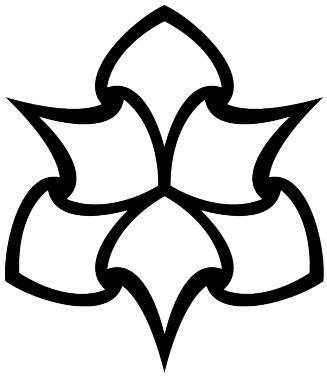

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Quantitative EEG and cholinergic basal forebrain atrophy in Parkinson's disease and mild cognitive impairment

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Abstract

Cholinergic degeneration is a key feature of dementia in neurodegenerative conditions including Alzheimer's disease (AD) and Parkinson's disease (PD). Quantitative EEG metrics are altered in both conditions from early stages, and recent research in people with Lewy Body and AD dementia suggests these changes may be associated with atrophy in cholinergic basal forebrain nuclei (cBF). To determine if these relationships exist in pre-dementia stages of neurodegenerative conditions, we studied resting-state EEG and *in vivo* cBF volumes in 31 people with PD (without dementia), 21 people with mild cognitive impairment (MCI), and 21 age-matched controls. People with PD showed increased power in slower frequencies and reduced alpha reactivity compared to controls. Volumes of cholinergic cell clusters corresponding to the medial septum and vertical and horizontal limb of the diagonal band, and the posterior nucleus basalis of Meynert, correlated positively with; alpha reactivity in people with PD ($P < 0.01$); and pre-alpha power in people with MCI ($P < 0.05$). These results suggest that alpha reactivity and pre-alpha power are related to changes in cBF volumes in MCI and PD without dementia.

Keywords
Parkinson's disease, mild cognitive impairment, EEG, MRI, cholinergic

Introduction

Cortical cholinergic denervation is widely reported in Alzheimer's disease (AD) and Lewy body parkinsonian disorders (LBD), including Parkinson's disease (PD) and in particular Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) (Bohnen et al., 2018; Craig et al., 2020). Cortical cholinergic innervation originates primarily in the nucleus basalis of Meynert (nbM) of the basal forebrain (BF) (Mesulam et al., 1983). Early neuropathological studies reported severe nbM neuronal loss in the advanced stages of these diseases (Candy et al., 1983; Liu et al., 2015). More recently, in-vivo structural MRI combined with stereotactic mapping of the BF (Kilimann et al., 2014) revealed that nbM degeneration may occur early, and is associated with emerging cognitive deficits in AD (Kilimann et al., 2014; Schmitz and Spreng, 2016), PD (Ray et al., 2018; Schulz et al., 2018) and DLB (Schumacher et al., 2020b).

Resting-state quantitative EEG (qEEG) may index pathophysiological changes associated with cognitive neurodegenerative disorders. The dementia stage of AD and LBD is characterised by increased EEG slowing compared to healthy controls, which is typically more severe in LBD (Babiloni et al., 2011; Bonanni et al., 2008; van der Zande et al., 2018). Studies conducted in the mild cognitive impairment (MCI) stage suggest that early qEEG abnormalities may be specific to LBD (Bonanni et al., 2015; Schumacher et al., 2020a).

Changes to alpha activity are frequently reported (Bonanni et al., 2008). Alpha reactivity represents the magnitude of alpha rhythm attenuation, from eyes-closed to eyes-open. Lower alpha reactivity may reflect EEG slowing (i.e. failure of alpha rhythms to emerge) and/or lack of neural desynchronization (i.e. failure to supress alpha rhythms). Reduced alpha reactivity has been reported in PDD and DLB (Schumacher et al., 2020b), AD (Babiloni et al., 2010; Fonseca et al., 2011; Schumacher et al., 2020b; van der Hiele et al., 2007b), and MCI (Babiloni et al., 2010).

The mechanistic underpinnings of these EEG abnormalities are not fully understood, but cholinergic system changes may play a role (Babiloni et al., 2013; Riekkinen et al., 1991). Recently, neuroimaging reports have suggested that cortical cholinergic

pathways may mediate alpha reactivity. Wan et al. (2019) reported that in healthy individuals, increased functional connectivity (measured with functional MRI) between the nbM and the visual cortex was associated with greater alpha reactivity. In the same paper, reduced alpha reactivity was shown to correlate with white matter hyperintensity load along nbM-visual cortex fibre tracts in older participants. More recently, greater loss of alpha reactivity was reported among DLB and PDD in comparison to AD, which was also associated with smaller nbM volumes in PDD (Schumacher et al., 2020b).

The research described above implies that qEEG measures may be associated with cholinergic changes that underpin cognitive neurodegenerative conditions. Whether this relationship exists in predementia stages of PD and other dementias is still to be determined. The first aim of the current study was to assess qEEG measures in a clinically diverse predementia cohort including people PD (without dementia), MCI (associated with AD or vascular dementia), and age-matched controls. Secondly, we explored the relationship between qEEG measures and volumetric changes within cholinergic basal forebrain nuclei.

Materials and methods

Participants

This study involved a total of 73 participants. Thirty-one were diagnosed with PD according to UK PD Society Brain Bank Criteria Twenty-one had been diagnosed with MCI based on established criteria (Albert et al., 2011). Twenty-one were healthy controls of a similar age to those with a neurodegenerative diagnosis. People with PD and MCI were recruited from the Movement Disorders Clinic and the Memory Clinic at the University Medical Centre Ljubljana, respectively. Consecutive patients who were eligible and willing to take part were included. Healthy controls were recruited from the local community from advertisements in waiting rooms and newsletters. Data collection took place at University Medical Centre Ljubljana in 2013 and 2014, and forms part of a larger observational study with the broad aim of developing markers of cognitive decline and neurodegeneration. Ethical approval for the study

was provided by the Slovenian National Medical Ethics Committee. All participants provided informed written consent in accordance with the Declaration of Helsinki.

Exclusion criteria for all groups included; history of neurological disease or mental disorders (clinical disorders or acute medical conditions), including previous large-artery stroke or cerebral haemorrhage, history of moderate to severe head injury, major depression, prior or current drug or alcohol abuse, and contraindications to MRI. No participants with MCI met diagnostic criteria or had characteristic clinical features to suggest other disorders. Those with PD and MCI were excluded if cognitive symptoms and examination suggested a diagnosis of dementia. No healthy controls met diagnostic criteria for MCI based on cognitive and neuropsychological assessment (Albert et al., 2011).

EEG acquisition and pre-processing

Resting state EEG recordings were always conducted between the hours of 09:00 and 11:00. Recordings were acquired from all participants from 32 active Ag/AgCl electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, TP9, CP5, CP1, CP2, CP6, TP10, P7, P3, Pz, P4, P8, PO9, O1, Oz, O2, PO10), mounted on an actiCAP (Brain Products GmbH, Germany), positioned in accordance with the extended 10-20 system (Jasper, 1958), with FCz serving as the physical reference and AFz as ground. Recordings were amplified with a BrainAmp MR plus amplifier (Brain Products GmbH, Germany) and digitized at a sampling frequency of 512 Hz. Filtering of the raw EEG data was not used. Before recording, the subjects' scalp was gel-abraded under each electrode to lower impedances under 5 kΩ homogenously across electrodes. Approximately 300 seconds of data were recorded from each participant in each of the eyes-closed and eyes-open conditions.

Pre-processing of EEG data was performed using the EEGLAB toolbox (Delorme and Makeig, 2004) and MATLAB 2019a (Mathworks, USA). Recordings were first band-pass filtered between 0.5 and 40 Hz. Noisy data segments and bad channels were removed using the default parameters of the clean_artifacts function (default parameters: Channel: 0.85, Line noise: 4, Burst: 5, Window: 0.25) within EEGLAB, which uses the artifact subspace reconstruction method to identify contaminated data. Bad

channels were replaced using spherical spline interpolation and remaining data were recomputed against the average reference. Across all participants, an average of 2 channels were removed. Data were then split into non-overlapping epochs of 2 seconds and subsequently decomposed using Independent Component Analysis (ICA, EEGLAB, Infomax algorithm; Makeig et al., 1996) to perform semi-automated and visual-inspection based rejection of epochs on the derived components (Delorme et al., 2007). To mark epochs for rejection, the following parameters were used in EEGLAB: abnormal values (+/- 25 SD), and abnormal spectra (+/- 50 dB in 0-2 Hz frequency range, +25 -100 dB in 20-40 Hz frequency range). Remaining epochs following automatic rejection underwent further visual inspection for artifacts. ICA was then performed on the remaining epoched data, to inspect and reject components contaminated with eye-movement and muscle artifacts, indicative of non-neural activity. The number of epochs accepted for further analysis ranged from 80-90, in each of the eyes-closed and eyes-open conditions.

For each 2 second epoch, a power spectral density (PSD) was estimated using Welch's method (50% Hamming window), providing a frequency resolution of 0.5 Hz, which was then averaged across all epochs to provide a power spectral density for each electrode.

Global EEG frequency analysis

Global (over all electrodes) relative power was estimated for standard EEG frequency bands including delta: 2–4 Hz, theta: 4–5.5 Hz, pre-alpha: 5.5-8 Hz, alpha: 8–13 Hz, beta: 13-30 Hz, calculated as the sum of EEG power in each frequency band divided by the total EEG power between 2-30Hz. The pre-alpha band was included based on previous studies in LBD (Bonanni et al., 2008; Schumacher et al., 2020a).

Using global relative power, two ratios were also calculated: (i) slow/fast frequencies = sum of delta, theta, and pre-alpha power, divided by the sum of alpha and beta power (Latreille et al., 2016); (ii) theta/alpha = theta power divided by alpha power (Schumacher et al., 2020a).

EEG Alpha reactivity analysis

EEG data from three occipital electrodes (O1, O2, Oz) were used for alpha reactivity analysis, following (Schumacher et al., 2020b; Wan et al., 2019). The PSD for each of these electrodes was averaged for eyes-open and eyes-closed conditions, separately. Alpha reactivity was then calculated as:

$$alphareactivity = \frac{eyesclosedalphapower - eyesopenalphapower}{eyesclosedalphapower}$$

Using the above formula, alpha power was calculated as the relative power within a frequency bin (± 2 Hz) around the individual alpha peak frequency (Schumacher et al., 2020b). Individual alpha peak frequency (IAF) corresponds to the peak in the PSD in an extended alpha frequency band from 6-14 Hz, using the eyes-closed data (Babiloni et al., 2010). Individual alpha peak frequency was used to obtain alpha power, in place of the standard alpha boundaries, to account for the shift of the alpha peak to slower frequencies in cognitive neurodegenerative conditions (Babiloni et al., 2010). Accordingly, a larger alpha reactivity value indicates greater attenuation of alpha power from eyes-closed to eyes-open.

EEG was not performed in 6 participants from the PD group, 2 from MCI, and 4 from controls. EEG analysis therefore included 25 PD, 19 MCI, and 17 controls.

MRI acquisition

MRI data were acquired using a 3T Philips Achieva MRI system. T1-weighted structural MRI data were acquired using a 3D-TFE sequence (repetition time = 9.9 ms, echo time = 4.5 ms, flip angle = 8°, matrix of 320x320x237, isotropic 0.8 mm resolution).

MRI pre-processing

T1 weighted images were automatically segmented into grey matter, white matter, and cerebrospinal fluid (CSF) partitions of 1.5mm voxel size using the Statistical Parametric Mapping 12 toolbox (SPM, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 2019a (Mathworks, USA). The resulting grey and

white matter partitions of each participant were then high-dimensionally registered together using DARTEL (Ashburner, 2007). The grey matter segments were then warped to MNI space using the individual flow fields from DARTEL registration, and voxel values were modulated for volumetric changes introduced by the high-dimensional normalisation.

Regions of interest (ROI) cholinergic BF (cBF) nuclei were identified using a stereotactic map, created via MRI and histological preparation of a post-mortem brain of a 56-year-old male who died without any evidence of cognitive decline or psychiatric illness (Kilimann et al., 2014). Cholinergic nuclei were identified and delineated on digital pictures of the stained brain slices, following Mesulam's nonclamenture (Mesulam et al., 1983), then manually transferred into the corresponding magnetic resonance slices. Transformation of the delineations from the space of the dehydrated brain into the space of the *in situ* brain scan was performed using a high-dimensional non-linear registration between the two brain scans (Ashburner and Friston, 1999) before final transformation from *in situ* space into MNI space using the DARTEL (Diffeomorphic Anatomic Registration using Exponentiated Lie algebra) registration method (Ashburner, 2007; Klein et al., 2009).

The cholinergic subdivisions of interest for the current analysis include cell clusters corresponding to the medial septum, and the vertical and horizontal limb of the diagonal band (Ch1-2 in Mesulam's nomenclature (Mesulam et al., 1983)), nbM (Ch4), and a posterior nbM region (Ch4p). Grey matter volumes in cBF ROIs were calculated by summing the grey matter voxel values within the corresponding region of interest masks in template space (Ashburner, 2009). Global grey matter and cBF volumes were further scaled via ANCOVA, using total intracranial volume (TIV) as a covariate, to extract unstandardised residual values which were then used as input variables in further analyses. Therefore, negative cBF values indicate smaller volumes than expected given head size, while cBF values above zero indicate larger volumes than expected given head size.

MRI data were not acquired from 1 participant from the PD group, 1 from MCI, and 1 from controls. Analysis of cBF volumes therefore included 30 PD, 20 MCI, and 20 controls.

Statistical Analyses

Statistical analyses were conducted in IBM SPSS statistics 26. Univariate ANOVAs (controlling for age, sex, and TIV-normalised grey matter (GM) volume (for volumetric data only)) were used to compare demographics, qEEG metrics, and TIV-normalised cBF volumes between groups (PD, MCI, controls). Significant group level differences were followed up with post-hoc pairwise comparisons, with Bonferroni adjustment at $p<0.05$.

Partial correlations were conducted in each group separately to determine the relationship between subregional cBF volumes and qEEG metrics. These were controlled for age, sex, and TIV-normalised GM volume to ensure relationships were independent of demographic characteristics and degeneration across the wider brain. All p-values from partial correlation analyses were false discovery rate (FDR)-corrected.

Outlier data that fell 2.5 SD beyond the group mean were removed before conducting statistical tests. Since relative power was not normally distributed in all groups, these variables were log-transformed.

Results

Demographics

There were no significant differences in age among the groups: PD (67.8 ± 6.3), MCI (70 ± 7.4), controls (66.3 ± 7.3 years; $F = 1.55$, $p = 0.22$). The proportion of male participants was smaller in MCI (24%) and controls (33%), and equal in PD (52%).

Group differences: qEEG metrics and cholinergic basal forebrain volumes

Univariate ANOVAs (controlling for age and sex) revealed group differences (Table 1) in pre-alpha power ($F(2, 54) = 6.98$, $p = 0.002$). Post-hoc tests showed that pre-alpha power was increased in the PD group compared to controls ($p=0.001$), and a trend for increased pre-alpha power in MCI compared to controls ($p=0.07$). There were no differences between PD and MCI ($p=0.71$) (Fig. 1).

Group differences (Fig. 1) in the ratio of power in slow to fast frequencies ($F(2, 54) = 3.36$, $p = 0.042$), showed a larger ratio in PD compared to controls ($p=0.037$), but no differences between MCI and controls ($p=0.78$), or PD and MCI ($p=0.55$). There were no group differences in delta, theta, alpha, or beta power, or theta/alpha ratio ($F < 2.30$, $p > 0.11$).

There was an overall effect of group (Fig. 1) on alpha reactivity ($F(2, 53) = 4.10$, $p = 0.02$). Post-hoc tests revealed that alpha reactivity was significantly reduced in PD compared to controls ($p = 0.04$), and a trend in PD compared to MCI ($p=0.07$). There were no differences in in MCI compared to controls ($p=0.98$).

Finally, ANOVAs (controlling for TIV normalised GM, age, and sex) revealed no significant group differences (Fig. 1) between Ch1-2 volume ($F(2, 64) = 0.57$, $p = 0.57$), Ch4 volume ($F(2, 64) = 2.78$, $p = 0.07$), or Ch4p volume ($F(2, 64) = 1.30$, $p = 0.28$).

Table 1

EEG metrics and cholinergic basal forebrain volumes

	PD	MCI	CONTROL
Delta power	2.33 (0.41)	2.20 (0.60)	2.14 (0.52)
Theta power	1.98 (0.41)	1.82 (0.55)	1.64 (0.41)
Pre-alpha power	2.44 (0.56)**	2.14 (0.55)	1.75 (0.43)
Alpha power	3.76 (0.29)	3.77 (0.47)	3.76 (0.40)
Beta power	3.08 (0.35)	3.08 (0.54)	3.34 (0.49)
Theta/alpha ratio	0.54 (0.15)	0.50 (0.19)	0.45 (0.15)
Slow/fast frequencies ratio	0.79 (0.16)*	0.72 (0.16)	0.65 (0.14)
Alpha reactivity	0.04 (0.06)*	0.10 (0.09)	0.10 (0.08)
Ch1-2	0.001 (0.04)	-0.011 (0.03)	0.011 (0.04)
Ch4	-0.003 (0.06)	-0.005 (0.04)	0.008 (0.05)
Ch4p	-0.001 (0.05)	-0.011(0.04)	0.014 (0.04)

Mean (standard deviation). Pairwise comparisons adjusted for multiple comparisons with Bonferroni correction. Cholinergic basal forebrain volumes (Ch1-Ch4p) scaled by total intracranial volume. PD = Parkinson's disease; MCI = mild cognitive impairment; Ch1-2 = region corresponding to the medial septum and vertical limb of the diagonal band, Ch4 = region corresponding to the nucleus basalis of Meynert; Ch4p = region corresponding to the posterior nucleus basalis of Meynert.

Metrics in bold were significantly different at $P<0.05$ between groups in a whole-sample univariate analysis (controlling for age, sex and, TIV-normalised grey matter volume (for volumetric data only)).
* indicates groups who were significantly different to controls at $P<0.05$ (Bonferroni corrected for multiple pairwise comparisons).
** indicates groups who were significantly different to controls at $P<0.01$ (Bonferroni corrected for multiple pairwise comparisons).

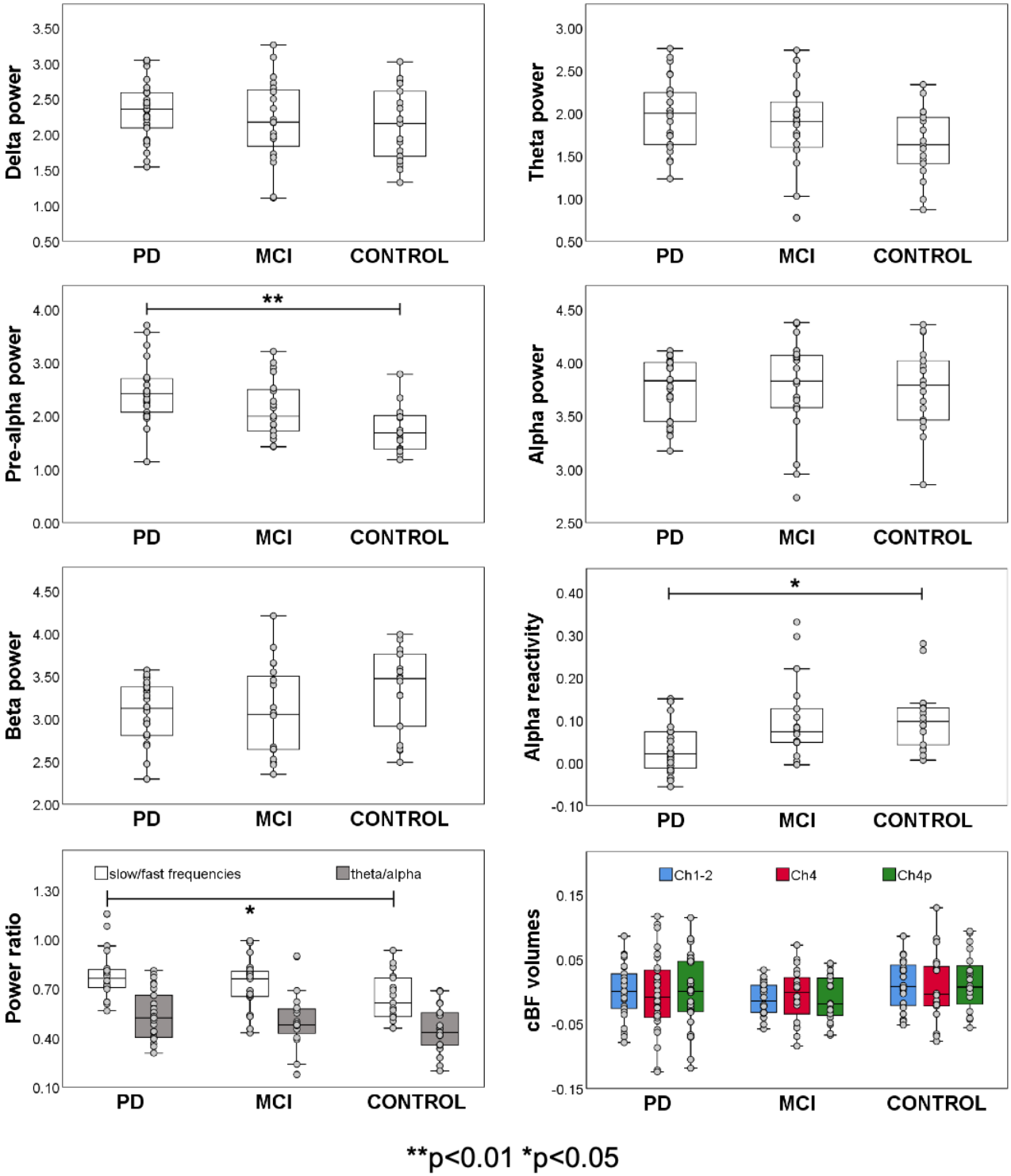

Fig. 1. Comparison of EEG metrics and cholinergic basal forebrain volumes between groups. Abbreviations: cBF, cholinergic basal forebrain; Ch1-2, region corresponding to the medial septum and vertical limb of the diagonal band; Ch4, region corresponding to the nucleus basalis of Meynert; Ch4p, region corresponding to the posterior nucleus basalis of Meynert; MCI, mild cognitive impairment; PD, Parkinson's disease.

Group-specific relationships between qEEG metrics and cholinergic basal forebrain volumes

In the PD group, partial correlations (controlling for TIV normalised GM, age, and sex) revealed positive correlations between alpha reactivity and Ch1-2 ($r = 0.69$, $p = 0.003$) and Ch4p ($r = 0.63$, $p = 0.009$) volumes (Fig. 2A). In the MCI group, pre-alpha power was positively correlated with Ch1-2 ($r = 0.67$, $p = 0.02$) and Ch4p ($r = 0.64$, $p = 0.04$) volumes (Fig. 2B). There were no significant correlations between qEEG metrics and cBF volumes in controls ($r < 0.55$, $p > 0.17$) (Table 2).

Table 2

Partial correlations between cholinergic basal forebrain volumes and qEEG metrics

	PD			**MCI**			**CONTROL**		
	Ch1-2	Ch4	Ch4p	Ch1-2	Ch4	Ch4p	Ch1-2	Ch4	Ch4p
Delta power	-0.10	0.06	-0.18	0.27	-0.08	0.13	-0.34	-0.11	-0.15
Theta power	-0.27	0.02	-0.25	0.45	0.06	0.29	-0.41	-0.04	-0.25
Pre-alpha power	-0.29	0.12	-0.07	0.67*	0.29	0.64*	-0.25	0.03	0.01
Alpha power	0.13	-0.06	0.14	-0.20	-0.02	-0.29	0.54	0.31	0.20
Beta power	0.15	-0.32	0.01	-0.06	-0.17	-0.07	-0.24	-0.34	-0.02
Theta/alpha ratio	-0.22	0.06	-0.22	0.40	0.09	0.38	-0.50	-0.15	-0.27
Slow/fast frequencies ratio	-0.20	0.28	-0.13	0.57	0.15	0.49	-0.50	0.02	-0.29
Alpha reactivity	0.69**	0.33	0.63**	-0.19	0.47	0.23	0.23	-0.27	0.13

Pearson correlation coefficient (controlling for age, sex and, TIV-normalised grey matter (GM) volume). * indicates significant correlation at $P < 0.05$; ** indicates significant correlation at. $P < 0.01$ (false discovery rate corrected for multiple comparisons). Abbreviations: Ch1-2, region corresponding to the medial septum and vertical limb of the diagonal band; Ch4, region corresponding to the nucleus basalis of Meynert; Ch4p, region corresponding to the posterior nucleus basalis of Meynert; MCI, mild cognitive impairment; PD, Parkinson's disease.

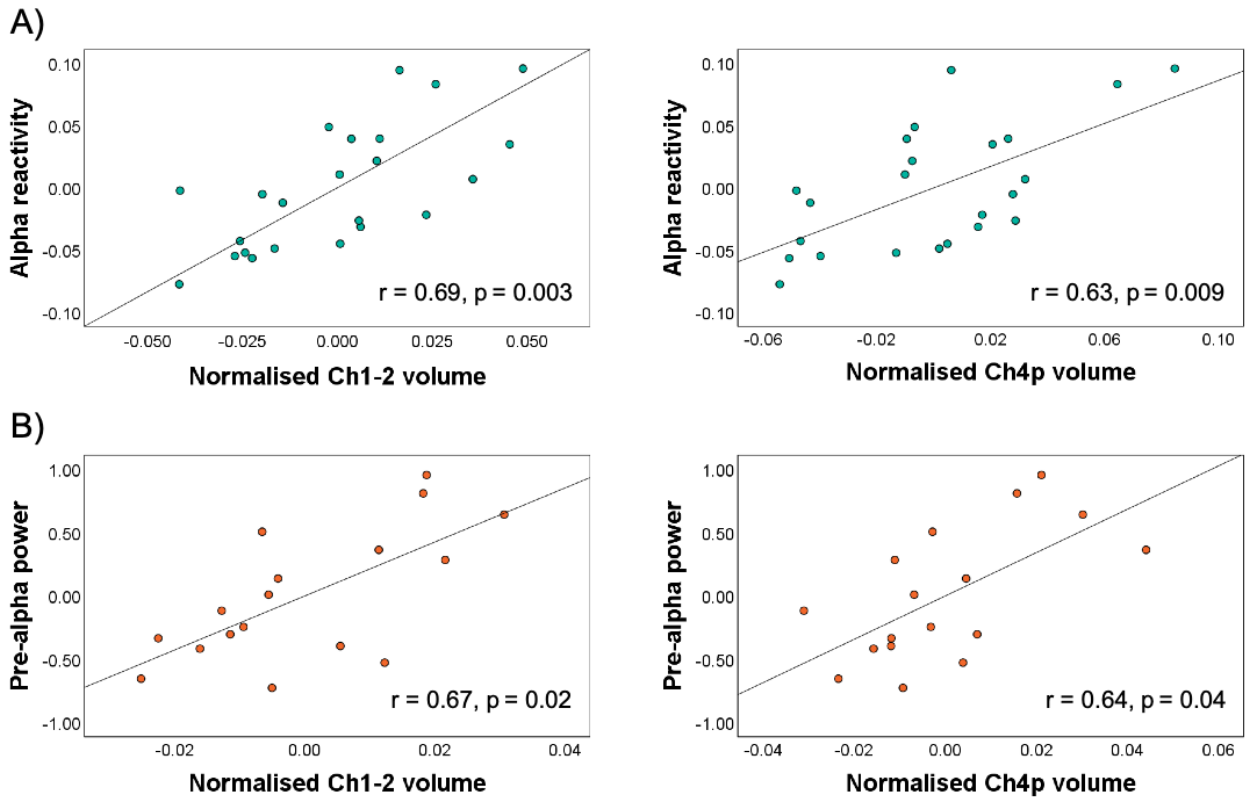

Fig. 2. Partial correlations between qEEG metrics and cholinergic basal forebrain volumes in (A) Parkinson's disease (PD) and (B) mild cognitive impairment (MCI). Abbreviations: Ch1-2, region corresponding to the medial septum and vertical limb of the diagonal band; Ch4p, region corresponding to the posterior nucleus basalis of Meynert.

Discussion

In this study, we explored the relationship between regional cBF atrophy and qEEG changes in a heterogenous sample comprising individuals with PD (without dementia), MCI (not related to PD), and age-matched controls. There were four main outcomes: (i) people with PD showed increased power in slower frequencies compared to controls. In particular, increased pre-alpha power, and a larger ratio of power in slow to fast frequencies; (ii) people with PD showed an impairment in EEG alpha reactivity from eyes-closed to eyes-open conditions; (iii) alpha reactivity correlated positively with Ch1-2 and Ch4p volumes in people with PD; and (iv) pre-alpha power correlated positively with Ch1-2 and Ch4p volumes in people with MCI. We discuss these outcomes in more detail below.

Increased power in slow EEG frequencies in PD

We found an increase in pre-alpha power and a larger slowing ratio in people with PD compared to controls. These findings are consistent with previous studies which generally report an increase in slow wave activity, even early in PD (for review see: Geraedts et al., 2018).

We did not observe differences in eyes-closed qEEG metrics when directly comparing PD and MCI groups. Few studies have compared early changes in qEEG characteristics between these clinical groups, but some differences have been reported. For example, in the MCI disease stage, LBD patients presented with increased pre-alpha, and decreased beta and dominant frequency, compared to AD (Schumacher et al., 2020a). However, attempts to classify MCI-LBD from MCI-AD with EEG measures have been unreliable, providing only moderate-no diagnostic accuracy (Babiloni et al., 2018; Schumacher et al., 2020a). Group level differences between MCI-LBD and MCI-AD have also been shown for the alpha/theta ratio, however, MCI-AD did not differ from PD without cognitive impairment (Massa et al., 2020). Taken together with results from the current study, these findings suggest that EEG changes appear early, and are more pronounced in LBD compared to AD, but with some degree of overlap. This is also consistent with previous reports showing less pronounced slowing in the dementia stage of AD compared to LBD (Bonanni et al., 2016, 2008; Schumacher et al., 2020b; van der Zande et al., 2018).

We revealed a non-significant trend ($p = 0.07$) for increased pre-alpha power in people with MCI compared to controls, which could indicate the emergence of early EEG alterations in this group. Indeed, longitudinal studies in MCI have shown a decrease in power of posterior alpha sources over time (Babiloni et al., 2014). However, in line with the current findings, a number of cross-sectional studies have revealed no significant differences between MCI and controls in resting-state qEEG measures (Massa et al., 2020; Stam et al., 2003; van der Hiele et al., 2007a).

Reduced alpha reactivity in PD

We found a reduction in alpha reactivity among people with PD compared to controls, indicating a smaller suppression of alpha power upon opening the eyes. We

also observed a non-significant trend for lower alpha reactivity in PD when compared to MCI (p=0.07). This is consistent with a previous study in the dementia stage of LBD (including DLB and PDD) in which alpha reactivity impairments distinguished LBD from AD (Schumacher et al., 2020b). We therefore extend these findings to the earlier, predementia stage of PD.

Similar to previous studies, we found no differences in alpha reactivity between MCI and controls (Kurimoto et al., 2008; van der Hiele et al., 2007b), though see (Babiloni et al., 2010). People with MCI have heterogeneous underlying pathology (i.e. AD or vascular) (Dong et al., 2017). It is possible that alpha reactivity changes in MCI are obscured by such heterogeneity.

Reduced alpha reactivity was associated with smaller Ch1-2 and Ch4p volumes in PD

We observed no between-group differences in sub-regional volumes of the cBF. More substantial cholinergic deficits are observed in PDD compared to earlier predementia stages of PD (Bohnen et al., 2018; Craig et al., 2020) - when cholinergic degeneration can be variable (Bohnen et al., 2012). Consistent with our findings, Ray et al. (2018) observed no cross-sectional differences in cBF volumes between controls and people with PD.

We did, however, see associations between alpha reactivity and cBF volumes in people with PD. More specifically, smaller volumes of cholinergic cell clusters corresponding to the medial septum, and the vertical and horizontal limb of the diagonal band (Ch1-2), as well as the posterior nbM region (Ch4p), were related to a loss of alpha reactivity. Previous work suggests that deficits in cholinergic signalling may contribute to EEG alterations (Riekkinen et al., 1991), which is supported by the reversal of EEG slowing with acetylcholinesterase inhibitors in PD and AD (Babiloni et al., 2013; Bosboom et al., 2009). More recently, a combined MRI and EEG study revealed that loss of alpha reactivity was correlated with volume loss within the nbM in PDD (Schumacher et al., 2020b). Our findings therefore extend this work to early PD stages, and provide additional evidence for the possible role of cholinergic system

changes and impairments to neuronal desynchronisation from eye-closed to eyes-open states.

In the context of lack of group-level differences in cBF volumes, the associations with EEG measures we observe here may relate to functional changes in cortical cholinergic pathways occurring without significant neuronal degeneration. Ch1-2 projects to limbic regions including the hippocampus, while Ch4 projects to the entire cortical mantle (Mesulam et al., 1983). In PD without dementia, reduced neocortical and hippocampal ChAT activity has been reported in absence of Ch4, and Ch1-2 degeneration, respectively. Interestingly, these participants also presented with alpha synuclein inclusions in Ch1-2 and Ch4 neurons, suggesting that Lewy depositions may play a role in early cholinergic dysfunction (Hall et al., 2014).

Increased pre-alpha power was associated with larger Ch1-2 and Ch4p volumes in MCI

In people with MCI, pre-alpha power was increased in those with larger Ch1-2 and Ch4p volumes. Given the small sample size, the lack of confirmation re: diagnostic cause of MCI symptoms, and the cross-sectional nature of the study, we can only speculate that increased pre-alpha activity is not associated with cBF pathology. As such, those with MCI not associated with cholinergic system loss have more preserved cBF volumes, but pathology in the wider brain results in increased pre-alpha rhythms and cognitive decline. The lack of relationship between this rhythm and cBF volumes in PD, despite those participants having more prominent increases in pre-alpha, are consistent with this speculation. However, studies with confirmed diagnoses that distinguish pathological causes in MCI participants are needed to test these ideas.

Strengths and limitations

A key strength of the current study is the application of multimodal techniques to study the early disease stages of a clinically diverse sample. Both MRI and EEG are widely available, non-invasive, and relatively low-cost, making them attractive candidates for use in clinical settings. Few studies have combined these tools to explore

their relationship in the context of cholinergic changes in different neurodegenerative conditions. Our results are derived from resting-state EEG metrics that are relatively straightforward to implement, do not require advanced analysis or expertise, and can be easily replicated.

However, the nature and extent of the relationship between qEEG and cBF volumes, and its clinical relevance, require further exploration. Future work will therefore aim to extend the current analysis to investigate additional measures of cholinergic system degeneration, and their relationship with cortically measured EEG. From a clinical perspective, further development of accessible markers of cholinergic system changes in different neurodegenerative conditions has the potential to help determine those who may benefit most from cholinergic medications in the early disease stages.

There are some limitations to the current study. Our small sample size and relatively large number of statistical comparisons increases the statistical uncertainty of our findings. We aimed to limit the range of metrics included in our analysis in attempt to constrain the number of statistical comparisons. However, it is possible that additional spectral EEG features that are not included here may also be sensitive to early changes within these diseases. Relatedly, our analysis includes only spectral features. While beyond the scope of this study, connectivity and network features are likely to be of relevance to cholinergic system changes, and may provide greater group-level discriminative power (Gratwicke et al., 2015; Hassan et al., 2017). Finally, although participants showed no clinical characteristics to suggest alternative neurodegenerative diagnoses, our lack of biomarker evidence means that concomitant AD, LB, or vascular pathology cannot be fully ruled out.

In conclusion, we show that EEG abnormalities are present in the early, predementia stages of PD when compared to controls. Specifically, alpha reactivity was reduced, and power in slow frequencies (pre-alpha in particular) was increased. Furthermore, the results suggest that early EEG changes may be related to changes occurring within cortically projecting cholinergic nuclei. In MCI and PD (without dementia), smaller Ch1-2 and Ch4p volumes were associated with increased pre-alpha power,

and decreased alpha reactivity, respectively. In these neurodegenerative conditions, structural and functional changes within the cBF system occur against a backdrop of disease related pathology. Additional data with control for pathologies in the wider brain are necessary to confirm the nature of the relationship between cBF integrity and qEEG measures, particularly in the early disease stages.

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Disclosure statement

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Abbreviations

AD = Alzheimer's disease; cBF = cholinergic basal forebrain; Ch1-2 = region corresponding to the medial septum and vertical limb of the diagonal band; Ch4 = region corresponding to the nucleus basalis of Meynert; Ch4p = region corresponding to the posterior nucleus basalis of Meynert; DLB = dementia with Lewy bodies; GM = grey matter; LBD = Lewy body disorders; MCI = mild cognitive impairment; nbM = nucleus basalis of Meynert; PD = Parkinson's disease; PDD = Parkinson's disease dementia; PSD = power spectral density; qEEG = quantitative electro-encephalography; TIV = total intracranial volume.