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Anterior Cingulate Integrity: Executive and Neuropsychiatric Features in Parkinson's Disease

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Abstract

Patients with advanced Parkinson's Disease (PD) commonly suffer with significant executive dysfunction and concomitant visual hallucinations. Although the underlying pathophysiology remains poorly understood, numerous studies have highlighted the strong association between these neuropsychiatric features suggesting that they may share common neural pathways. Whilst previous neuroimaging studies have identified widespread volume loss across a number of cortical regions, to date no studies have utilised Proton Magnetic Resonance Spectroscopy (MRS) to provide insights into how neurometabolic changes may relate to such symptoms. In this study, twenty patients underwent MRS to determine the N-Acetyl Aspartate/Creatine ratio, which reflects the degree of neuronal integrity in neurodegenerative diseases. Voxels were obtained from a test region within the anterior cingulate cortex, an area critical for a wide range of executive mechanisms as well as from a control volume in the posterior cingulate cortex. Lower N-Acetyl Aspartate/Creatine ratios in the anterior but not the posterior cingulate cortex significantly correlated with poorer executive function on tasks of attentional set-shifting and response inhibition. In addition, lower levels of this metabolite were associated with more severe psychotic symptoms (as measured by the Scales for Outcomes in Parkinson's disease-Psychiatric Complications) and poorer performance on the bistable percept paradigm, a recently developed neuropsychological probe of visual hallucinations in PD. Levels of N-Acetyl Aspartate/Creatine were significantly lower in hallucinators compared to non-hallucinators within the anterior cingulate cortex but did not differ in the posterior cingulate cortex. These results suggest that loss of neuronal integrity within the anterior cingulate cortex plays an important role in the pathophysiology underlying executive functioning and visual hallucinations in PD.

Introduction

Given their significant contribution to disease burden, the non-motor symptoms of Parkinson's Disease (PD) are gaining increasing recognition (for review see [1]). Deficits in executive function are common in PD [2] and previous work has highlighted the association between this pattern of cognitive impairment and the presence of visual hallucinations [3, 4]. This relationship suggests that these neuropsychiatric features may share common neural pathways and a greater understanding of this pathophysiology would therefore be of importance for the development of future therapeutic strategies.

Executive dysfunction in PD has commonly been related to frontostriatal mechanisms [5, 6] whereas visual hallucinations have been linked to Lewy Body pathology within temporal cortical structures, such as the amygdala and parahippocampus [7]. Structural imaging studies have confirmed atrophy across these limbic regions in hallucinating PD patients [8, 9], as well as degeneration across frontal and visual association regions [3, 10]. Work utilising functional MRI (fMRI) has demonstrated that PD patients with visual hallucinations respond to the presentation of simple visual stimuli with greater frontal and caudate nucleus activation and less visual cortical activation than non-hallucinating subjects [11]. This finding implicates frontostriatal circuitry where impaired processing of visual information may trigger 'higher order' frontal regions, recruited via the basal ganglia. These regions could then modulate the selection of behavioural outputs, to generate a 'false' internal image in an effort to compensate for poor stimulus characterisation. However, a recent fMRI paradigm utilising the presentation of more complex visual stimuli failed to find any evidence to support this 'top-down' compensatory process [12], thus the contribution of neocortical processes in hallucinations remains unclear.

A number of researchers have highlighted the likely role of reduced visual processing and integration in the generation of hallucinations arising from sensory perceptual impairments [13-15]. More recently, our own group has proposed an Attentional Control hypothesis, which highlights the key role of the brain's Default Mode Network (DMN, centred in the posterior cingulate and limbic regions) and Ventral Attention Network (VAN, centred in the ventral frontal, temperoparietal, basolateral amygdala and ventral striatal regions) over the Dorsal Attention Network (DAN, centred in the dorsolateral prefrontal, posterior parietal and striatal regions). In brief this hypothesis posits that the pathophysiology underlying PD disrupts these systems leading to a relative inability to recruit activation in DAN in the presence of an ambiguous percept. This in turn leads to an over-reliance on DMN processing and salience arising from the VAN which generates visual misperceptions and hallucinations [16]. Attentional deficits consistent with reduced activity in DAN are well known in PD hallucinators [17] and a recent empiric study utilising a novel neuropsychological task (the Bistable Percept Paradigm - BPP) which probes such activity found reduced performance in PD patients with visual hallucinations [18]. Thus it appears that hallucinations in PD represent a failure in the tight regulation across networks that normally coordinate attention and the accurate perception of a stimulus.

Whilst Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) has been used extensively to assess metabolic brain activity across a range of neurodegenerative diseases, this technique has not been targeted for the specific investigation of

executive dysfunction or hallucinations in PD. Previously the N-Acetyl Aspartate (NAA) and Creatine (Cr) ratio (NAA/Cr) has been found to be a reliable indicator of neuronal integrity and studies in PD have demonstrated that a reduced level of this metabolite in the Posterior Cingulate (PCC) and temporoparietal cortices is associated with memory impairment and PD dementia [23-25]. A large body of work has identified the anterior cingulate cortex (ACC) as a key region in the integration and switching between the attentional control networks (for review, see Neurosci Biobehav Rev. 2012 Jan;36(1):90-110 [19]) and this region is a known predeliction site for the classic Lewy body pathology of PD (Acta Neuropathol. 2001 Oct;102(4):355-63). Given these observations, we hypothesise that a loss of neuronal integrity within the ACC (but not the PCC central to the DMN) directly associates with the severity of executive dysfunction and the severity of hallucination symptoms in patients with PD. To test this hypothesis, this study conducted ^{1}H-MRS to measure neural integrity (NAA/Cr ratio) in both the ACC and PCC in twenty PD patients who had undergone tests of executive functioning as well as neuropsychiatric assessment for hallucinations.

Methods

Participants

Twenty patients were recruited from the Brain and Mind Research Institute PD Research Clinic. All patients satisfied UKPDS Brain Bank criteria and were deemed unlikely to have dementia [26] or major depression according to DSM-IV [27] criteria by consensus rating of a Neurologist (SJGL) and a Neuropsychologist (SLN). Demographic details are presented in Table 1. Permission for the study was obtained from the local research ethics committee and all patients gave written informed consent.

All patients underwent assessment in their 'on' state and Dopamine Dose Equivalence (DDE, mg/day) was calculated for their PD medications [28]. The patients were all rated as between Hoehn and Yahr stages I–IV and were assessed on section III of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Eighteen of the twenty patients were taking levodopa, while one patient was using a rotigotine patch and one patient was untreated. Of the eighteen patients taking levodopa, five were on an additional dopamine agonist, seven were on levodopa alone and six of the patients combined their levodopa with entacapone. Five of the patients in the cohort were taking a selective serotonin reuptake inhibitor for mood and three were taking a nocturnal benzodiazepine to aid sleep.

Neuropsychiatric Assessment

Cognition was assessed by a Clinical Neuropsychologist using standardised tests. Executive functioning was measured using Part B of the Trailmaking Test [29], reflecting set-shifting under timed conditions [30]. Response inhibition was examined using the Delis Kaplan Executive Functioning System (DKEFS) Stroop task (inhibition subtask, age-scaled score) [31]. For reporting purposes the MMSE was also administered [32].

In addition to this battery, all patients performed the Bistable Percept Paradigm (BPP) described in detail elsewhere [18]. In brief, the BPP is a computer-based task that requires participants to process visual stimuli and records whether information is

being correctly or incorrectly interpreted. Subjects evaluate a series of monochromatic images, which represent either bistable/ambiguous or stable/non-ambiguous percepts. The task assesses whether patients fail to characterise all of the content presented in a bistable percept (representing a failure to engage the DAN and missing a bistable percept) or misperceive the images being presented (representing a failure in the DMN and VAN). As detailed previously [18], a BPP error z-score was calculated for patients relative to an aged-matched healthy control sample.

The presence of visual hallucinations and misperceptions were assessed by a semi-structured interview in conjunction with a witness (most commonly a spouse), utilizing the Scales for Outcome in PD-Psychiatric Complications (SCOPA-PC). This questionnaire contains a subsection of four questions (SCOPA-PC$_{1\text{-}4}$) that specifically query the presence of visual misperception and hallucinations, as well as probing for the presence of delusional thinking [27]. Depressive and anxiety symptoms were measured using the Hospital Anxiety and Depression Scales [33].

Neuroimaging

Imaging was conducted on the day of clinical assessment and took place at the Brain & Mind Research Institute imaging centre on a 3-Tesla GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) using an 8-channel phased array head coil. The following images were acquired in order: (a) Three-dimensional sagittal whole-brain scout for orientation and positioning of subsequent scans; (b) a T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) sequence producing 196 sagittal slices (TR = 7.2ms; TE = 2.8ms; flip angle = 10°; matrix 256 x 256; 0.9mm isotropic voxels) to aid in the anatomical localisation of sampled voxels; and (c) Single voxel ^{1}H-MRS using Point RESolved Spectroscopy (PRESS) acquisition with two chemical shift-selective imaging pulses for water suppression. Spectra were shimmed to achieve full-width half maximum (FWHM) of <13Hz.

Spectra were acquired separately from voxels placed midline in the ACC and PCC (see Figure 2). A voxel measuring 2x2x2cm was used for both locations using identical imaging parameters (TE = 35ms, TR = 2000ms and 128 averages). Anatomical localisation of voxel placement was based on the Talaraich brain atlas [34] and positioning was guided by the T1 MPRAGE image. Following MRS acquisition, data was transferred offline for post processing using the LCModel software package [35]. As demonstrated in Figure 3, all spectra were visually inspected separately by two different raters to ensure consistent spectra and poorly fitted metabolite peaks as reflected by large Cramer–Rao lower bounds (>20) were excluded from further analysis. For each patient, NAA was computed relative to Creatine (NAA/Cr).

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (version 19 for Mac). Pearson coefficients were used for all correlations unless otherwise stated. Partial correlations were used when a covariate was included. Analyses between hallucinators and non-hallucinators were conducted using students t-tests. All analyses were 2-tailed and used an alpha level of 0.05.

Results

Table 1 displays the demographic, neurological and neuropsychiatric details for this sample. On average, patients in the study were 62 years of age (range 51-74 years), with an average disease duration of almost six years (range = 1-13). Table 2 demonstrates the relationship between the NAA/Cr ratio and neurological and neuropsychiatric data. The NAA/Cr ratio in the PCC was only significantly associated with motor symptom severity, and not with executive functioning, BPP performance or the presence of hallucinations, as predicted. Also, the NAA/Cr ratio in the PCC was not significantly different between hallucinators and non-hallucinators ($t = -0.5$, ns).

The ACC NAA/Cr ratio did not correlate with MMSE, disease duration, DDE or affective symptoms, but there were lower ACC NAA/Cr ratios with increasing age and motor symptom severity (UPDRS III). As predicted, poorer performance on (the age-adjusted) tasks of executive functioning (set-shifting, TMT-B and response inhibition, Stroop) and the BPP correlated with lower ACC NAA/Cr ratios (Figure ??), even after adjusting for motor symptom severity. Furthermore, lower ACC NAA/Cr levels were also associated with higher psychiatric symptoms, as measured by the SCOPA-PC (Figure ??), even after correcting for motor symptom severity. The ACC NAA/Cr ratio was significantly lower in patients who reported having visual hallucinations compared to those who did not report this symptom ($t = 2.2$, $p < 0.05$), despite there being no differences in age ($t = -1.7$, ns), motor severity ($t = -1.4$), disease duration ($t = -0.2$, ns), DDE ($t = -0.01$, ns) or affective symptoms (HADS depression: $t = -0.9$, ns; HADS anxiety: $t = -0.8$, ns) between the two groups.

Discussion

This study represents the first use of ^{1}H-MRS in the investigation of executive dysfunction and hallucinations in PD. Reduced levels of NAA/Cr within the ACC were correlated with impairments on attentional set-shifting and response inhibition, as well as self-reported symptoms of hallucinations and performance on the BPP, a task that can probe the severity of visual hallucinations in PD. Importantly, these findings did not simply reflect the likely confounds of disease severity. Nor did they relate to disease duration, dopamine dose equivalence or affective disturbance. By contrast, the NAA/Cr ratio within the PCC did not reveal any such correlations. These findings suggest that neuronal integrity within the ACC may play a critical role in the pathophysiology underlying the related neuropsychiatric features of executive dysfunction and hallucinations in PD.

NAA represents an abundant amino acid concentrated within neurons rather than glial cells in the brain. It is believed to have a wide range of possible functions and has been implicated in mediating osmoregulation and acid-base homeostasis [36], serving as a storage form for aspartate [37], initiating protein synthesis through donation of an acetyl group [38], and transporting carbon molecules from pyruvate into lipids across the mitochondrial membrane [39]. Thus reduced levels of the metabolite NAA on ^{1}H-MRS has been taken to represent either a depletion of neuronal populations or a loss of neuronal function in these regions [40]. Although there is currently a dearth of studies exploring clinicopathological correlations of the NAA/Cr ratio in PD, a small number of studies have been conducted in patients with Alzheimer's disease [41]. These have revealed significant decreases in NAA levels, which have been further correlated with

cognitive decline and increasing pathological change including counts of amyloid plaques and neurofibrillary tangles (for review see [42]).

A recent clinicopathological study has reported that compared to PD patients without visual hallucinations those who did report this symptom had significantly higher Lewy body densities in the ACC, as well as middle frontal, middle temporal and transentorhinal cortices [43]. These findings suggest that the pathology underlying visual hallucinations is more widespread than the temporal lobe and is likely to disrupt frontostriatal circuitry. However, it should be noted that the pathology may not necessarily be diffuse, given that the authors of this clinicopathological study did not find significant changes throughout the parietal cortex.

The ACC has been highly implicated in the control of executive functions [19] and is considered to be a key hub across the attentional networks [20-22]. A recent attentional control hypothesis of hallucinations and misperceptions in PD [16] has proposed that that there is a relative inability to recruit activation in the DAN in the presence of an ambiguous percept, leading to an over-reliance on DMN processing and salience arising from the VAN. The loss of functional integrity in the region of the ACC found in this study gives weight to this proposal and might suggest that hallucinations arise from a breakdown between competing yet complementary attentional networks.

In addition to attentional deficits, perceptual difficulties have been widely acknowledged as playing a major role in the generation of visual hallucinations in PD. A wide range of potential pathophysiological mechanisms have been suggested including retinal impairments right through to the higher integration of external sensory information with pre-formed internal images [14, 15, 44-46]. In support of these hypotheses, previous volumetric studies have revealed grey matter loss in PD hallucinators across the visual association regions [3, 10]. However, the current study did not perform ^{1}H-MRS in any voxel from the visual association cortex and clearly this would represent an important consideration for future spectroscopy studies.

Although further work will be required to confirm the findings presented here, a greater understanding of the pathophysiology underlying executive dysfunction and hallucinations has significant clinical implications in PD, as well as a host of other conditions that experience this phenomenon. It is possible that ^{1}H-MRS of the NAA/Cr ratio might represent a useful clinical biomarker in PD allowing for the prediction of cognitive decline and hallucinations, as well as for the objective monitoring of therapeutic interventions.

Table 1:
Demographic, neurological, psychiatric and spectroscopic details of the sample (n = 20)

	Mean	**SD**
Age, years	62.3	5.5
Education, years	13.9	3.0
H & Y, stage	2.2	0.2
UPDRS-III	23.3	9.5
Disease duration, years	5.9	3.1
Dopamine dose equivalence, mg	806.3	526.4
Mini-Mental State Examination	27.9	2.0
HADS, anxiety	4.2	3.4
HADS, depression	3.7	3.9
SCOPA-PC (1-4)	1.3	2.1
Stroop, age-scaled score	10.3	3.5
Trailmaking Test, Part B, z-score	-0.1	1.0
Bistable percept paradigm, errors, z-score	-1.7	2.0
NAA/Cr ratios		
Anterior Cingulate	1.2	0.2
Posterior Cingulate	1.4	0.1

Table 2:
Correlations between anterior and posterior cingulate NAA/Cr and neurological and neuropsychiatric data (n=20)

	Anterior	**Posterior**
Age, years	-0.56**	-0.35
H & Y, stage	-0.03	0.03
UPDRS-III	-0.45*	0.51*
Disease duration, years	-0.23	-0.07
Dopamine dose equivalence, mg/day	0.34	0.18
Mini Mental State Examination	0.05	-0.29
HADS, anxiety	-0.36	0.36
HADS, depression	-0.31	0.28
SCOPA-PC (1-4)	-0.45*	-0.25
Trailmaking Part B, z-score[a]	0.68**	0.39
Stroop, age-scaled score[a]	0.54*	0.03
Bistable percept paradigm, error z-score[a]	-0.61**	-0.15

[a] Spearman correlation, * $p < 0.05$, ** $p < 0.01$

HADS, Hospital Anxiety and Depression Scale

SCOPA-PC, Scales for Outcome in Parkinson's Disease- Psychiatric Complications

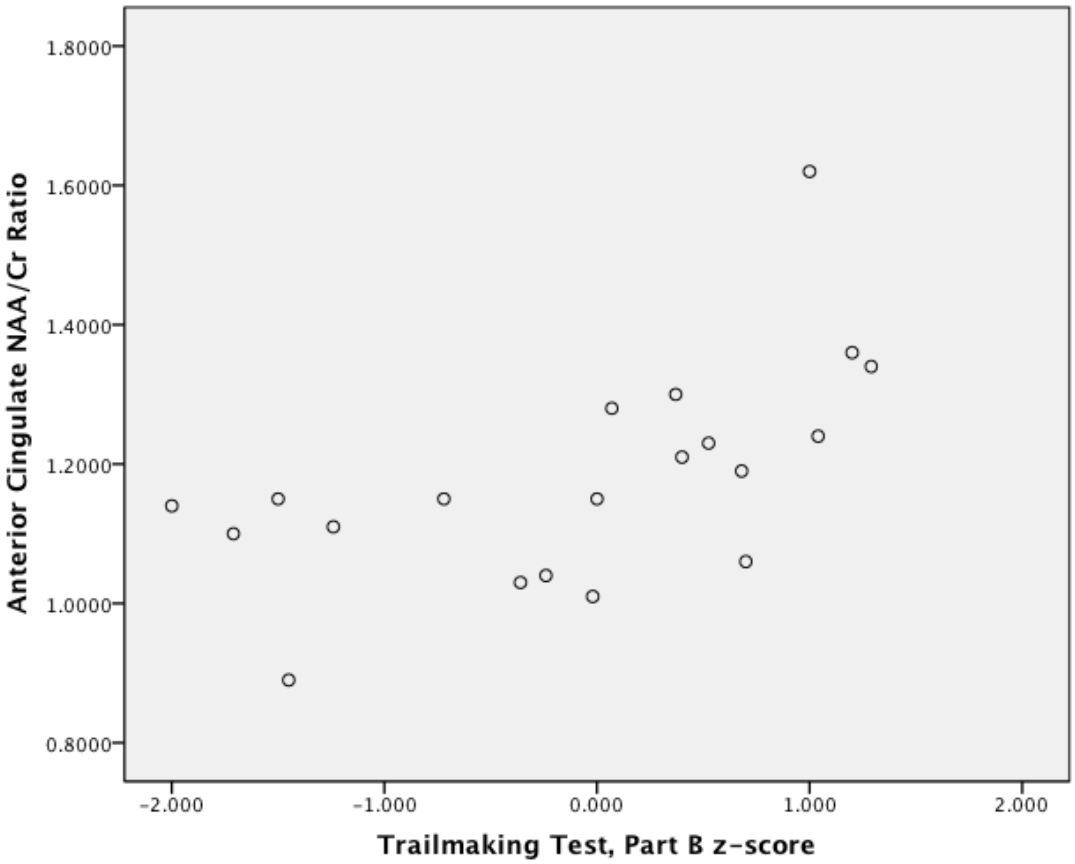
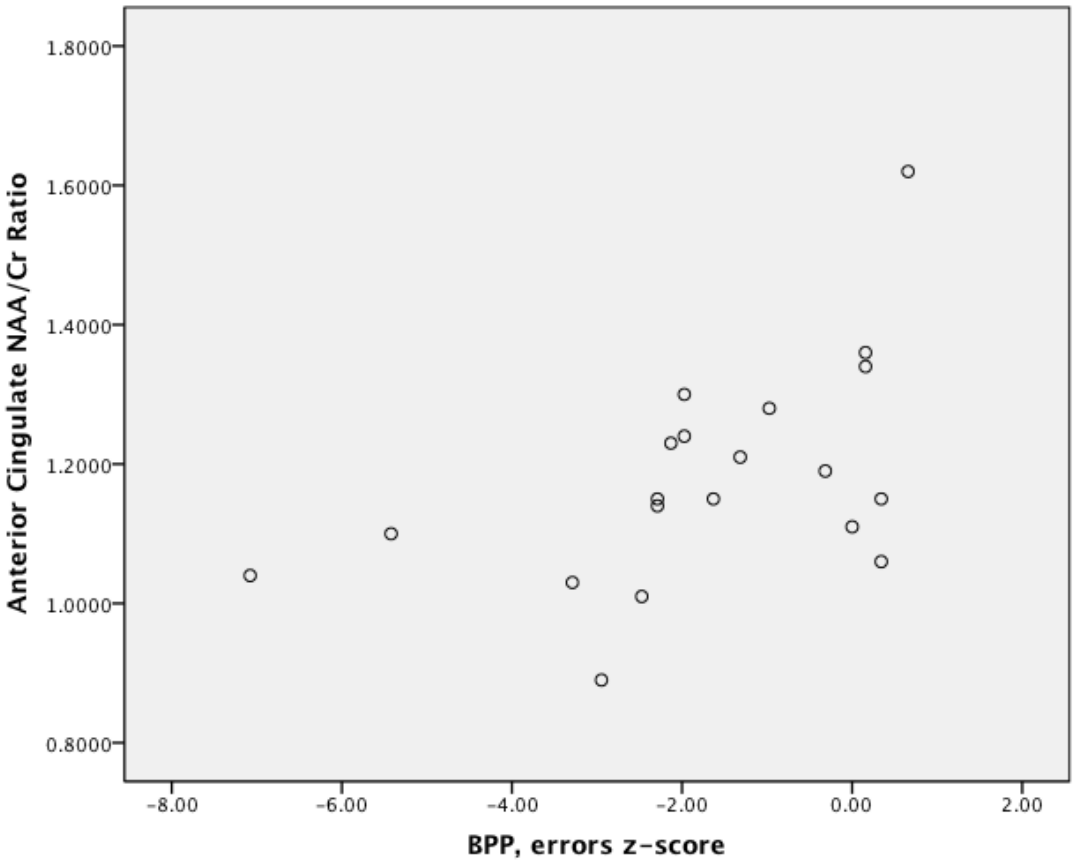


Figure 1: Scatterplot demonstrating the relationship between Anterior Cingulate NAA/Cr ratios and performance on a task of set-shifting (Part B of Trailmaking Test, z-score).


Anterior Cingulate NAA/Cr Ratio
1.8000
1.6000
1.4000
1.2000
1.0000
0.8000
-8.00
-6.00
-4.00
-2.00
0.00
2.00
BPP, errors z-score

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