Longitudinal degeneration of the basal forebrain predicts subsequent dementia in Parkinson's disease

Joana B. Pereira, Sara Hall, Mattis Jalakas, Michel J. Grothe, Olof Strandberg, Erik Stomrud, Eric Westman, Danielle van Westen, Oskar Hansson

Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden
Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmo, Sweden
Memory Clinic, Skåne University Hospital, Malmo, Sweden
German Center for Neurodegenerative Diseases (DZNE) – Rostock/Greifswald, Rostock, Germany
Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain

ARTICLE INFO
Keywords:
Parkinson's disease
Dementia
Basal forebrain
Longitudinal MRI
Cognitive decline

ABSTRACT

Objectives: Cholinergic dysfunction plays a prominent role in cognitive impairment in Parkinson's disease (PD). The aim of this study was to assess the relationship of baseline and longitudinal basal forebrain atrophy with cognitive decline and dementia in PD.

Methods: We included 106 non-demented PD patients, 19 PD dementia (PDD) patients and 42 controls with longitudinal structural MRI and cognitive testing. After 4.2 ± 1.8 years, 20 non-demented PD patients were diagnosed with dementia (PD-dementia converters), whereas the rest of PD patients remained non-demented (stable-PD). We compared MRI volumes of the medial septum/diagonal band (Ch1/Ch2) and nucleus basalis of Meynert (Ch4) between groups. Cox regression analyses were applied to test whether Ch1/Ch2 or Ch4 atrophy could predict future dementia and linear mixed models assessed their association with cognitive decline.

Results: Compared to controls, we found reduced Ch4 baseline volumes in PD-dementia converters (p = .003) and those who already had PDD (p < .001) but not in stable-PD. Over time, there was a greater loss in Ch1/Ch2 volumes in PD-dementia converters and PDD compared to the other groups (p = .004). Baseline and longitudinal Ch4 volumes were associated with cognition (p < .002) and longitudinal Ch4 atrophy predicted future dementia (p = .009).

Conclusions: Atrophy of Ch4 precedes and predicts future dementia in PD and is followed by changes in Ch1/Ch2, reflecting a posterior-anterior pattern of basal forebrain atrophy. This pattern could be used to track the spread of cholinergic degeneration and identify patients at risk of developing dementia.

1. Introduction

Parkinson's disease (PD) is a heterogeneous disorder characterized by a wide range of cognitive deficits that vary substantially from patient to patient (Kehagia et al., 2010). Previous studies have found that the loss of neurotransmitters that extend beyond the dopaminergic system may contribute to the clinical heterogeneity observed in PD (Gratwicke et al., 2015). In particular, cholinergic dysfunction occurs in a subset of PD patients and is associated with cognitive decline and dementia (Hilker et al., 2005). Thus, markers of cholinergic dysfunction might predict cognitive decline in patients with PD.

The main source of cholinergic input to the brain is the basal forebrain, which can be divided into areas with different projection sites: the medial septum (Ch1) and vertical limb of the diagonal band (Ch2) provide input to the hippocampus, whereas the nucleus basalis of Meynert (Ch4) supplies the cortical mantle and amygdala (Ballinger et al., 2016). Thanks to recent advances in neuroimaging, it is now possible to measure atrophy in these subregions in vivo on structural magnetic resonance imaging (MRI) (Kilimann et al., 2014). Using this technique, previous studies found that atrophy in Ch4 at is associated with baseline cognitive deficits (Barrett et al., 2019; Gargouri et al., 2019) as well as longitudinal cognitive changes in non-demented PD (Ray et al., 2017; Schulz et al., 2018).

To this date, no studies have performed longitudinal MRI analyses...
of the basal forebrain or assessed whether they are associated with future conversion to dementia in PD. Hence, in this study we addressed these questions in a cohort of patients with PD dementia (PDD) and non-demented PD patients who either remained cognitively normal (stable-PD) or progressed to dementia during the clinical follow-up period (PD-dementia converters). We assessed the patterns of baseline and longitudinal atrophy in the basal forebrain nuclei in different patient groups using the controls as a reference. To determine the biological value of basal forebrain volumes, we tested their ability to predict future dementia in non-demented PD patients and assessed their relationship with cognitive decline over a period of 10 years. Based on previous evidence supporting the role of Ch4 in cognitive impairment in PD, (Ray et al., 2017; Schulz et al., 2018) we hypothesized that Ch4 volumes would show atrophy over time and that this would be associated with conversion to dementia.

2. Materials and methods

2.1. Participants

One hundred sixty-seven individuals from the prospective and longitudinal Swedish BioFINDER study (http://biofinder.se/) were included. This cohort consisted of 106 patients with PD who were non-demented at baseline, 19 patients with PDD and 42 cognitively healthy controls, who underwent structural MRI and neuropsychological assessment. Twenty PD patients converted to PDD during the study follow-up period of 10.0 ± 0.2 years (PD-dementia converters), whereas the rest of PD patients remained cognitively stable (stable-PD), and PDD patients were still demented at follow-up. All subjects had a structural MRI scan at baseline and a subsample underwent a second longitudinal MRI scan after 3.1 ± 1.2 years (77%). In PD-dementia converters, the second longitudinal scan took place before or at the same time of conversion to dementia (3.0 ± 1.1 years). All subjects included in the study underwent at least two cognitive evaluations at 2.0 ± 0.2 years (90.4%), 4.0 ± 0.2 years (81.4%), 6.0 ± 0.3 years (49.7%) or 10.0 ± 0.2 years (5.4%).

The diagnosis of PD was performed according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria (Golb et al., 1999), and patients diagnosed with PD met the clinical diagnostic criteria for dementia associated with PD at Level I by Dubois et al. (2007) and the DSM-V criteria. Cognitively healthy controls were required not to present objective cognitive impairment or any significant parkinsonian symptoms. Exclusion criteria for all participants included being older than 90 years old, participation in a medical study in the last 30 days, generalized cancer, vascular dementia, Alzheimer’s disease, frontotemporal dementia, other serious neurological diseases, and current alcohol or substance abuse.

Motor function was assessed in all individuals using the Unified Parkinson’s disease Rating Scale part-III (Fahn, 1987) and the Hoehn & Yahr scale (Hoehn and Yahr, 1967), whereas activities of daily living were assessed with the Schwab & England scale. Depression was assessed using the UPDRS - I item for depression. In addition, all subjects underwent a cognitive battery of tests that assessed global cognition (mini-mental state examination, MMSE) (Folstein et al., 1975), executive functions (semantic and phonemic fluency) (Seballd et al., 2009), attention and processing speed (A Quick Test of cognitive speed, AQT) (Wiig et al., 2002) and episodic memory (delayed word list recall from the ADAS-Cog: Alzheimer’s Disease Assessment Scale – Cognitive Sub-scale) (Rosen et al., 1984). For the attention and episodic memory tests, higher scores indicated worse cognitive performance. Semantic and phonemic fluency were assessed using an animal and single letter categories.

A physician with experience in neurodegenerative disorders performed a detailed history and neurological exam at every visit, as well as a review of the patient’s charts. The evaluation of the patients for presence of PDD at baseline or conversion to PDD at every follow up visit was based on the following: a) clinical test scores with deficits in two or more cognitive domains b) assessment of global functioning at home and in society through a qualitative interview, and c) high clinical dementia rating (CDR) scores. To define deficits in clinical test scores we used the MMSE items: serial 7’s (cut-off: at least two incorrect responses), three-word memory (cut-off: at least one missing word), overlapping pentagons (cut-off: not including two pentagons that overlap), clock drawing (cut-off: inability to insert the correct clock face numbers and/or the clock hands pointing to the correct time) and months backwards (cut-off: omission of two or more months, incorrect sequencing of the months, or failure to complete the test within 90 s). In addition, we also used the phonemic fluency (cut-off ≤ 9), semantic fluency (cut-off ≤ 15), AQ (cut-off: not able to complete within 90 s) and ADAS delayed word recall (cut-off ≥ 5) tests. The cut-offs we used to define deficits in the previous cognitive tests were based on Dubois et al. (2007). For dropouts, patients’ medical records were also reviewed for information about cognitive decline and global functioning decline at home and in society consistent with dementia, or dementia diagnosis made in other clinics.

Regarding medication, the levodopa equivalent doses were calculated for each patient. In addition, anticholinergic drugs and cholinesterase inhibitors were also recorded. Seventeen subjects were receiving one anticholinergic at the time of the study such as amantadine, de-trasitol, karmazepin, pargitan, saroten or vesicare, whereas four PDD patients were taking a cholinesterase inhibitor.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the regional ethical review boards in Lund. All participants provided written informed consent to participate in the study.

2.2. Image acquisition and analysis

Baseline and longitudinal T1-weighted images were acquired from all individuals on a 3 T Siemens Skyra MR scanner using a magnetization-prepared rapid acquisition with the following parameters: 176 slices, repetition time = 1900 milliseconds; echo time = 2.54 milliseconds; inversion time = 900 milliseconds; flip angle = 9 degrees; voxel size = 1 mm³. These images were preprocessed using the VBM8 toolbox running under the statistical parametric mapping software (SPM8, https://www.fil.ion.ucl.ac.uk/spm/) with two different pipelines: cross-sectional and longitudinal. After reorientation, all images were segmented into gray matter, white matter and cerebrospinal fluid. For the cross-sectional analyses, the resulting gray and white matter tissues of baseline images were normalized to MNI standard space using a high-dimensional warping algorithm (DARTEL) (Ashburner and Friston, 2011). For the longitudinal analyses, after an initial intra-subject realignment, the gray and white matter tissues of every pair of images for each individual were averaged and used as a reference for spatial normalization. In both cases, the resulting normalized images were modulated to preserve the total amount of gray matter volume.

The volumes of two basal forebrain subregions corresponding to Ch1/Ch2 and Ch4 were then extracted from normalized images using the masks of a stereotactic map (Fig. 1A) (Kilimann et al., 2014). This map was obtained by combining post-mortem MRI with subsequent histological analysis. In addition, to account for differences in head size in the statistical analyses, the total intracranial volume of each subject was calculated as the sum of gray matter, white matter and cerebrospinal fluid.

3. Statistical analyses

Differences between groups in baseline characteristics were analyzed using Chi-squared (X²) tests for binary variables and Mann-Whitney tests for continuous variables. To assess whether basal forebrain volumes differed by group, we carried out an analysis of covariance (ANCOVA), including Ch1/Ch2 and Ch4 volumes as dependent
variables, as a group (a factor (controls, stable-PD, PD-dementia converters, PDD) and age, sex, education and intracranial volume as covariates.

In addition, to assess how many patients had basal forebrain volumes outside the range of controls, we built linear regression models to predict Ch1/Ch2 and Ch4 volumes from age, sex and intracranial volume as predictors. The beta weights from these regressions were used to calculate expected Ch1/Ch2 and Ch4 volumes in patients. Patients with volumes below one standard deviation from the control group were classified as having reduced volumes, whereas the rest of patients were considered to have normal volumes.

In order to evaluate whether longitudinal changes in the basal forebrain differed between groups, we fitted linear mixed effect models, implemented in R using “lme4”. In these models, we included Ch1/Ch2 and Ch4 volumes as dependent variables, and group, time (baseline, follow-up), age, sex, education and intracranial volume as fixed effects. These models included all main effects, the interaction between group and time, and random effects for intercepts. Separate models were built for Ch1/Ch2 and Ch4 volumes.

Similarly, to assess whether basal forebrain volumes were associated with longitudinal cognitive decline in all patients, we fitted linear mixed effect models using cognitive test scores as dependent variables and baseline Ch1/Ch2 and Ch4 volumes, age, sex, education, cognitive group (stable-PD, PD-dementia converters, PDD), and intracranial volume as fixed effects. We also repeated these analyses using measures of percentage longitudinal change in Ch1/Ch2 and Ch4 volumes as dependent variables and baseline Ch1/Ch2 and Ch4 volumes, age, sex, education, cognitive group (stable-PD, PD-dementia converters, PDD), and intracranial volume as fixed effects. In these models, we included Ch1/Ch2 and Ch4 volumes as dependent variables, and group, time (baseline, follow-up), age, sex, education and intracranial volume as fixed effects.

Table 1

| Characteristics of the sample. |
|--------------------------------|
| **Controls** (n = 42) | **Cognitively stable-PD** (n = 86) | **PD-dementia converters** (n = 20) | **PDD** (n = 19) |
| Age (mean ± SD) | 65.7 (41.3–83.2) | 64.9 (21.4–83.1) | 72.4 (63.7–82.5) | 74.0 (61.4–83.6) |
| Sex (m/f) | 17/26 | 57/30 | 12/8 | 12/7 |
| Education (mean ± SD) | 13.2 (7–20) | 11.0 (2–28) | 11.9 (2–23) | 11.1 (7–22) |
| UPDRS III (mean ± SD) | 1.6 (0–13) | 12.5 (0–46) | 16.9 (5–43) | 34.1 (13–56) |
| HY (mean ± SD) | 0 (0–0) | 1.8 (0–4) | 2.2 (1–4) | 2.9 (2–5) |
| Disease duration (mean ± SD) | – | 3.2 (3.8) | 3.5 (4.3) | 8.9 (6.0) |
| Levodopa Equivalent Doses (mg) | – | 484.5 | 527.3 | 800.5 (493.0) |
| Anticholinergic drugs (n) | 2 | 8 | 2 | 2 |
| Cholinesterase inhibitors (n) | 0 | 0 | 0 | 0 |
| UPDRS I - Depression (mean ± SD) | 0 (0–2) | 0 (0–2) | 1 (0–4) | 1 (0–2) |
| Activities Daily Living (mean ± SD) | 100.0 (0) | 91.2 (9.1) | 87.5 (9.7) | 75.0 (11.7) |
| Baseline MMSE (mean ± SD) | 28.3 (23–30) | 28.4 (22–30) | 27.2 (23–30) | 23.0 (16–29) |
| Baseline Semantic fluency (mean ± SD) | 23.3 (12–38) | 22.4 (10–38) | 17.7 (7–26) | 11.2 (3–22) |
| Baseline Phonemic fluency (mean ± SD) | 17.5 (7–35) | 15.0 (0–32) | 13.9 (3–28) | 8.7 (2–15) |
| Baseline AQT (mean ± SD) | 63.0 (10.7) | 65.9 (13.9) | 81.6 (28.9) | 144.7 (82.3) |
| Baseline Delayed recall (mean ± SD) | 2.1 (0–6) | 2.8 (0–10) | 4.3 (0–10) | 6.2 (0–10) |
| Follow-up time cognitive assessments (years) | 5.9 (2–10) | 5.1 (1.8–10.3) | 4.6 (1.9–9.8) | 4.3 (1.9–6.5) |
| Second MRI scan (years) | 3.0 (0.9) | 3.0 (1.3) | 3.0 (1.1) | 4.2 (1.2) |

Values represent medians followed by range, unless otherwise specified. * Significant differences between: a Controls and Cognitive stable-PD, b Controls and PD-dementia converters, c Controls and PDD. * Cognitive stable-PD and PD-dementia converters, * Cognitive stable-PD and PDD, * PD-dementia converters and PDD (FDR, q < 0.05). PD, Parkinson’s disease; PDD, Parkinson’s disease with dementia; UPDRS, Unified Parkinson’s disease Rating Scale; HY scale, Hoehn & Yahr scale; MMSE, mini-mental state examination; AQT, A Quick Test of cognitive speed.
disease duration as covariates. In addition, to ensure that our results were specific to the basal forebrain, we also included longitudinal changes in whole gray matter volume and hippocampal volume as additional predictors in the previous analyses.

Adjustment for multiple comparisons was carried out in all analyses using false discovery rate (FDR) corrections at q < 0.05.

4. Results

4.1. Participants

Characteristics of the sample are summarized in Table 1. As expected, all patient groups showed greater motor impairment relative to controls (UPDRS-III, p < .001; HY stage, p < .001). In addition, cognitively stable-PD patients were less educated (p = .030) and had worse executive (phonemic fluency, p = .026) scores, whereas PD-dementia converters were older (p = .003) and had worse scores in executive (semantic fluency, p = .001; phonemic fluency, p = .024), attention (AQT, p = .001) and memory (delayed recall, p = .001) tests. PD dementia patients were significantly older (p = .014), less educated (p = .023) and had worse scores on all cognitive tests.

Compared to cognitively stable-PD patients, PD-converters also showed greater motor impairment (HY stage, p = .028) and worse attention (AQT, p = .002) and memory (delayed recall, p = .015). For other significant differences between patient groups, please see Table 1. There were no significant differences in number of years of follow-up between patient groups.

4.2. Basal forebrain volumes at baseline

There were no significant differences in basal forebrain volumes in the cognitively stable-PD group relative to controls (Fig. 1B, C). In contrast, PD-dementia converters (p = .003) and PDD patients (p < .001) had significantly lower Ch4 volumes compared to controls, and PDD patients also had lower Ch4 volumes (p = .002) compared to cognitively stable-PD (Fig. 1C), after correcting for FDR (p < .05). There were no differences in baseline Ch1/Ch2 volumes between any groups (Fig. 1B). There were no significant differences in basal forebrain volumes between PD patients taking anticholinergic drugs or cholinesterase inhibitors compared to patients not taking these medications.

4.3. Prevalence of reduced basal forebrain volumes

There was a linear relationship between higher prevalence of Ch4 atrophy and worse cognitive impairment. Specifically, we found reduced Ch4 volumes in 17.4% of cognitively stable-PD patients, in 30% of PD-dementia converters and in 52.6% of PDD patients. This increase in prevalence of reduced Ch4 volumes across the three groups was statistically significant (p = .005, FDR-corrected) (Fig. 2B). In contrast, we found that Ch1/Ch2 volume was reduced in 20.9% of cognitively stable-PD, 35% of PD-dementia converters and 26.3% of PDD patients. These differences in prevalence across groups were not significant (Fig. 2A).

4.4. Longitudinal basal forebrain atrophy

Using mixed effects models, we identified a significant interaction between time and group in Ch1/Ch2 volumes (p = .004, FDR-corrected), indicating that PD-dementia converters and PDD patients showed greater Ch1/Ch2 atrophy over time compared to controls and cognitively stable-PD patients (Fig. 3). There was also a trend towards significance (uncorrected for FDR) when the interaction between time and group was tested while treating the PD-dementia converters (p = .036) and PDD (p = .013) groups separately. There were no significant interactions in the model with Ch4 volumes, suggesting that the longitudinal atrophy pattern in this subregion did not differ between groups (supplemental table 1). When anticholinergic drugs or cholinesterase inhibitors were included in the previous models as covariates, the results remained unchanged. Stratifying subjects in groups based on whether they were receiving or not these medications did not reveal any significant interactions with time in longitudinal basal forebrain volumes.

4.5. Relationship with cognition

In the whole patient sample, we observed a significant interaction between time and longitudinal changes in global cognition (MMSE, p < .001) as well as semantic fluency (p < .001) in baseline Ch4 volumes (Fig. 4A, B, supplemental table 2), after adjusting for FDR (p < .05). This interaction indicated that patients with reduced Ch4 volumes at baseline had worse global and executive functioning over time compared to those with higher baseline volumes. We also observed a significant interaction between time and phonemic fluency in longitudinal Ch4 changes, indicating that patients who showed greater longitudinal Ch4 atrophy also performed worse in phonemic fluency (p = .002), after adjusting for FDR (p < .05) (Fig. 4C, supplemental table 2). All results remained significant after including depression as a covariate (MMSE: p < .001, semantic fluency: p = .001, phonemic fluency: p = .002).

There were no associations between longitudinal changes in Ch1/Ch2 and cognition. In addition, no relationship was found between longitudinal basal forebrain changes with motor scores (UPDRS-III) or with cognitive tests that had a motor speed component (AQT), while adjusting for motor severity.

4.6. Longitudinal Ch4 atrophy is associated with development of subsequent dementia in PD

The Cox regression models showed that changes in longitudinal Ch4 volumes were significantly associated with conversion to dementia in PD (HR = 1.389; 95% CI: 1.085–1.778; p = .009). This result indicates that patients with greater longitudinal Ch4 atrophy have 38.9% higher risk of developing dementia over a period of 10 years. Longitudinal changes in Ch1/Ch2 volumes (p = .294), whole brain gray matter volume (p = .931) or hippocampal volume (p = .758) were not significant predictors in these models.

5. Discussion

With increasing life expectancy, Parkinson’s disease dementia (PDD) is set to become even more prevalent in the future (Gratwicke et al., 2015). Thus, neuroimaging markers of dementia are urgently needed to identify individuals at high risk of developing PDD, but also to understand better the underlying disease pathophysiology (Lanskey et al., 2018). In this study we show that MRI-derived basal forebrain atrophy might be a readily accessible non-invasive marker of dementia for PD. Specifically, we found that the nucleus basalis of Meynert (Ch4) is atrophied in patients who will convert to or already have dementia. These changes were followed by longitudinal atrophy in the medial septum and diagonal band (Ch1/Ch2). Altogether, these findings suggest that the basal forebrain shows a posterior-anterior pattern of atrophy with worse disease progression and conversion to dementia in PD and that different subregions could potentially be used to stage disease progression.

Despite the well-known contribution of cholinergic dysfunction to cognitive decline in PD, a cholinergic imaging marker has long been lacking in the field (Gratwicke and Foltynie, 2017). In this study, we combined detailed stereotactic mapping of cholinergic nuclei with MRI morphometry to measure the volumes of two important cholinergic regions, which have wide projection sites to the cortex, amygdala and hippocampus. These subregions could be easily added to any MRI-based
model or future study trying to predict the development of dementia in PD.

We found that one of these subregions, the nucleus basalis of Meynert (Ch4), was significantly reduced in patients that progressed to dementia as well as those who already had dementia at baseline. This result is in line with recent findings showing that atrophy in the nucleus basalis of Meynert is associated with impaired cognition and development of cognitive impairment in early stages of PD (Barrett et al., 2019; Gargouri et al., 2019; Ray et al., 2017; Schulz et al., 2018). However, the range and severity of cognitive deficits in early PD is highly variable, with many patients with mild cognitive impairment reverting to normal cognition after a few years (Domellöf et al., 2015; Pedersen et al., 2013). Here we show that the presence of baseline and future dementia in PD is associated with atrophy in the nucleus basalis of Meynert, providing direct evidence for the role of this structure in PD-related dementia, independently of the previous confounding factors.

Although there is evidence supporting the role of cholinergic denervation in PD, it is also well recognized that there is substantial heterogeneity in the amount of this denervation (Bohnen et al., 2012). To address this, we used the normative data from controls to calculate expected cholinergic nuclei volumes for each individual patient and assess whether these volumes were below or within the normal range. We found that the prevalence of reduced nucleus basalis of Meynert volumes increased with worse cognition, from cognitively stable-PD, to PD-dementia converters and PDD patients. These increases indicate that atrophy in this subregion is a sensitive marker of cognitive dysfunction, being present in up to 52% of patients with dementia at baseline.

To our knowledge, our study is the first in assessing longitudinal changes in the basal forebrain in PD. In contrast to the nucleus basalis of Meynert, which did not show a different atrophy pattern over time between groups, the medial septum and diagonal band showed increased longitudinal atrophy in PD-dementia converters and PDD patients. These increases indicate that atrophy in this subregion is a sensitive marker of cognitive dysfunction, being present in up to 52% of patients with dementia at baseline.

To our knowledge, our study is the first in assessing longitudinal changes in the basal forebrain in PD. In contrast to the nucleus basalis of Meynert, which did not show a different atrophy pattern over time between groups, the medial septum and diagonal band showed increased longitudinal atrophy in PD-dementia converters and PDD patients. These results indicate that the anterior basal forebrain also becomes atrophied in PD, but only after the nucleus basalis of Meynert has

![Fig. 2. Frequency of normal and reduced basal forebrain volumes across patient groups. Percentage of cognitively stable-PD (PD-s), PD-dementia converters (PD-c) and PDD patients with normal and reduced Ch1/Ch2 and Ch4 volumes based on the normative data from controls. * Significant FDR-corrected differences in diagnostic group between patients with normal and reduced volumes.](image-url)

![Fig. 3. Significant longitudinal changes in basal forebrain volumes. PD-dementia converters (PD-c) and PDD patients showed a steeper decline over time in Ch1/2 volumes compared to cognitively stable-PD (PD-s) and controls (CTR), after adjusting for FDR (p < .05) across all linear mixed models. PD-s, cognitively stable-PD.](image-url)

![Fig. 4. Prediction models showing a significant relationship between longitudinal cognitive decline and Ch4 volumes. Predicted trajectories for global cognition (A), semantic fluency (B) and phonemic fluency (C) in patients with high (> 50th percentile) and low (< 50th percentile) baseline Ch4 volumes (A, B) and patients with high (> 50th percentile) and low (< 50th percentile) longitudinal Ch4 volumes (C), after adjusting for FDR (p < .05). NBM, nucleus basalis of Meynert.](image-url)
undergone substantial volume loss. Thus, these two subregions could potentially be used to perform in vivo staging of cholinergic denervation, in which pathology would begin in the nucleus basalis of Meynert before spreading to the medial septal and diagonal band, similarly to what has been observed in a previous study assessing longitudinal basal forebrain degeneration in the course of Alzheimer's disease (Grothe et al., 2013).

Regarding cognition, we found that baseline volumes and longitudinal changes in the nucleus basalis of Meynert were associated with worse global cognition, semantic and phonemic fluency abilities. Verbal fluency tests measure executive functions, an ability that is typically impaired in patients with PD (Svenningsson et al., 2012). However, in contrast to phonemic fluency, which relies on frontal areas, semantic fluency relies on posterior parietal and temporal brain regions and was found to be a specific marker of dementia in PD by a series of previous studies (Williams-Gray et al., 2007, 2009, 2013). Our findings suggest that the nucleus basalis of Meynert is associated with both typical cognitive deficits in PD and those that are more specific to the development of dementia. They are also in line with previous reports showing that cortical cholinergic innervation is strongly implicated in working memory, rule-switching and response inhibition (Bohnen et al., 2006), all of which are required by verbal fluency tests. The fact that no relationship was found between basal forebrain volumes and attention in our study could be due to the specific test (AQT) that we used to assess this function, which relies in part on psychomotor speed and may therefore be not so sensitive to cholinergic function.

Finally, in this study we found that changes in CH4 volumes were a significant predictor of subsequent dementia in PD, after adjusting for several confounders, including disease duration and disease stage. In particular, patients with greater longitudinal CH4 atrophy had a 38.9% higher risk of converting to PDD. Although this result might appear counterintuitive since CH4 volumes did not show significant changes over time in PD-converters compared to controls, it suggests that even subtle changes in CH4 have an important prognostic value and are associated with worse disease progression. Thus, our results indicate that longitudinal CH4 atrophy could potentially be used by future studies as an in vivo cholinergic biomarker of dementia in PD. In these prediction models, we also assessed whether hippocampal or whole brain atrophy were associated with a higher risk of developing dementia. These analyses showed that these two additional brain regions did not predict dementia in PD, confirming the specificity of CH4 volumes as a dementia predictor. Previous studies in postmortem PD cases have shown that Lewy body pathology occurs first in the nucleus basalis of Meynert compared to the hippocampus or cortical brain regions (Braak et al., 2003). According to the staging proposed by Braak, lesions in this nucleus occur around stage III and are followed by pathological changes in the temporal cortex, hippocampus, frontal cortex and other cortical association areas. Thus, by the time PD patients convert to dementia, the nucleus basalis of Meynert might be more severely atrophied compared to other brain regions. In addition, it has been previously suggested that atrophy in this nucleus might be responsible for dementia due to its widespread cholinergic cortical projections (Bosboom et al., 2004; Kalaitzakis et al., 2009). Altogether, these reports provide support to the nucleus basalis of Meynert as a more specific predictor of dementia in PD and its potential contribution to pathological changes in other brain areas.

Our study has some limitations. Unfortunately, some individuals did not have a follow-up MRI scan, which could have limited our ability to detect stronger changes over time in basal forebrain volumes. Moreover, our cognitive test battery was limited and did not allow us to assess all cognitive domains in our patient sample or their relationship with basal forebrain atrophy. We tried to classify PD patients into those that were cognitively normal and those with mild cognitive impairment using the cognitive tests that were available, but our results showed that only 42% of PDD patients were classified as having MCI, suggesting that the cognitive test battery we had was not sufficient to do MCI classifications.

6. Conclusions

In conclusion, in this study we showed that the basal forebrain undergoes dynamic changes in the course of PD. Specifically, baseline atrophy in the posterior part was followed by longitudinal changes in the anterior part with worse disease progression and conversion to dementia. This spreading of atrophy could potentially be used to assess disease severity in PD.

Funding

Work at the authors' research center was supported by the European Research Council, the Swedish Research Council, the Knut and Alice Wallenberg foundation, the Marianne and Marcus Wallenberg foundation, the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Swedish Alzheimer Foundation, the Swedish Brain Foundation, The Parkinson foundation of Sweden, The Parkinson Research Foundation, the Skåne University Hospital Foundation, the Swedish federal government under the ALF agreement, the Swedish Foundation for Strategic Research (SSF), the Strategic Research Programme in Neuroscience at Karolinska Institutet (StratNeuro), Stiftelsen Olle Engkvist Byggmästare, Birgitta och Sten Westerberg, and the Åke Wiberg Foundation. The funding sources did not have any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of Competing Interest

OH has acquired research support (for the institution) from Roche, GE Healthcare, Biogen, AVID Radiopharmaceuticals, Fujiyebio, and Euroimmun. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Biogen and Roche. The rest of authors have no conflicts of interest.

Acknowledgements

We would like to thank the patients for their participation in the study. Michel Grothe is supported by the "Miguel Servet" program [CP19/00031] of the Spanish Instituto de Salud Carlos III (ISICII-PEDER).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2020.104831.

References

Ashburner, J., Friston, K.J., 2011. Diffeomorphic registration using geodesic shooting and gaus–Newton optimisation. NeuroImage 55 (3), 954-967.
Ballinger, E.C., Ananth, M., Talmage, D.A., Role, L.W., 2016. Basal forebrain cholinergic circuits and signaling in cognition and cognitive decline. Neuron 91 (6) 1199-1218.
Barrett, M.J., Sperling, S.A., Blair, J.C., et al., 2019. Lower volume, more impairment: reduced cholinergic basal forebrain grey matter density is associated with impaired cognition in Parkinson disease. J. Neurol. Neurosurg. Psychiatry 90 (11), 1251–1256 2019.
Bohnen, N.I., Kaufu, D.I., Hendrickson, R., et al., 2006. Cognitive correlates of cortical cholinergic denervation in Parkinson’s disease and parkinsonian dementia. J. Neurol. Neurosurg. Psychiatry 77 (2), 242–247.
Bohnen, N.I., Muller, M., Kotagal, V., et al., 2012. Heterogeneity of cholinergic denervation in Parkinson`s disease without dementia. J. Cereb. Blood Flow Metab. 32 (8), 1609-1617.
Bosboom, J.L., Stoffers, D., Wolters, E.C., 2004. Cognitive dysfunction and dementia in Parkinson’s disease. J. Neural Transm. 111 (10/11), 1303–1315.
Braak, H., Del Tredici, K., Rub, U., et al., 2003. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol. Aging 24 (2), 197–211.
Dodelit, M.E., Ekman, U., Forsgren, L., Elgh, E., 2015. Cognitive function in the early
phase of Parkinson’s disease, a five-year follow-up. Acta Neurol. Scand. 132, 79–88.

Dubois, B., Burn, D., Goetz, C., et al., 2007. Diagnostic procedures for Parkinson’s disease dementia: recommendations from the movement disorder society task force. Mov. Disord. 22 (16), 2314–2324.

Fahn, S., E.F. UPDRS Program Members, 1987. Unified Parkinson’s disease rating scale. In: Fahn, S., Marsden, C.D., Goldstein, M., Calne, D.B. (Eds.), Recent Developments in Parkinson’s Disease. Flarharm Park. Macmillan Healthcare Information, NJ, pp. 153–163.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Gargouri, F., Gallea, C., Mongin, M., et al., 2019. Multimodal magnetic resonance imaging investigation of basal forebrain damage and cognitive deficits in Parkinson’s disease. Mov. Disord. 34, 516–525.

Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. Arch. Neurol. 56, 33–39.

Gratwicke, J.P., Foltynie, T., 2017. Early nucleus basalis of Meynert degeneration predicts cognitive decline in Parkinson’s disease. Brain 141, 7–10.

Gratwicke, J., Jahanshahi, M., Foltynie, T., 2015. Parkinson’s disease dementia: a neural networks perspective. Brain 138, 1454–1476.

Grothe, M., Heinsen, H., Teipel, S., 2013. Longitudinal measures of cholinergic forebrain atrophy in the transition from healthy aging to Alzheimer’s disease. Neurobiol. Aging 34, 1210–1220.

Hillier, R., Thomas, A.V., Klein, J.C., et al., 2005. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology 65, 1716–1722.

Hoehn, M.M., Yahr, M.D., 1967. Parkinsonism: onset, progression, and mortality. Neurology 17, 427.

Kalaitzakis, M.E., Christian, L.M., Moran, L.B., et al., 2009. Dementia and visual hallucinations associated with limbic pathology in Parkinson’s disease. Parkinsonism Relat. Disord. 15, 196–204.

Kehagia, A.A., Barker, R.A., Robbins, T.W., 2010. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson’s disease. Lancet Neurol. 9, 1200–1213.

Kilimann, I., Grothe, M., Heinsen, H., et al., 2014. Subregional forebrain atrophy in Alzheimer’s disease: a multicenter study. J. Alzheimers Dis. 40, 687–700.

Landeck, J.H., McColgan, P., Schrag, A.E., et al., 2018. Can neuroimaging predict dementia in Parkinson’s disease? Brain 141, 2545–2560.

Pedersen, K.F., Larsen, J.P., Tynnes, O.B., Alves, G., 2013. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol. 70, 580–586.

Ray, N.J., Redburn, S., Murgatroyd, C., et al., 2017. In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson’s disease. Brain 141, 165–176.

Rosen, W.G., Mohs, R.C., Davis, K.L., 1984. A new rating scale for Alzheimer’s disease. Am. J. Psychiatry 141, 1356–1364.

Schulz, J., Pagano, G., Fernández Bonfante, J.A., Wilson, H., Politi, M., 2018. Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson’s disease. Brain 141, 1501–1516.

Sebaihia, R., Dalziel, W., Massoud, F., et al., 2009. Detection of cognitive impairment and dementia using the animal fluency test: the DECIDE study. Can. J. Neurol. Sci. 36, 599–604.

Svenningsson, P., Westman, E., Ballard, C., Aarsland, D., 2012. Cognitive impairment in patients with Parkinson’s disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 11, 697–707.

Wiig, E.H., Nielsen, N.P., Minthon, L., Warkentin, S., 2002. A Quick Test of Cognitive Speed (AQT). San Antonio, TX, PsychCorp.

Williams-Gray, C.H., Foltynie, T., Brayne, C.E., Robbins, T.W., Barker, R.A., 2007. Evolution of cognitive dysfunction in an incident Parkinson’s disease cohort. Brain 130, 1787–1798.

Williams-Gray, C.H., Evans, J.R., Goris, A., et al., 2009. The distinct cognitive syndromes of Parkinson’s disease: 5-year follow-up of the CamPaIGN cohort. Brain 132, 2958–2969.

Williams-Gray, C.H., Mason, S.L., Evans, J.R., et al., 2013. The CamPaIGN study of Parkinson’s disease: 10-year outlook in an incident population-based cohort. J. Neurol. Neurosurg. Psychiatry 84, 1258–1264.