBS, hallucinations are thought to be the result of cortical hyper-excitability in response to deafferentation of the visual cortex (Burke, 2002) with spontaneous increases in activity in specialised visual cortical areas leading to hallucinations of the specialised visual attribute (ffytche et al., 1998). In contrast, VH in PD and DLB are thought to relate to combined dysfunction of attentional and visual perceptual processes (Collerton et al., 2005) and dysfunctional integration of attentional networks (Shine et al., 2011, 2014), with several neurotransmitter systems implicated but without the suggestion of hyper-excitability in visual cortices.

Although the accounts of hallucinations in eye-disease and PD are very different, one aspect they share is the absence of a role for the cerebellum. While traditionally considered a coordinator of complex motor behaviour, a broad body of research now implicates the cerebellum in a range of higher functions including language (Mariën et al., 2013), emotion (Adamaszek et al., 2017), perception (Baumann et al., 2015) with recent evidence emerging to suggest it may be involved in the auditory-verbal hallucinations of schizophrenia (Cierpka et al., 2017). Furthermore, cerebellar atrophy has been found in structural imaging studies comparing hallucinators and controls in PD (Rollins et al., 2019) and increased volume of regions within the cerebellum in CBS compared to eye-disease controls has been reported (Russell, 2014). The neurophysiological significance of these cerebellar associations with hallucinations in PD and CBS and their relation to theories of hallucination mechanisms in these conditions is entirely unclear. Here we use imaging methodology specialized for cerebellar anatomy to examine the cerebellar correlates of VH in PD and eye-disease to better understand the subregions involved in each condition and determine whether there are shared cerebellar mechanisms that transcend clinical context.

2. Materials and methods

Below we report all data exclusions, all inclusion/exclusion criteria which were established prior to data analysis, all data manipulations, and all measures in the study. We analysed data from two studies, one related to VH in eye-disease (Non-drug treatments for VH, Macular Society, MDHAL) and one related to VH in PD (Functional magnetic resonance imaging study of visual processing and hallucinations in Parkinson's Disease, Parkinson's UK, PDHAL) which defined the sample size. The study procedures and study analysis plan were not pre-registered in a time-stamped, institutional registry prior to the research being conducted.

2.1. Study data

Both MDHAL and PDHAL explored structural imaging, functional imaging and cognitive differences in patients with and without hallucinations. In MDHAL, patients with eye-disease with and without hallucinations were matched for age, MMSE and visual impairment (Snellen acuity, contrast sensitivity and central visual field loss). In PDHAL, PD patients with and without hallucinations were matched for age, MMSE, disease duration and L-Dopa medication; eye-disease was an exclusion criterion. The PD patients with hallucinations had worse PD motor symptoms than those without hallucinations as measured by UPDRS parts III and IV. All patients gave informed written consent and the studies were approved by research ethics committees (MDHAL: King's College Hospital Research Ethics Committee reference 08/H0808/125; PDHAL: Camberwell St Giles Research Ethics Committee reference 07/Q0706/23). The ethics approval did not include public archiving of anonymised study data. Readers seeking access to the data should contact the lead author Dr D H ffytche or the local ethics committees for MDHAL and PDHAL. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of clinical data, including completion of a formal data sharing agreement and approval of the local ethics committees.

2.2. Participants

Structural imaging data was available from N = 21 patients with eye-disease (age-related macular degeneration, AMD) and N = 16 patients with PD. Table 1 describes the phenomenology of the hallucinations in the subgroup of eye-disease patients with VH (CBS, N = 12) and subgroup of PD patients with VH (PDHAL N = 7). CBS participants experienced a range of simple (shapes, dots and colours) and complex hallucinations (patterns, faces, figures, animals, text, objects). PDHAL

Table 1 – A summary of the phenomenology and clinical characteristics for each patient exhibiting hallucinations.

Participant	Age	Sex	MMSE[a]	Left Eye	Right Eye	Presence	Passage	Content of hallucination
CBS1	89	F	27	Dry AMD	Wet AMD	–	–	*1 month since onset* Last hallucination 4 days before assessment • Blue chicken wire pattern on walls • Pink and sage green oblongs • House • Figures of women in old fashioned clothes (a tulip shaped skirt) • Gold circles whizzing overhead
CBS2	81	F	26	Dry AMD	Wet AMD	–	–	*2 years since onset* Hallucination on day of assessment (net and pattern) • Everything covered with frozen peas • Garlands of flowers • Explosion of colours • Nets • While being driven saw person walking duplicated into three in people in a row.
CBS3	77	F	28	Dry AMD[b]	Dry AMD[b]	–	–	*15 years since onset* Last hallucination in week before assessment • Dots • Shimmering glass • Colours blue/purple • Tapestry with gap in middle corresponding to scotoma (like a vaulted ceiling on one occasion)
CBS4	82	F	27	Wet AMD	Dry AMD	–	–	*3 years since onset* Hallucination on day of assessment (patterns and 3D undulations) • Words on screen and lines of print. • Faces
CBS5	76	M	26	Dry AMD[c]	Dry AMD[c]	–	–	*3 – 4 years since onset* Last hallucination 2–3 days before assessment • Rust sheet and jagged shapes • White horse • Wife and daughter's face start to transform and disintegrate

(*continued on next page*)

Table 1 – (*continued*)

Participant	Age	Sex	MMSE[a]	Left Eye	Right Eye	Presence	Passage	Content of hallucination
CBS6	87	F	28	Wet AMD	Wet AMD	–	–	*20 years since onset* Last hallucination a few days before assessment • Children's faces • Musical notes (whole sheet with staves etc). • Words • Plate with blue geometric pattern around edge like kaleidoscope and with an eye in middle • Figure with weapon
CBS7	78	F	27	Dry AMD	Dry AMD	–	–	*4 years since onset* Hallucination on day of assessment (Catherine wheels) • Catherine wheels • Stained glass window in Art deco home from childhood reappeared • A bishop sitting in room in purple robes. • Cats
CBS8	84	F	28	Dry AMD	Dry AMD	–	–	*1 year since onset* Hallucination on day of assessment (netting and kaleidoscope colours) • Kaleidoscope of colours. • Chicken wire/netting • Text • Caterpillars
CBS9	73	M	27	Trauma	Wet AMD	–	–	*5 years since onset* Last hallucination 3 days before assessment • Grass in plants • Mauve and dark blue flowers in blind area of right eye like a bunch of Michaelmas daisies • Fireplace filled in with stones. • Real hedge in country lane had a stone wall beneath it (while being driven) • Complete gargoyle • Circle filled in with moving white sparks (like plasma ball)

CBS10	73	F	26	Wet AMD	Wet AMD	–	–	*2-3 years since onset* Last hallucination 4 days before assessment • Blonde stranger on the sofa, wearing a check shirt, and grinning, • Seed head with red borders, white middle and black dots/lines. Multiple seed heads across visual field. • Herds of animals running, e.g., zebras • Lattice (cane chair pattern). • Stick men • Real faces with distortions (e.g., a trunk, funny ears, Pinocchio nose)
CBS11	80	M	26	Dry AMD	Wet AMD	–	–	*2 years since onset* Last hallucination a few weeks before assessment • Photograph of a tram with writing on side (e.g., destination, cheap day fares, number)
CBS12	73	F	24	Dry AMD	Wet AMD	–	–	*5 years since onset with recent increase* Hallucination on day of assessment (trees and hedge) • Car crashing into people crossing the road. • Troll staring and leering • Brickwork and cobweb • When out shopping with daughter sees • groups of people walking near her (these may be real people) that re-appear later as a hallucination. Not sure if it is exactly the same groups on both occasions • Saw 4 young girls in a row (ribbon and bow in hair). • Green hedges and trees moving

Participant	Age	Sex	MMSE[a]	UPDRS	Presence	Passage	Content of hallucination
PDHAL1	58	M	30	19	+	–	*More than one year since onset* • Statues of roman soldiers • Faces • Figures • Bear's head • People and animals • Dogs and foxes in the garden

(*continued on next page*)

Table 1 – (*continued*)

Participant	Age	Sex	MMSE[a]	UPDRS	Presence	Passage	Content of hallucination
PDHAL2	71	M	19	59	+	+	*3 years since onset* • A dustbin which turns into a person • Faces • Cat and a lamppost • Misinterpretation of shift hanging as a person
PDHAL3	75	F	30	37	–	–	*Onset not recorded* • Scottish man wearing a white cloak • Talk bald man wearing a white vicars cassock • Faces that look like their father
PDHAL4	66	F	29	45	–	–	*Onset not recorded* • Furballs or ants on the ground (black shapes which move around)
PDHAL5	74	M	25	50	+	+	*Less than one year since onset* • Gold bugs on the floor all over the house (tries to stamp on them)
PDHAL6	61	F	25	42	–	+	*8-12 months since onset* • Misinterpretations, e.g., pile of rubbish as a face or animal • Coat or cardigan draped over furniture • Faces and figures in pictures
PDHAL7	76	F	30	28	+	+	*More than one year since onset* • Spaceman across the road • Bird or bat flying past the window • A brown, fuzzy fox in the garden • Row of sofas

UPDRS: Unified Parkinson's Disease Rating Scale (combined score for Parts 3 and 4).

[a] MMSE: Mini-Mental State Exam. (Standard 30 point MMSE in PD but reduced to 28 point MMSE in eye-disease to remove items requiring intact vision).

[b] Atypical epithelial detachment.

[c] atypical, drusen linked to renal disease.

participants experienced a range of complex hallucinations (figures, faces, people and animals) as well as illusions, passage, and presence hallucinations. None of the AMD control participants had experienced hallucinations during the course of their illness. PD participants were considered controls if they had not experienced complex hallucinations.

2.3. Neuroimaging data acquisition and analysis

High-resolution structural T1-images for both studies were acquired on a 1.5 T GE Signa HDx scanner (fast spoiled gradient echo sequence, 256 × 256 matrix; 146 slices, 1.09 × 1.09 × 1.1 mm resolution). Processing and analysis were conducted using Statistical Parametric Mapping software package version 12 (https://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB 8.0.0 (R2012) (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States). Data pre-processing was conducted using the Spatially Unbiased Atlas Template of the cerebellum and brainstem (SUIT) toolbox (http://www.diedrichsenlab.org/imaging/suit_function.htm). The benefits of SUIT are preservation of anatomical detail through a nonlinear atlas generation algorithm as well as being spatially unbiased in respect to affine alignment to Montreal Neurological Institute (MNI) space, i.e., if the same brain is normalised using the MNI whole-brain template and the SUIT template, on average a given structure should end up at the same coordinate in atlas space (Diedrichsen, 2006; Diedrichsen et al., 2009). Specifically for VBM, it offers better overlap of cerebellar structures and, by masking the image before reslicing into Atlas space, supratentorial GM cannot bias the results (Diedrichsen, 2006).

All images were visually inspected for gross anatomical abnormalities and scanner artefacts. The origin was set to the anterior commissure for each image and necessary adjustments were made to ensure correct orientation. The isolate function within the SUIT toolbox was used to segment the cerebellum and brainstem from the rest of the brain. This makes use of the unified segmentation approach that combines tissue classification with registration to a template into a single probabilistic framework in order to segment an image into each separate tissue type (Ashburner & Friston, 2005). These are then used to calculate the posterior probability of each voxel belonging to cerebellum or brainstem. The cerebellar masks generated were visually inspected using FSLview to ensure no tissue from outside the brainstem and cerebellum was included. The GM and WM segmentation maps were normalised to the SUIT template using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration (Ashburner, 2007). The affine transformation matrix and the flow field were used for the linear and non-linear portion of normalisation respectively, alongside the corrected cerebellar masks, in order to bring the images into Atlas space. Normalised modulated images were analysed with and without spatial smoothing (FWHM 2 mm) to preserve the spatial resolution required to identify cerebellar subfields and to meet the Gaussian distribution requirement for SPM statistical inference.

SPM12's tissue calculator tool was used to calculate total intracranial brain volume for each individual as the summated volume of their GM, WM, and CSF. Whilst other options are available, total intracranial volume is the preferred measure when analysing ageing and neurodegenerative disease populations (Malone et al., 2015).

Separate two-factor ANOVA models were used for GM and WM with condition (eye-disease and PD) and hallucination status (hallucinators and disease-matched controls) to investigate volume differences associated with hallucinations across and within conditions. Age, sex and total intracranial volume were included as nuisance variables. T-contrasts were used for the comparisons: hallucination main effect (CBS, PDHAL < AMD, PD; CBS, PDHAL > AMD, PD) hallucination effects in each condition (CBS < AMD; CBS > AMD; PDHAL < PD, PDHAL > PD) and interaction effects (difference between CBS < AMD and PDHAL < PD). Differences were considered significant at a cluster-level threshold of $p < .05$ with family-wise error (FWE) correction for multiple comparisons.

The Flatmap generator within SPM12's SUIT toolbox was used to display differences in GMV. This algorithm takes the surface of the cerebellum and, through introducing cuts, represents this 3D structure as an unfurled 2D surface. This representation is artificially compressed in the vertical dimension compared to a flattened representation that fully accounts for microscopic folding of the cerebellar anatomy (Van Essen, 2002).

3. Results

3.1. Demographics

Table 2 summarises the demographic data for all 4 groups: eye-disease & hallucinations (CBS), eye-disease controls (AMD), PD with hallucinations (PDHAL), and PD controls (PD). There was no difference in the proportion of patients prescribed L-Dopa and/or dopamine agonists in the PDHAL and PD groups suggesting the hallucinations in Parkinson's disease were not simply a side-effect of medication.

3.2. Voxel Based Morphometry

3.2.1. Cerebellar analysis of grey matter: hallucinators versus controls across both conditions

The main effect of hallucinations on GMV is shown in Fig. 1A/B and Table 3. Hallucinators exhibited lower GMV than non-hallucinators, peaking within both right ($x = -18$, $y = -44$, $z = -50$, $p = .000$) and left ($x = -14$, $y = -42$, $z = -56$, $p = .000$) hemispheric lobules VIIIb, both right ($x = 6$, $y = -54$, $z = -52$, $p = .002$) and left ($x = -1$, $y = -56$, $z = -57$, $p = .018$) hemispheric lobule IX, as well as left hemispheric lobule VIIIa ($x = -29$, $y = -63$, $z = -46$, $p = .001$). The cluster in right hemispheric lobule VIIIb was extensive ($k = 1880$) and spanned into hemispheric lobule VIIIa (Fig. 1A). The findings were the same when we used GM images smoothed images at 2 mm with bilateral clusters peaking within hemispheric lobules VIIIb ($p = .000$) that subsume the other clusters. This suggests that a broad area of lobules IX, VIIIa, VIIIb, and VIIb are affected (Fig. 1B) with local sub-clusters identified in Table 2. These regions of reduced GMV also remained significant when disease duration was included as a nuisance variable alongside age, sex and total intracranial volume. Regions of lower

Table 2 – A summary of the demographic data in each clinical group.

Characteristic	CBS (N = 12)		AMD (N = 9)		PDHAL (N = 7)		PD (N = 9)		*p* value	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	CBS versus AMD	PDHAL versus PD
Age (Years)	79.4	5.19	76	5.54	68.7	6.63	65.1	6.57	.18	.33
Intracranial volume	1.41	.14	1.49	.16	1.45	.09	1.55	.13	.81	.87
MMSE[a]	26.7	1.11	26.8	.91	26.9	3.83	29.7	.47	.82	.061
UPDRS	–	–	–	–	40.0	12.4	25.6	6.2	–	.01
Disease duration[b]	11.5	5.43	8.00	4.87	8.71	4.43	5.8	2.39	.18	.14
Sex	3M:9F		3M:6F		3M:4F		7M:2F		.68[c]	.15[c]
Medication (number of patients)	–		–		L-dopa = 2; L-dopa + DA = 4; DA = 1		L-dopa = 2; L-dopa + DA = 4; DA = 3		–	.68[c]

DA: Dopamine agonist; UPDRS: Unified Parkinson's Disease Rating Scale.
[a] Standard 30 point MMSE in PD but reduced to 28 point MMSE in eye-disease to remove items requiring intact vision.
[b] Data missing for one AMD and one CBS participant.
[c] Chi-squared test.

Table 3 – Results of the voxel based morphometry analysis: Coordinates given in MNI space. K = cluster size. P values are cluster level family wise error corrected.

	MNI coordinates					
	X	Y	Z	K	T	FWE *p*
Regions of lower GMV in hallucinators across conditions						
Right hemispheric lobule VIIIb	18	−44	−50	1880	5.45	.000
Left hemispheric lobule VIIIb	−14	−42	−56	674	5.00	.000
Left hemispheric lobule VIIIa	−29	−63	−46	331	4.67	.001
Right hemispheric lobule IX	6	−54	−52	292	4.27	.002
Left hemispheric lobule IX	−1	−56	−57	206	4.03	.018
Regions of lower GMV in hallucinators within PD						
Right hemispheric lobule VIIIb	18	−44	−50	3806	6.43	.000
Left hemispheric lobule VIIIb	−11	−43	−54	781	5.59	.000
Right hemispheric lobule IX	5	−57	−60	279	4.39	.003
Left hemispheric lobule VIIIa	−30	−63	−47	967	4.24	.000
Left hemispheric lobule IX	−6	−56	−60	327	3.56	.001
Regions of GMV more affected In PD than Eye-disease						
Right Crus 1	46	−74	−31	381	4.98	.001
Left Crus 1	−14	−86	−24	189	5.03	.061
Regions of GMV negatively correlated with UPDRS score						
Right substantia nigra	17	−17	−10	253	5.46	.000
Regions of lower WMV in hallucinators across conditions						
Medulla	4	−47	−60	694	5.85	.000
Regions of WMV more affected In PD than Eye-disease						
Medulla	6	−46	−61	174	4.01	.024
Regions of WMV negatively correlated with UPDRS score						
Midbrain	−5	−30	−5	259	4.09	.000
Right cerebellum	27	−40	−34	160	5.02	.000

GMV were also observed bilaterally in Crus 1 (Fig. 1B), however, these failed to reach the corrected threshold of significance. There were no regions of significantly increased GMV in hallucinators compared to controls.

3.2.2. *Hallucinators versus controls within each condition*

Hallucination effects for PD and eye-disease groups separately are shown in Fig. 2 and Table 3. A similar pattern of reduced GMV in hallucinators compared to non-hallucinators was found in both PD and eye-disease. The interaction effect analyses revealed that the GMV reduction in hallucinators compared to non-hallucinators was significantly greater in PD than CBS within right ($p = .001$) Crus 1 and borderline significant in left ($p = .061$) Crus 1.

3.2.3. *Cerebellar analysis of white matter*

Hallucinators versus controls across both conditions The main effect of hallucinations on WMV is shown in Fig. 3 and Table 3. Hallucinators displayed a region of lower WMV in the medulla compared to non-hallucinators ($x = 4$, $y = -47$, $z = -60$, $p = .000$). There were no regions of significantly increased WMV in hallucinators compared to controls.

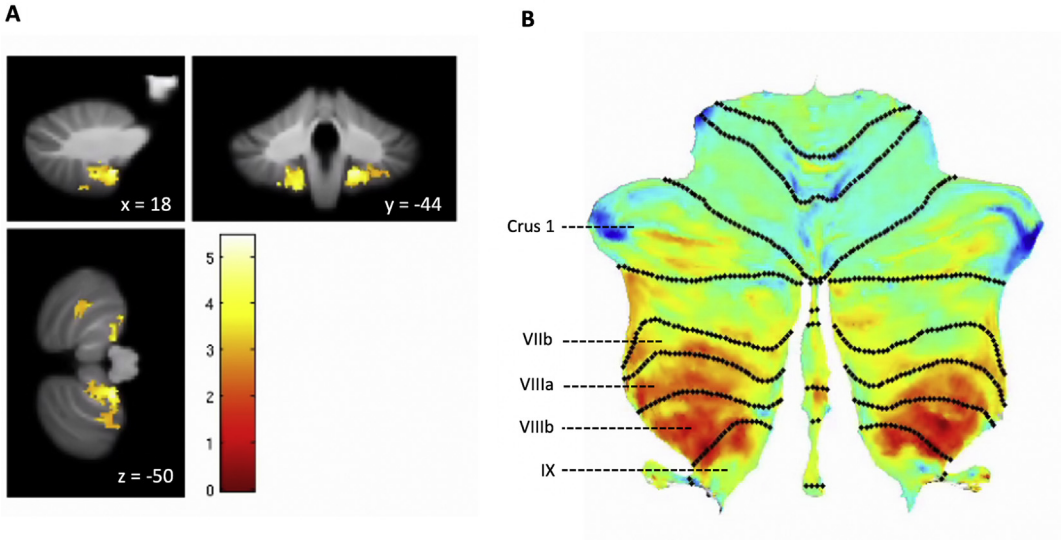

Fig. 1 – (A) Regions exhibiting lower GMV in hallucinators compared to non-hallucinators across both conditions, (B) The same contrast represented on a cerebellar flatmap: (A) The result of second level t-tests, for illustrative purposes presented at $p < .005$ uncorrected for height, k > 200. The colour bar represents T values. The co-ordinates refer to the region of reduced GMV in right hemispheric lobule VIIIb. (B) Relevant hemispheric lobules are labelled. Left of image is left cerebellar hemisphere.

3.2.4. *Hallucinators versus controls within each condition*

WMV hallucination effects for PD and eye-disease groups separately are shown in Fig. 4 and Table 3. This shows the reduction in GMV was greater in PD than eye-disease, confirmed in the interaction analysis (x = 6, y = −46, z = −61, $p = .024$).

3.3. *Correlation with UPDRS score*

As UPDRS scores differed between PDHAL and PD groups, we considered the possibility that the differences in GMV and WMV identified might reflect differences in PD motor symptoms or disease stage rather than hallucinations per se. We therefore looked for positive or negative correlations between UPDRS score and the GMV or WMV images in the PD group. None of the regions linked to hallucinations showed a significant association with UPDRS; however, GMV in the right substantia nigra showed a significant negative correlation with UPDRS score (x = 7, y = −17, z = −10, $p = .000$). Similarly, small regions of WMV in the midbrain (x = −5, y = −30, z = −5, $p = .000$) and right cerebellar hemisphere (x = 27, y = −40, z = −34, $p = .000$) showed significant negative correlation with UPDRS score.

3.4. *Grey and white matter correlation*

In order to establish whether the GM and WM findings might be related, GM and WM volume estimates for each participant

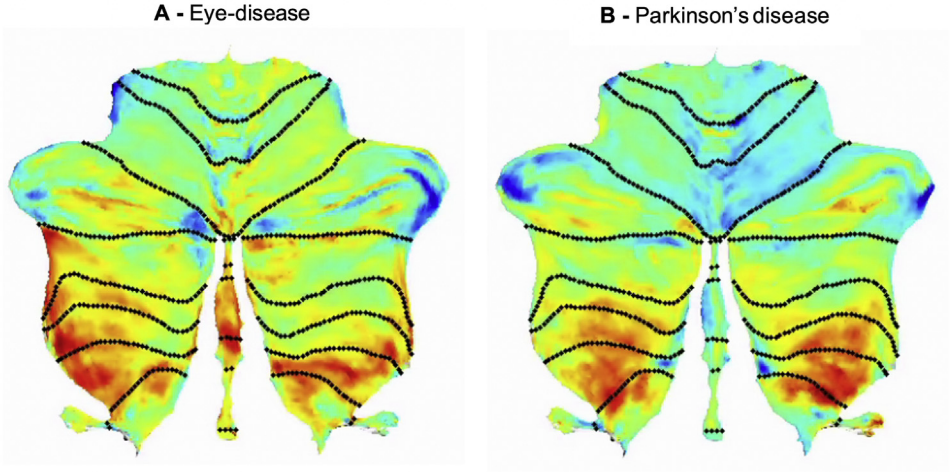

Fig. 2 – Regions exhibiting lower GMV in hallucinators compared to non-hallucinators within: (A) eye-disease and (B) PD. Left of each image is left cerebellar hemisphere.

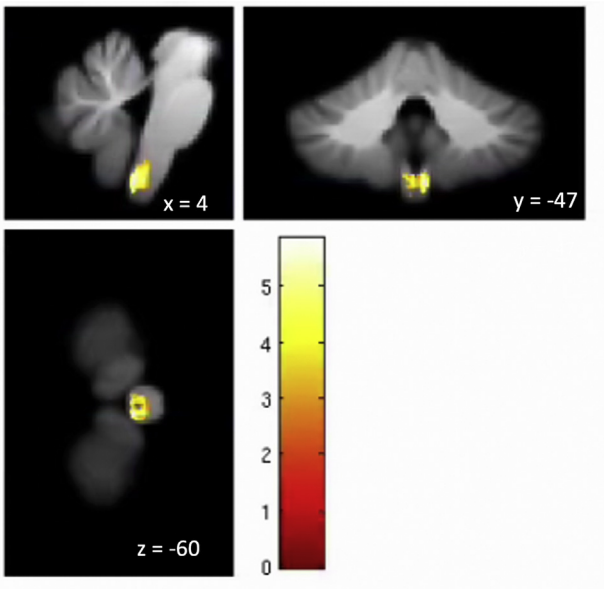

Fig. 3 – Regions exhibiting lower WMV in hallucinators compared to non-hallucinators across both conditions: The result of second level *t*-tests, for illustrative purposes presented at $p < .005$ uncorrected for height, $k > 200$. The colour bar represents T values. One cluster in the medulla reached statistical significance.

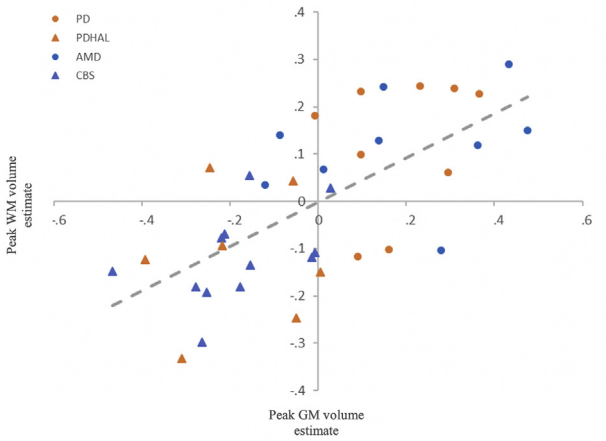

Fig. 5 – The relationship between GM (left cerebellar hemisphere VIII cluster) and WM volume estimates from the across conditions contrast: controlling for age, sex, and total intracranial volume. A positive correlation ($R^2 = .45$) was found across both conditions. No difference in the relationship was observed between conditions.

were extracted from clusters showing hallucination main effects for GM in both left ($x = -14$, $y = -42$, $z = -56$) and right ($x = 18$, $y = -44$, $z = -50$) hemispheric lobules VIIIb and medullary WM ($x = 4$, $y = -47$, $z = -60$) and examined in a regression analysis. A positive correlation was observed between the peak GM and WM volume estimates (left hemispheric lobule VIIIb, $R^2 = .45$; Right hemispheric lobule VIIIb, $R^2 = .36$) while controlling for age, sex, and total intracranial volume (Fig. 5). GM volume from a randomly selected cerebellar region ($x = 18$, $y = -53$, $z = -24$) was not correlated with medullary WM volume ($R^2 = .07$) suggesting the relationship is specific to the hallucination-effect GM and WM regions rather than a non-specific correlation between overall cerebellar and brainstem volume. The correlation was also independent of disease group with a similar relationship found for PD and eye-disease. In both groups, participants with VH were at the lower end of the distribution of WMV and GMV (left lower quadrant in Fig. 5).

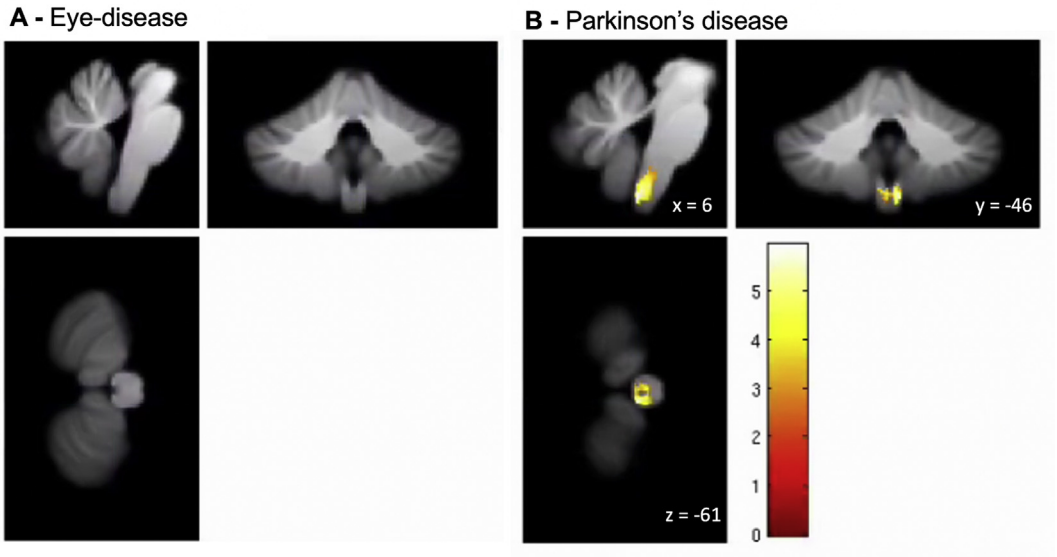

Fig. 4 – Regions exhibiting lower WMV in hallucinators compared to disease matched controls within: (A) Eye-disease, and (B) PD: The regions shown are the result of second level *t*-tests, for illustrative purposes presented at $p < .005$ uncorrected for height. The colour bar represents T-values.

4. Discussion

In this structural MRI study, utilizing cerebellum optimized voxel-based morphometry, we compared patients with and without susceptibility to hallucinations across eye-disease and Parkinson's disease and identified bilateral hemispheric regions of lower cerebellar GMV and a region of lower brainstem WMV in patients who experience hallucinations. Below we discuss the putative role of these regions and their relationship to current theories of hallucination pathophysiology.

4.1. *Attentional theories of hallucinations and the cerebellum*

Perception is thought to be fundamentally predicated upon prediction, in which prior information guides interpretation of incoming information, but also attention, which acts to prioritise these events towards behaviourally relevant aspects of the world. The current conceptualisation of the neural substrates of attention is a multitude of synergistic networks (Corbetta & Shulman, 2002; Michalka et al., 2015; Rosen et al., 2016). One of these, the Dorsal Attention Network (DAN), also known as the frontoparietal network, is thought to direct top-down mediated voluntary allocation of attention, as well as short-term memory (Courtney et al., 1998; Sprague & Serences, 2013). Cerebellar hemispheric lobules VII, VIII, and IX have been argued to comprise a functional node within the DAN based on task-based and resting-state fMRI studies investigating networks subserving attention and memory (Habas et al., 2009; Buckner et al., 2011; Brissenden et al., 2016; Ramanoel et al., 2018).

The perception attention deficit model argues that concurrent attentional and visual perceptual deficits, alongside scene representations, produce the activation of incorrect but environmentally expected perceptual proto-objects, which are pre-attentive structures with limited spatial and temporal coherence (Collerton et al., 2005; Russell et al., 2014). Shine et al. also assert the primacy of attentional deficits with VH arising from a combination of impaired sensory inputs, alongside a relative impairment of recruiting the DAN, resulting in an overreliance on other networks poorly suited to perceptual processing: the Ventral Attentional Network (VAN) and Default-Mode Network (DMN) (Shine et al., 2011, 2014). The VAN is thought to monitor bottom-up information flow and, given this generally requires top-down modulation from the DAN, these two networks are often functionally interactive with concomitant deactivation of the DMN (Asplund et al., 2010; Spreng et al., 2010; Fornito et al., 2012). Hallucinations occur when DMN and VAN intrude due to a failure of modulation by the DAN (Shine et al., 2014). The regions of reduced GMV in hallucinators in the present study were located within DAN cerebellar regions, adding neuroanatomical credence to these cognitive attentional theories of VH. GMV in DAN regions were lower in both PD and eye-disease hallucinator groups, without significant interaction, suggesting DAN involvement may extend beyond PD to other conditions.

The cerebellar regions identified are also involved in visual cognition. Recent studies have evidenced fragmented ipsilateral retinotopic maps within the cerebellum (Brissenden et al., 2018; van Es et al., 2019). A task that required allocation of visual attention across a visual display implicated hemispheric lobules VIIb and VIIIb (Brissenden et al., 2018; van Es et al., 2019); regions of lower GMV found in the present study. These lobules have been found to differentially code visual working-memory and visual attention (Brissenden et al., 2018). Alongside spatially selective responses, a functional gradient of visuospatial attention has been found extending dorsomedial to ventrolateral across lobules VII and VIII (Brissenden et al., 2018). The dorsomedial portions show greater activation during spatial aspects of a task, whilst ventrolateral regions are activated more by increasing demand on visual working-memory. These findings imply involvement of these lobules in spatial attention and working memory and predict deficits of these functions in patients susceptible to hallucinations. Neither the PDHAL or MDHAL study included specific tests of visual attention or working memory so the deficits predicted by the cerebellar findings cannot be tested within the present data set. The general attention score of the MMSE was at ceiling (5/5) in almost all participants across both studies and unlikely to be sensitive to deficits of visual attention.

4.2. *Hallucination phenomenology and crus 1*

The CBS and PDHAL groups both reported complex VH, although differed in reports of passage hallucinations and presence hallucinations that form part of the spectrum of symptoms referred to as PD psychosis (ffytche et al., 2017). These perceptual experiences have been linked to visual motion processing systems and the parietal cortex (Diederich et al., 2014; ffytche et al., 2017). Kellerman et al. identified a corticocerebellar circuit comprised of Crus 1, V5, and Posterior Parietal Cortex (PPC) engaged during an attention-to-motion paradigm (Kellermann et al., 2012). Psychophysical interaction analysis revealed that, during attention, there is enhanced connectivity between the cerebellum and regions of the dorsal visual stream including V5 and PPC. Subsequent dynamic causal modelling indicated that, during attention, V5 influence over PPC was reduced, suggesting diminished bottom-up information flow (Kellermann et al., 2012). Furthermore, V5 was more sensitive to inputs from Crus 1 during attention. The significantly greater difference in Crus 1 GMV between hallucinators and controls in PD than eye-disease, provides a possible explanation for the difference in phenomenology in the two groups. The greater prevalence passage hallucinations in PD may result from greater dysfunction of cerebellar modulation of V5, PPC and the dorsal stream.

4.3. *Serotonin systems and the relationship between GMV and WMV findings*

Imaging studies have previously purported that genetic serotonergic differences, such as different 5HTTLPR alleles, can affect GMV in various brain regions (Canli et al., 2005; Frodl et al., 2008). The short version of this gene confers structural cerebellar differences: increased and decreased GMV in left and right cerebellar hemispheres respectively (Canli et al., 2005). A 5-HT2a inverse agonist has recently shown efficacy in PD psychosis (Cummings et al., 2014),

suggesting that serotonergic dysfunction has a role in hallucinations, opening the possibility of future research identifying contributory genes (Lang et al., 2007; Ballanger et al., 2010; ffytche et al., 2017). The region of reduced WMV identified here overlaps with the caudal raphe nuclei, which provides serotonergic innervation to cerebellar cortex (Saitow et al., 2013), though not specifically to the hallucination-related subregions identified here. The positive correlation between WMV within the brainstem and cerebellar GMV in lobule VIIIb implicated in hallucinations suggests a functional link. The association was found in both PD and eye-disease and was present irrespective of hallucination status. Furthermore, patients with hallucinations fell towards the lower end of both WMV and GMV distributions (lower left quadrant in Fig. 5). It seems unlikely that projections from the caudal raphe nuclei could offer direct explanatory value for cortical 5HT2a upregulation in PD hallucinators, given their limited connectivity to supratentorial structures (Theofilas et al., 2016). Our findings seem to implicate some infratentorial predisposing factor to hallucinate linked to the serotonin system common to both PD and eye-disease, with structural differences in the medullary brainstem likely to contribute to cortical function indirectly through cerebellar projections, rather than directly.

4.4. *Cerebellum and hallucinations in other clinical conditions*

A previous voxel-based morphometry study investigating cerebellar changes associated with auditory-verbal hallucinators in schizophrenia identified similar regions to those found in our study (Cierpka et al., 2017). Lower GMV was found in hemispheric lobule VIIIa when compared to non-hallucinators, and VIIb/VIIIa when compared to healthy controls, as well as an inverse correlation between the GMV and overall positive symptoms (Cierpka et al., 2017). Several case studies provide further evidence of a link between the cerebellum and hallucinations, with reported onset of hallucinations following lesions of the cerebellum (Miyazawa et al., 2009; Bielawski & Bondurant, 2015; Kim et al., 2019). Large-scale imaging studies of hallucinations have not reported cerebellar changes in PD or schizophrenia (for example: Ramírez-Ruiz et al., 2007; García-Martí et al., 2008; Modinos et al., 2009, 2013; Nenadic et al., 2010; Janzen et al., 2012; Watanabe et al., 2013; Gama et al., 2014; van Tol et al., 2014; Lenka et al., 2015). However, this may reflect the methodology used as VBM employing conventional whole-brain templates is suboptimal for normalisation with regards to the cerebellum (Diedrichsen, 2006). This is particularly problematic for parcellating relatively small scale cerebellar subdivisions as the standard templates can result in poor alignment of cerebellar subregions due to considerable inter-individual differences (Diedrichsen, 2006; Cierpka et al., 2017). Alongside such methodological issues, the pervasive notion that the cerebellum is a purely motor structure may have contributed to dismissal of any structural changes identified within larger analyses. We did not replicate the Russell, 2014 finding of increased GMV within cerebellar regions associated with CBS. It is possible that this reflects heterogeneity in cerebellar structural differences within these patients, or methodological differences between the two studies. We made use of the more specifically infratentorial SUIT toolbox and controlled for total brain volume and age in our analysis. Since generalised cerebral atrophy was noted in the Russell study in some of the control and CBS MRI scans, the increased volume in cerebellar regions found in the CBS group might have related to differences in overall brain volume, rather than a specific cerebellar change. Finally, it remains unclear whether the cerebellum and associated pathophysiology may hold explanatory value for CBS caused by visual pathway stroke and cerebrovascular disease. In this clinical context, stroke may cause CBS through a combination of damage to the visual pathway, with consequent deafferentation, together with involvement of the visual cortex itself, contrasting with CBS caused by eye disease alone. Further application of SUIT-based VBM within such populations may shed further light onto the contribution of the cerebellum to hallucinations in CBS caused by cerebral lesions.

4.5. *Limitations*

The primary limitation of this study was the small sample sizes and retrospective nature of the analysis. With larger sample sizes, other aspects of cognition and attention could be included in the analysis to help refine the interpretation of the findings. Imaging at higher field strengths may also help better delineate the cerebellar subfields and brainstem structures involved. Finally, given the cross-sectional design, the hypothesised causative role for the cerebellum in hallucinations outlined here remains entirely speculative as the temporal relationship between GMV or WMV loss and the emergence of symptoms cannot be ascertained.

4.6. *Conclusion*

This study has demonstrated structural cerebellar differences across two aetiologically disparate clinical diagnoses, with associated brainstem WM changes, that are consistent with physiological involvement of attentional systems and visual cognition; both highly influential processes in cognitive and computational aetiological theories of hallucinations. Similar cerebellar findings have been reported for auditory verbal hallucinations in schizophrenia. Thus, whilst this study remains incapable of fully delineating causality, there is a physiologically and conceptually compelling link between these structural cerebellar changes and the susceptibility to generate visual hallucinations which transcends clinical diagnoses.

Author contributions

Mr Timothy Lawn: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Roles/Writing - original draft; Writing - review & editing.

Dr Dominic ffytche: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing - review & editing.

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Declaration of competing interest

The authors declare no competing financial interests.

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