

Theta oscillations and minor hallucinations in Parkinson's disease reveal decrease in frontal lobe functions and later cognitive decline

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Cognitive decline and hallucinations are common and debilitating non-motor symptoms, usually occurring during later phases of Parkinson's disease (PD). Minor hallucinations (MH) appear early in the disease course and have been suggested to predict cognitive impairment and decline in PD, however, this has not been well-established by clinical research. Here, we investigated whether, in the absence of dementia, patients with PD and MH (without differences in frontal–subcortical and posterior cognitive functions) show altered brain oscillations and whether such MH-related electrophysiological changes are associated with cognitive impairments that increase over time. Combining model-driven electroencephalography analysis with neuropsychiatric and neuropsychological examinations in 75 patients with PD, we reveal enhanced frontal theta oscillations in patients with PD suffering from MH and link these oscillatory changes with lower cognitive frontal–subcortical functions. Neuropsychological follow-up examinations five years later revealed a stronger decline in frontal–subcortical functions in patients with MH, anticipated by stronger frontal theta alterations measured during the first assessment, defining an MH- and theta-oscillation-based early marker of a cognitive decline in PD.

Approximately 3% of the population over 65 years are affected by Parkinson's disease (PD)¹ and this is expected to double by 2040, rising faster than any other neurological disorder and reaching an estimated total of 15–18 million people worldwide². Although PD is traditionally defined as a movement disorder with the typical motor symptoms of resting tremor, rigidity and bradykinesia, PD pathology also affects

several non-motor circuits leading to a wide variety of non-motor symptoms that appear early in the disease course³. Among the latter symptoms, hallucinations are highly prevalent^{4,5}. Half of individuals experience regular hallucinations^{5,6}, increasing up to 70% at advanced stages of the disease^{7,8}, and often becoming a dominant non-motor symptom, together with dementia⁶. Hallucinations in PD have a major

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negative impact on patients, families, and society, and have been associated with a more severe form of the disease with poor cognitive outcome and dementia^{4,5,9–15}, as well as earlier home placement^{9,11,16–18}, and higher mortality^{17,18}.

Clinical and neuroimaging studies investigating the pathophysiology of hallucinations in PD^{19–24}, consistently highlight impairments in posterior visual–perceptual and frontal executive–attentional functions and related brain networks. Impairments in visual–perceptual functions are consistent with the frequent visual nature of hallucinations in PD (formed visual hallucinations)^{20,24,25} and alterations in fronto-striatal networks have been proposed to account for executive frontal–subcortical deficits^{26,27}. Both findings link the occurrence of hallucinations with cognitive impairments and related brain networks^{12–15}. This past work on hallucinations has predominantly focused on visual hallucinations, which are structured hallucinations of people or animals. However, because visual hallucinations occur most often at later stages of the disease, with cognitive decline (or dementia) already present, they are not suitable as an early marker of cognitive decline in PD, as has been proposed for MH.

MH consist of presence hallucinations, passage hallucinations, and pareidolias^{28,29}. MH are usually experienced at earlier stages of the disease^{5,6} and can even precede parkinsonian motor symptoms³⁰. However, compared with visual hallucinations, much less is known about the brain mechanisms of MH, although they have recently been shown to involve fronto-temporal brain regions related to executive sensorimotor function³¹. Brain alterations in patients with MH have also been reported to partially overlap with brain regions identified for visual hallucinations^{30,32} and for cognitive deficits in PD^{31,33}. Despite these promising findings, previous clinical work did not reveal cognitive impairments in patients with PD and MH (versus those without MH), in either visual–perceptual and/or executive frontal–subcortical functions^{30,31,33,34}, suggesting that the neuropsychological assessment instruments alone are not sensitive enough to detect early alterations associated with MH and that more sensitive measures are needed. Furthermore, it is currently not known whether MH could contribute to the early detection of patients with PD at risk of developing cognitive impairment and decline.

Beside neuropsychological and psychiatric investigations, electroencephalography (EEG) has also been explored in cognitive decline assessment in many neurological disorders, including PD (for example, refs. 35–38). EEG recordings have the advantage of wide availability (in most hospitals, clinics, and even in patients' homes³⁹), and allow for non-invasive measurements of brain activity (for example, oscillations). In PD, analysis of neural oscillations has revealed motor-related changes, such as enhanced beta oscillations in subcortical regions (for example, subthalamic nucleus) and between subcortical structures and the motor cortex (for example, ref. 40–44). Concerning cognitive decline in PD, cross-sectional studies comparing patients at different stages of the disease (for example, PD with normal cognition versus PD with cognitive impairments, independent from hallucinations) revealed enhanced power in lower frequency bands, as well as a reduction in higher frequency bands (for example, refs. 35–38,45,46). Despite the putative role of such oscillatory changes in cognitive decline, it is not known whether these changes can already be detected in patients with early PD (with no or mild cognitive impairments) or whether they are only manifest at later stages of the disease, associated with prominent cognitive impairments. Critically for our study, it is currently unknown how the presence of MH is related to brain oscillations and whether the blending of neuropsychological, neuropsychiatric, and EEG data might help in detecting subtle cognitive changes in PD patients with MH, at an early stage of the disease.

Here, we investigated whether patients with PD and MH show altered brain oscillations and whether such MH-related electrophysiological changes are associated with early cognitive deterioration over a period of 5 years. In 75 patients with PD, we applied a model-driven EEG

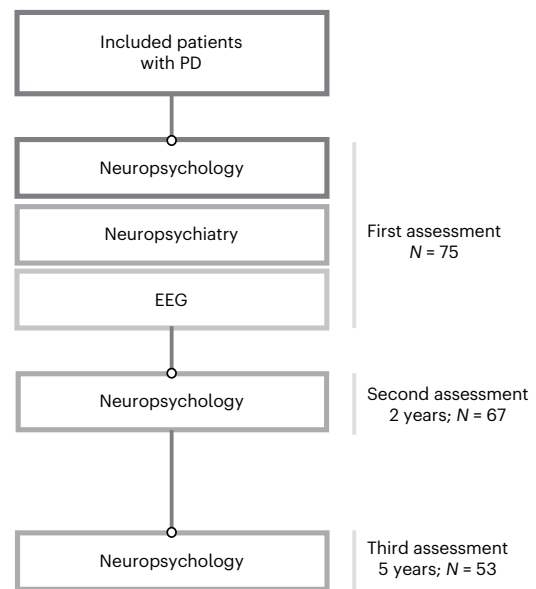


Fig. 1 | Flowchart of the study. Flowchart illustrating recruitment and follow-up testing.

approach⁴⁷ to measure periodic and aperiodic properties of the resting-state EEG data and combined it with comprehensive neuropsychiatric interviews and with neuropsychological examinations. We show that although the neuropsychological performance of patients with MH is comparable to those without MH, the presence of oscillatory alterations in the theta band over frontal regions in PD with MH is associated with lower cognitive frontal–subcortical functions, and a more rapid and severe decline in frontal–subcortical functions determined at a 5-year follow-up examination.

Results

Minor hallucinations (first assessment, semi-structured interview)

Based on the ‘hallucinations and psychosis’ item of the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part-I⁴⁸, and the administration of the semi-structured interview for the identification and characterization of psychotic phenomena in PD, 75 patients with early PD were grouped into those who reported MH (PD-MH; $N = 31$) and those without MH (PD-nMH; $N = 44$) (Fig. 1). In the PD-MH subgroup, in addition to MH, two patients also reported visual hallucinations, and one patient reported auditory hallucinations. Although the exact prevalence of MH in PD is still debated, evidence from previous studies suggests that approximately 50% of patients have MH, with presence and passage hallucinations being the most frequent^{28,49–51}. Our results corroborate the prevalence of MH in PD, with 41.37% (31 out of 75) of the patients experiencing MH. Patients can experience one MH only (for example, presence hallucination) or multiple MH (for example, presence and passage hallucination, not necessarily concomitant) (Fig. 2).

Demographical, clinical, and neuropsychological data (first assessment)

Our demographic data did not show any significant (all P values > 0.05) differences in age, disease duration, or sex between the two patient subgroups of patients (Table 1). MH have been associated with the dosage of dopaminergic medications (for example, ref. 52). Yet, they have also been observed before the onset of motor symptoms and in the absence of any intake of dopaminergic medications³⁰, leaving the role of those treatments in MH unresolved. Our results show that the dosages

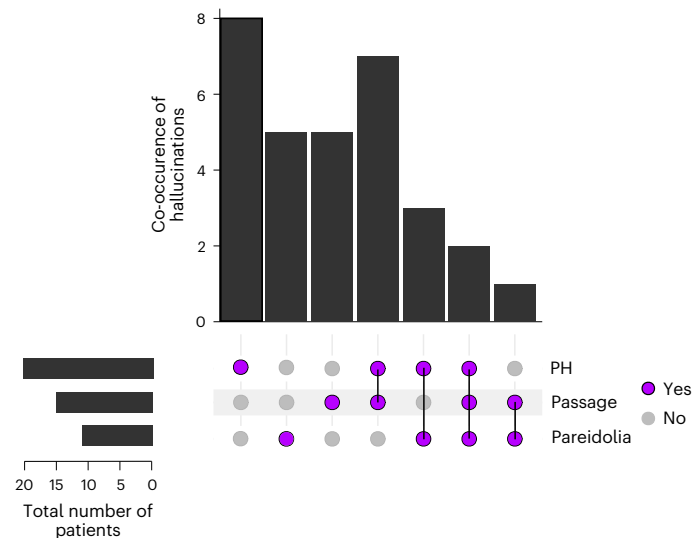


Fig. 2 | Prevalence of MH in PD. The figure illustrates the sum of patients with specific MH (left bar plot) among the PD-MH. The figure also illustrates the sum of patients experiencing only one MH (violet dots indicate which MH, top bar plot indicates the sum of patients experiencing the indicated MH) as well as the co-occurrence of multiple MH (two or more violet dots linked by a black line indicate which MH are co-experienced, the top bar plot indicates the sum of patients experiencing those MH). The figure was generated with UpSetR¹⁰⁵. ‘Yes’ and ‘no’ indicate whether a specific MH (presence hallucinations (PH), passage hallucinations and/or pareidolia) is experienced.

of the dopaminergic treatments were not significantly ($P = 0.29$ and $P = 1.0$; for levodopa equivalent dose and dopamine agonists equivalent dose, respectively) different between PD-MH and PD-nMH, supporting the hypothesis that MH are linked to PD rather than a medication-related side effect^{6,49}. To quantify the level of anxiety and depression in patients, we used the Hospital Anxiety and Depression Scale (HADS)⁵³. To quantify the level of apathy, we used the Starkstein Apathy Scale⁵⁴. No statistically significant differences were observed between the subgroups of patients (Table 1). Rapid eye movement (REM) sleep behavior disorder (RBD) has also been associated with MH⁴⁹, identified as a risk factor for early-onset psychosis in PD⁵⁵, and associated with oscillatory ‘slowing’⁵⁶. However, our data do not show any significant difference in the occurrence (assessed with the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q)⁵⁷) of RBD between the two groups (PD-MH (yes/no): 13/18; PD-nMH (yes/no): 16/27), nor in the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ⁵⁸; available for 43/75 patients) ($P = 0.13$ and $P = 0.12$ respectively; Table 1).

The results of the neuropsychological examination did not reveal any significant differences in cognitive functions between the patients in the PD-MH and PD-nMH subgroups. This was not found for the frontal–subcortical cognitive functions ($P = 0.20$) nor for the posterior functions ($P = 0.21$). The two patient subgroups also did not differ (Fisher exact test $P = 0.29$; odds ratio = 1.84) in the number of patients with mild cognitive impairment (MCI; defined as a Parkinson’s Disease-Cognitive Rating Scale (PD-CRS) total score ≤ 81 , ref. 59), PD-MH (yes/no MCI): 10/21; PD-nMH (yes/no MCI): 9/35. These results are in line with previous literature showing that, at the group level, patients with PD and MH do not differ from those without MH⁴⁹ in cognitive functions. We also analyzed whether the number of MH (sum of different hallucinations) experienced by a patient was associated with neuropsychological scores. Again, neither the frontal–subcortical cognitive score ($\rho = -0.14$, $P = 0.46$) nor the posterior cognitive score ($\rho = 0.04$, $P = 0.84$) was associated with the number of MH. These data show that PD-MH and PD-nMH do not differ in the demographic, clinical, and neuropsychological variables. The only difference between the two

Table 1 | Clinical and demographic variables for PD-MH and PD-nMH

	PD-MH (N=31)	PD-nMH (N=44)	P value
Age (years)	67.9±7.31	66.1±8.63	0.42 ^a
Gender (male/female)	23/8	26/18	0.22 ^b
Disease duration (years)	5.74±2.22	4.77±2.11	0.07 ^a
Education (years)	12.7±5.04	12.2±4.68	0.67 ^a
Equivalent dopamine agonists (mg/day)	162±137	153±99.4	1 ^a
LEDD (mg/day)	534±250	464±210	0.29 ^a
MDS-UPDRS part-III (ON state)	26.5±8.75	25.2±7.30	0.49 ^c
PD-CRS frontal–subcortical	60.2±15.4	63.8±15.1	0.2 ^a
PD-CRS posterior	28.5±1.95	28.2±1.94	0.21 ^a
RBDSQ	5.6±3.14	4.13±2.32	0.12 ^a
RBD1Q (present/absent)	13/18	16/27	0.13 ^b
Depression	2.29±2.40	2.23±2.82	0.48 ^a
Anxiety	3.55±2.43	3.57±2.89	0.81 ^a
Apathy	4.94±7.42	4.02±5.63	0.52 ^a
Hoehn and Yahr stage	2.33±0.38	2.18±0.3	0.08 ^c

LEDD indicates levodopa equivalent daily dose. MDS-UPDRS part-III was measured during the ON dopaminergic medication state. ^aMann–Whitney U test. ^bFisher exact test. ^cWelch test.

groups is the occurrence of MH. In addition, the amount the MH is not directly associated with cognitive impairment.

Periodic and aperiodic EEG signals

The EEG signal is characterized by the background activity (1/ f aperiodic signal; characterized by offset and slope; Supplementary Fig. 1) and the genuine oscillatory signals (periodic signals; characterized by the center, power, and bandwidth of the peak; Supplementary Fig. 1). Here, we separated the aperiodic from periodic signals to better understand and interpret EEG results⁴⁷ (Methods), focusing on the power and center frequency of the dominant oscillation; our analysis of the aperiodic signal included both the slope and offset. Based on the goodness of fit metrics, data were well fitted and no differences in fitting were observed between the two subgroups of patients (Supplementary Fig. 2 and Supplementary Results).

Frontal theta power (first assessment) is associated with lower frontal–subcortical cognitive functions in PD-MH, but not in PD-nMH

We analyzed whether the oscillatory power is modulated by MH and whether the oscillatory power is associated with lower cognitive performance (frontal–subcortical and posterior PD-CRS). Our results show that the frontal oscillatory power within the theta frequency band (4–8 Hz; Fig. 3a) was significantly ($P < 0.05$; FDR corrected; Supplementary Table 1) modulated by the frontal–subcortical cognitive functions and by MH (yes/no; that is, interaction between the two terms; Fig. 3b). Post-hoc analysis revealed that the association between theta power and frontal–subcortical cognitive functions was significant for PD-MH ($P = 0.0004$; Fig. 3c), but not for PD-nMH ($P = 0.28$; Fig. 3d). Moreover, our results indicate that for patients in PD-MH the theta oscillatory power was negatively associated with the frontal–subcortical score, with higher theta power associated with lower cognitive scores (Fig. 3c).

This association between oscillatory activity and frontal–subcortical functions (as a function of MH; interaction MH and frontal–subcortical PD-CRS) was specific for the theta frequency band, as no other frequency band (alpha: 8–13 Hz; beta: 13–30 Hz; gamma: 31–45 Hz) showed an association with frontal–subcortical cognitive

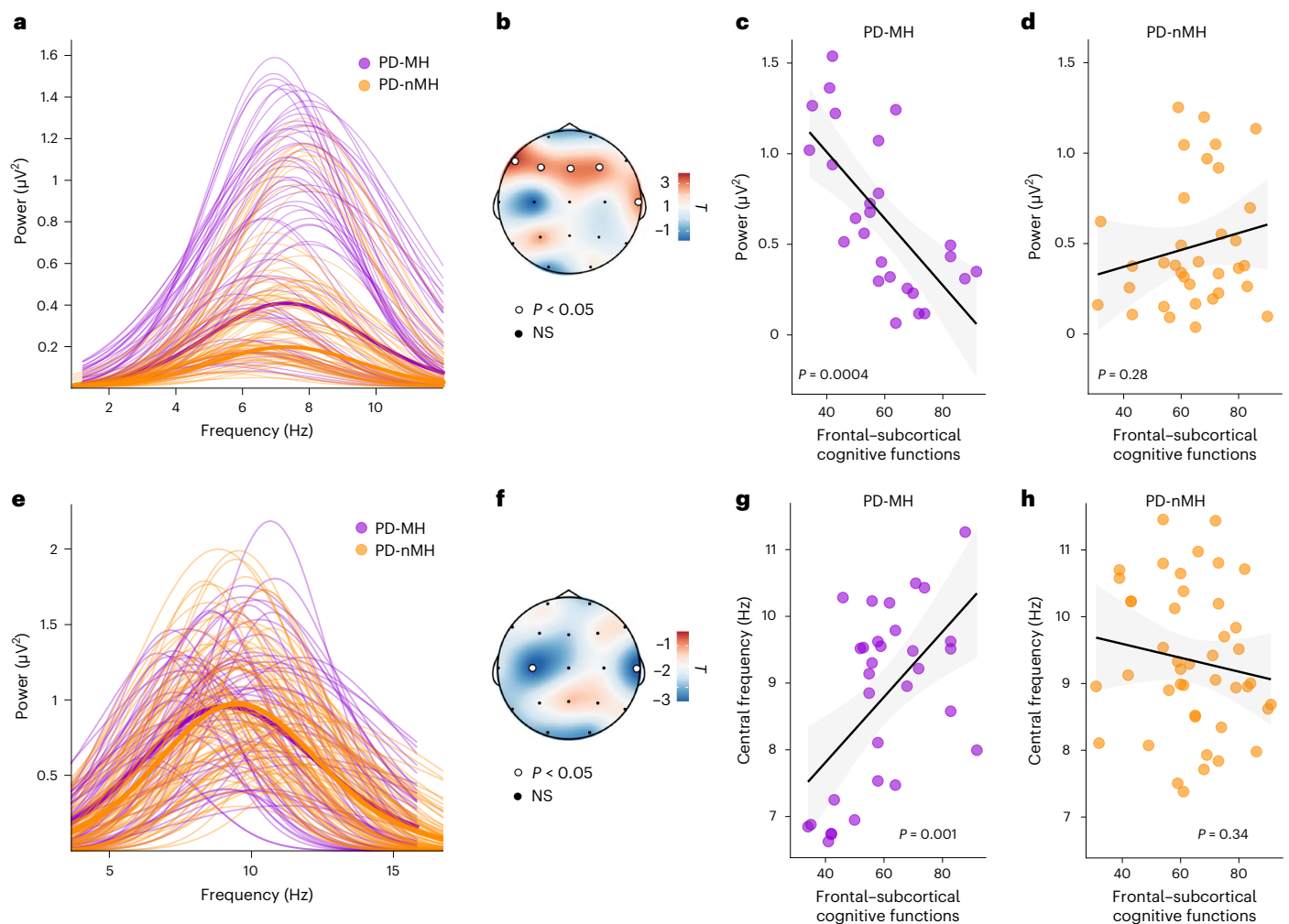


Fig. 3 | Association between frontal-subcortical cognitive functions and frontal theta power and center frequency in PD-MH. **a**, Reconstructed aperiodic-adjusted theta peaks, for PD-MH (violet) and PD-nMH (orange), thicker lines indicate the mean of each group. Thinner lines indicate single-patient data. **b**, Topography of T values indicating the interaction between patient group and frontal-subcortical cognitive functions. White highlighted dots indicate electrodes showing a significant interaction. P values were obtained from two-tailed permutation-based inference in linear regression models and FDR corrected. Note that four out of five electrodes showing a significant interaction were over frontal scalp regions, bilaterally. NS, not significant. **c**, Frontal theta oscillatory power is associated (linear regression two-tailed permutation; $P = 0.0006$) with frontal-subcortical cognitive functions in PD-MH. Higher power is associated with lower cognitive functions. Single dots represent the value for each patient (average of the electrodes showing a significant interaction between patient group and frontal-subcortical cognitive functions). The gray shading around the line represents the 95% confidence interval (CI). **d**, Frontal theta oscillatory power is not associated with frontal-subcortical cognitive functions in PD-nMH. Single dots represent the value for each patient. The gray shading around the line represents the 95% CI. Significance was obtained

with permutation tests and multiple comparisons were corrected with FDR. **e**, Reconstructed aperiodic-adjusted theta-alpha (4–13 Hz) peaks, for PD-MH (violet) and PD-nMH (orange), thicker lines indicate the mean of each group. Thinner lines indicate single-patient data. **f**, Topography of T values indicating the interaction between patient group and frontal-subcortical cognitive functions. White highlighted dots indicate electrodes showing a significant interaction for the center frequency (4–13 Hz) and the frontal-subcortical cognitive functions. P values were obtained from two-tailed permutation-based inference in linear regression models and FDR corrected. **g**, Center frequency is associated with frontal-subcortical cognitive functions in PD-MH (linear regression two-tailed permutation; $P = 0.001$). Lower center frequency is associated with lower frontal-subcortical cognitive functions. Single dots represent the value for each patient (average of the electrodes showing a significant interaction between patients' group and frontal-subcortical cognitive functions). The gray shading around the line represents the 95% CI. **h**, Center frequency is not associated with frontal-subcortical cognitive functions in PD-nMH (linear regression two-tailed permutation; $P = 0.34$). Single dots represent the value for each patient. The gray shading around the line represents the 95% CI.

functions (all interactions $P > 0.05$; false discovery rate (FDR) corrected; Supplementary Table 1). In addition, this association was specific for electrodes over the frontal region, as no other electrode showed a significant interaction ($P > 0.05$; FDR corrected; Supplementary Table 1). Finally, the frontal theta pattern in PD-MH was only found for frontal-subcortical functions, as there was no association between MH and the posterior cognitive functions in any of the tested frequencies and electrodes (all interactions $P > 0.05$; FDR corrected; Supplementary Table 2). These data show that by merging neuropsychological,

neuropsychiatric, and EEG data, we are able to identify that selective signs of decreases in cognitive frontal-subcortical functions in PD are associated with MH and enhanced localized (frontal) theta power (see Supplementary results for power changes associated with MH and Supplementary Tables 4 and 5).

Because enhanced theta (and beta) power has been associated with motor impairment and its severity in PD^{60,61} and because the degree of motor impairment has been associated with cognitive impairments (for example, ref. 62), it could be argued that the present findings (that is,

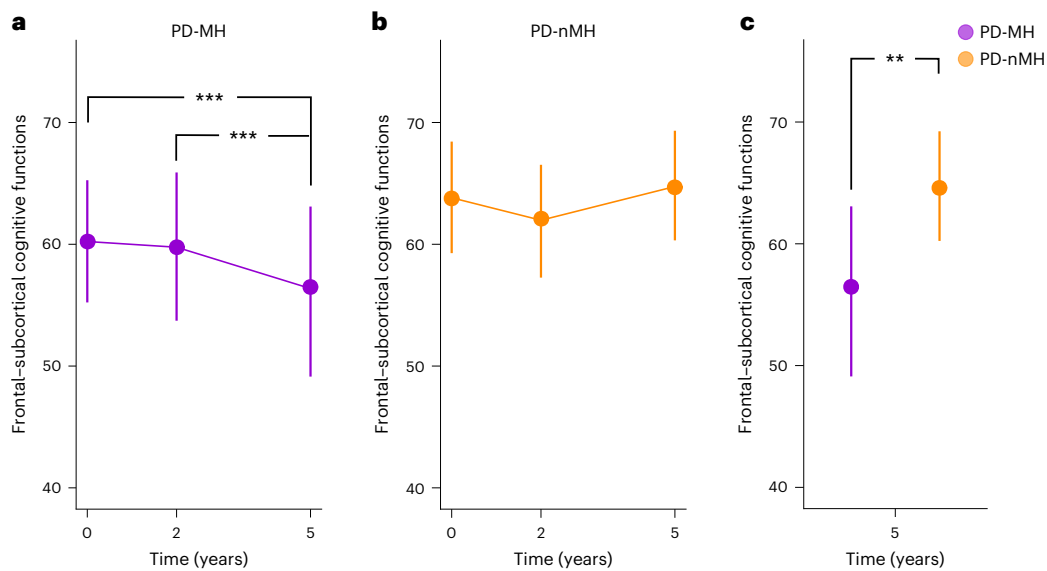


Fig. 4 | Longitudinal progression of the frontal–subcortical cognitive functions. **a**, In PD-MH frontal–subcortical cognitive functions decline significantly ($P < 0.05$) over 5 years. At this first assessment, 75 patients were included. **b**, In PD-nMH frontal–subcortical cognitive functions do not decline significantly over 5 years. At this second assessment, 67 patients were included. **c**, Difference in frontal–subcortical cognitive functions at the third assessment

(year 5). At this third assessment 54 patients were included. PD-MH shows a lower frontal–subcortical cognitive functions than PD-nMH. The bigger dots on the sides indicate the mean of the group. The error bars indicate 95% CI. ** $P < 0.01$, *** $P < 0.001$. Data were analysed using linear mixed models, and P values were calculated using parametric bootstrap.

enhanced theta oscillations associated with MH and frontal–subcortical cognitive impairments) may reflect differences in motor symptoms. However, this was not the case (Table 1). Additional control analysis, investigating whether changes in oscillatory activity are associated with MH and motor impairment (MDS-UPDRS part-III), did not show any significant frequency modulations in any brain region (for all interactions between MH and MDS-UPDRS part-III, $P > 0.05$; FDR corrected; Supplementary Table 3) between groups as a function of patients' motor impairment, and PD-MH and PD-nMH did not show any difference in the MDS-UPDRS motor scores (Table 1). Moreover, theta enhancement has been associated with dopamine-induced dyskinesia^{63,64}. However our results are not modulated by the presence or absence of dopamine-induced dyskinesia (see Supplementary results). These data show that the theta oscillatory changes associated with lower cognitive functions in PD-MH are not related to features of motor impairment.

Lower center frequency (first assessment) is associated with lower cognitive frontal–subcortical functions in PD-MH, but not in PD-nMH

Previous research on cognitive impairment in PD has described a frequency 'shift' or slowing down from predominant alpha oscillations to predominant theta oscillations, after the onset of dementia (for a review, see ref. 7). However, these interpretations were predominantly reached based on changes in power (intensity of the oscillation), rather than in the center frequency (the actual frequency, in hertz, at which the peak is observed). That is, the shift was inferred from having a reduced power in the alpha band and higher in the theta band, rather than a change in the frequency peak from 8–13 Hz (alpha) to 4–8 Hz (theta band). Therefore, we tested whether the association between theta oscillations, MH, and lower frontal–cognitive functions is also associated with a change in the center frequency (shift of the center frequency in the 4–13 Hz frequency band). We observed a significant ($P < 0.05$; FDR corrected; Supplementary Table 6) modulation of the center frequency in this theta–alpha range (Fig. 3e) as a function of the interaction between the two terms (frontal–subcortical cognitive functions and MH (yes/no)). This interaction was localized over a central left electrode and a temporal electrode (Fig. 3f and Supplementary

Table 6). Post-hoc analyses show that for PD-MH, the center frequency is significantly ($P = 0.001$, Fig. 3g) associated with the frontal–subcortical cognitive functions, in which a lower center frequency (that is, shifting from alpha to theta) is associated with lower cognitive functions. This association was not observed for PD-nMH ($P = 0.34$; Fig. 3h). None of the other electrodes showed a significant interaction (all $P > 0.05$; FDR corrected; Supplementary Table 6 and Supplementary Results). Collectively, these results show that the association between MH and frontal–subcortical cognitive function is due to both power and center frequency changes in the alpha–theta range (see Supplementary Results for center frequency changes associated with MH).

Aperiodic signals (exponent and offset; first assessment) are not associated with cognitive functions

The precise neural mechanisms that alter the aperiodic exponent of intrinsic neural activity remain an active area of research. However, a flattened exponent of the aperiodic signal has been correlated with age⁶⁵ and with age-related cognitive decline^{66,67}. Similarly, the offset of the aperiodic signal decreases with age^{68,69}. Therefore, we investigated whether modulations of exponent and/or offset might be related to changes as a function of MH (yes/no) and frontal–subcortical cognitive functions (interaction between the two terms). Our results show that neither exponent nor offset of the aperiodic signals are significantly modulated (all P values > 0.05 ; Supplementary Table 7) as a function of cognitive function (frontal–subcortical nor posterior) and MH. These results demonstrate that the theta modulations we observed are due to a change in oscillatory power and not to aperiodic modulations.

Second assessment (after 2 years) and third assessment (after 5 years) reveal that cognitive decline is more severe in PD-MH

Neuropsychological follow-up at the second assessment (2 years after the first assessment) was available in 67 patients and at the third assessment (5 years after the first assessment) in 53 of the 75 total patients included at the beginning of the study. Data show that the decline (over the three assessments) in frontal–subcortical cognitive functions was significantly different between the two groups of patients ($P = 0.01$;

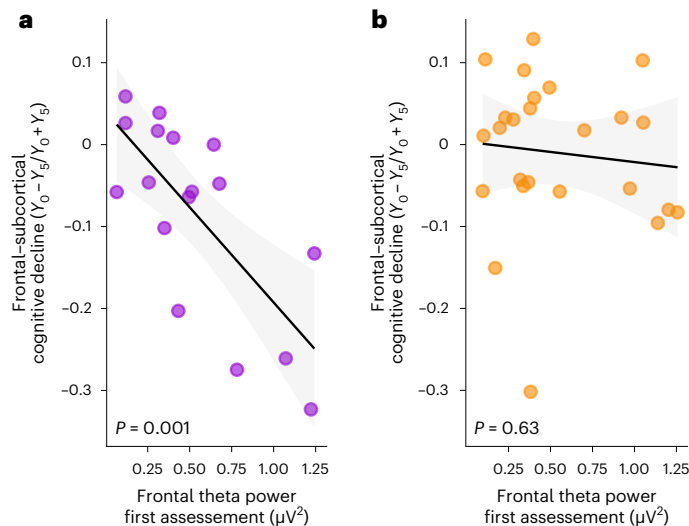


Fig. 5 | Frontal theta power during the first assessment anticipates cognitive decline occurring over 5 years. **a**, Results of the linear regression show that in PD-MH, frontal theta power, as measured during the first assessment, is associated with the frontal-subcortical cognitive decline as measured during the third assessment (5 years later; linear regression two-tailed permutation; $P = 0.001$). The gray shading around the line represents the 95% CI. **b**, Results of the linear regression show that in PD-nMH, frontal theta power, as measured during the first assessment, is not significantly (linear regression two-tailed permutation; $P = 0.63$) associated with the frontal-subcortical cognitive decline, as measured during the third assessment (5 years later). The gray shading around the line represents the 95% CI. P values are obtained from two-tailed permutation.

interaction between MH and follow-up; Fig. 4; Supplementary Fig. 6). Post-hoc analyses revealed that frontal-subcortical cognitive decline in PD-MH was significant when comparing the data from the first assessment with the third assessment (after 5 years; $P = 0.0001$; $t(1,127) = 4.01$), and when comparing the second with the third assessment ($P = 0.0013$; $t(1,126) = 3.3$) (Fig. 4a; Supplementary Table 8). This comparison was not significant when comparing data from the first assessment with the second assessment (after 2 years; $P = 0.41$; $t(1,125) = 0.83$). For PD-nMH, cognitive decline was not statistically different for either comparison (that is, neither when comparing the data from the first and second assessment ($P = 0.16$; $t(1,126) = 1.42$) nor from first and third assessment ($P = 0.42$; $t(1,127) = 0.8$)) (Fig. 5b). Additional post-hoc analyses revealed that frontal-subcortical cognitive functions in PD-MH are lower than those in PD-nMH only at 5-year follow-up ($P = 0.009$; $t(1,116) = -2.66$; Fig. 4c). No statistical difference was observed at the second assessment ($P = 0.45$; $t(1,102) = -0.76$) or the first assessment ($P = 0.33$; $t(1,96) = -0.97$). Concerning posterior cognitive function, despite a reduction in these functions in both groups of patients (main effect of time: $P = 0.003$), no significant statistical difference was observed between the two subgroups of patients (interaction: $P = 0.39$; main effect of group: $P = 0.98$).

Collectively, these results show that the occurrence of MH in patients with PD is associated with a more severe form of the disease (without yet differing in the number of patients with MCI) characterized by a more important cognitive decline, especially for the frontal-subcortical cognitive functions.

Cognitive decline in PD-MH (third assessment) is anticipated by the frontal theta enhancement measured 5 years earlier (first assessment)

Informed by our results showing that both the frontal theta power and the theta-alpha center frequency (4–13 Hz) are associated with frontal-subcortical cognitive score in patients with MH we investigated

whether frontal theta power and/or the center frequency measured during the first assessment anticipated frontal-subcortical cognitive decline measured 5 years later. Concerning theta power, when assessing frontal-subcortical cognitive functions over 5 years, results show a significant interaction ($P = 0.01$) between the oscillatory power (measured during the first assessment) and the groups of patients. Post-hoc analyses revealed that for PD-MH higher frontal theta power during the first assessment was associated with a stronger frontal-cognitive decline ($P = 0.001$; Fig. 5a) 5 years later, which was not the case for patients without MH ($P = 0.64$; Fig. 5b). None of the other frequencies showed this interaction (all P values > 0.05 ; also see Supplementary Results). Concerning the center frequency, we did not observe any significant association between this measure and the frontal-subcortical cognitive decline over 5 years (no interaction; $P = 0.20$). These results suggest that frontal theta power measured during the first assessment anticipates the cognitive decline occurring over 5 years, but only for PD-MH patients. In addition, these results show that by merging neuropsychological, neuropsychiatric, and EEG data, we are able to show that MH is associated with a higher risk of more rapid cognitive decline.

Because MH have been associated with subjective cognitive decline³³, we investigated whether MH also anticipate MCI. Our results show that, although PD-MH (versus PD-nMH) show a trend for a higher conversion to MCI after 5 years (Supplementary Results), the probability to develop MCI after 5 years is not anticipated by MH at the first assessment ($P = 0.35$, odds ratio = 0.53, after excluding patients with MCI during the first assessment; $P = 0.21$, odds ratio = 0.49 with all patients). These results suggest that MH alone are not sufficient to significantly anticipate MCI (see Supplementary Results for association with theta power and MH as predictors for MCI). This might be explained by the fact that the patients included in the current study were at an early stage of the disease and that the conversion from normal cognition to MCI in the tested patients might require a period longer than 5 years (for example, ref. 70).

Discussion

Conducting EEG, psychiatric and neuropsychological assessments in a group of 75 patients with PD, we report that specific alterations in frontal theta oscillations in patients with PD and MH (Fig. 3b,f) were associated with a decrease in frontal-subcortical cognitive functions (Fig. 3b,c,f,g). Frontal theta oscillatory alterations were not associated with posterior cognitive functions and were absent in patients with PD without MH (Fig. 3d,h). These data also show that the combination of MH and enhanced theta oscillation allows identification of patients with PD and a subclinical decrease in cognitive functions (Fig. 5).

The detection of cognitive impairments in PD is of major clinical importance, as it is associated with earlier home placement, lower quality of life, and higher mortality^{77,72}. Cognitive impairment is a frequent non-motor symptom in PD, up to six times more common in PD than in the healthy age-matched population⁷³, and its prevalence increases with disease progression⁷. Past neuropsychological and neuroimaging work in PD has identified deficits in posterior visual-perceptual, executive frontal-subcortical functions, and in related brain networks, thereby linking the neural mechanisms of hallucinations with cognitive impairments^{12–15}. However, two main limitations have prevented the wider use of hallucinations as ‘early’ predictors of cognitive decline in PD. First, previous work has focused on visual hallucinations, which tend to occur in later stages of PD and hence in patients already showing advanced cognitive impairments, therefore, inevitably excluding them as an ‘early’ marker of cognitive impairment. Second, although MH usually appear at earlier stages of the disease and before visual hallucinations^{5,6,28,50}, several clinical studies were not able to link them to cognitive dysfunction, failing to find significant cognitive impairments in patients with PD and MH^{30,33,34}. Our data provide evidence that MH allow the identification of patients with PD cognitive impairment, however, only when MH are associated with

specific EEG changes. Thus, when not taking EEG data into account, we confirm earlier data and show that patients with PD and MH do not show stronger or distinct cognitive impairments, compared to patients with PD without MH^{30,33,34}. However, by combining psychiatric interviews and EEG data, we reveal that PD-MH patients with predominant theta (power and center frequency) oscillations have lower cognitive scores in frontal-subcortical functions (Fig. 3c,g). These findings are specific because frontal theta oscillatory alterations in PD-MH were not associated with changes in posterior cognitive functions and were absent in PD-nMH (Fig. 3d,h). Further control analyses revealed that MH-specific theta oscillations cannot be explained by differences in the occurrence of visual hallucinations between groups, as only two of the investigated 75 patients reported structured visual hallucinations, nor by any other of the clinical-demographic variables (for example, age, disease duration, antiparkinsonian medication, or motor impairment), as the two groups of patients were similar in these variables. Moreover, our results are not due to differences in RBD, anxiety, depression, which have been associated with hallucinations^{28,55} or dopamine-induced dyskinesia⁶³.

Cognitive decline and dementia in PD, independently from hallucinations, have previously been associated with global (spatial and frequency) EEG changes, characterized by enhanced theta oscillatory power as well as decreased power in higher frequency bands (that is alpha and beta). Comparable oscillatory abnormalities have also been reported in other neurodegenerative disorders characterized by cognitive decline, for instance, in dementia with Lewy bodies^{46,74}. However, previous results highlighting oscillatory changes were obtained by either comparing patients with different neurodegenerative diseases (for example, ref. 46), by comparing patients with PD with age-matched healthy controls, or by investigating patients with PD at different stages of the disease and cognitive impairments (for example, with versus without dementia; for example, refs. 37,75–78). Accordingly, it is not known whether these previous oscillatory differences are only present in patients with cognitive deficits due to advanced PD, whether they depend on differences in disease duration or medication, or other clinical variables likely differing between previously tested groups. The present results extend and detail these findings. They are consistent with the importance of enhanced theta oscillations and cognitive decline in PD, but show changes that are more specific (as higher frequencies were not affected) and, critically, demonstrate them in a large group of patients with early PD and across two subgroups of patients that were clinically and demographically similar (differing only in MH), at a comparable stage of the disease, and were tested at a relatively early stage of the disease (mean of 5 years after PD diagnosis). The enhanced frontal theta activity in patients with cognitive decline that we described may reflect compensatory mechanisms caused by structural and functional changes⁷⁹, reflecting disruption of thalamocortical circuits⁸⁰ and/or differing involvement of prefrontal regions^{31,81–84}.

Moreover, we note that the present data on MH-specific theta alterations do not identify a general decrease in all tested cognitive functions and a global (whole scalp) increase in theta oscillations. Instead, our analysis revealed a focal decrease in cognitive functions and a focal enhancement in theta oscillations. Compatible with proposals suggesting that reduced frontal dysfunction and frontal brain atrophy are associated with a higher risk for cognitive impairments in PD^{85–88}, we report evidence that PD-MH show a decrease that is limited to frontal-subcortical functions and limited to an increase in frontal theta oscillations. This was corroborated by the absence of any differences in the tested posterior visual-perceptual functions (which are often observed in more advanced PD, associated with visual hallucinations and dementia^{34,89}), by the absence of changes in posterior theta oscillations, and by the absence of changes in higher frequencies as well as aperiodic EEG signals. In conclusion, the present data suggest that a focal decrease in frontal-subcortical cognitive functions in early PD (that is 5 years after diagnosis and in stage 2 of the illness assessed

by the Hoehn and Yahr scale⁹⁰) can be identified by combining neuropsychological data with theta power over frontal-subcortical brain regions and the presence of MH.

The data from the 5-year longitudinal neuropsychological follow-up further corroborate and extend these findings, revealing that patients with MH have a stronger decline in frontal-executive functions (Fig. 4) and that the enhanced frontal theta power, measured during the first assessment, is associated with a cognitive decline in frontal-subcortical functions occurring five years after the first assessment (Fig. 5a). Frontal-subcortical deficits are believed to be an indicator of MCI⁸⁸ and therefore predictor of later possible PD dementia. We note that the number of patients with MCI during the first assessment was not different between the two subgroups, showing that MCI cannot explain the more prominent reduction in cognitive functions in the PD-MH group. Similarly, the frontal-subcortical cognitive functions during the first assessment were comparable between the two groups. This was different at the third assessment, carried out 5 years later, when the PD-MH group (versus PD-nMH) now showed a significant difference in frontal-executive functions, with PD-MH having a significant more important cognitive impairment (the number of patients with MCI was again not (yet) different between the two groups). Critically, our longitudinal data show that only frontal theta power anticipates the severity of the frontal-subcortical cognitive decline by 5 years and only in those patients reporting MH. Again, these EEG results were specific for frontal theta power as no other frequency anticipated the frontal cognitive decline. Compared with previous studies that suggested that enhanced theta oscillations (but also other variables) might indicate an increased risk of developing dementia^{91,92}, our data show that the combination of MH and selective frontal theta power allow a quantitative and early prediction of cognitive frontal-subcortical decline, an indicator for early MCI⁸⁸. Finally, our results show that the theta power and not the center frequency in the theta-alpha band, anticipates cognitive decline in patients with PD and MH and that the power changes are not due to changes in the background activity of the brain typically associated with aging (aperiodic signals; for example refs. 66,67).

Limitations of the study

Our findings should be considered in the context of the following limitations. First, although the use of an EEG system with a limited number of electrodes has several advantages for clinical use and patient comfort, a higher number of electrodes will allow for more extensive analyses (for example, source localization). Second, we only measured EEG during the first assessment. Future studies should analyze frontal theta oscillations and other EEG signals during follow-up examinations. Third, behavioral and imaging studies of cognitive tasks (for example, ref. 93), in addition to resting-state EEG recordings, will be needed for a more in-depth characterization of the cognitive and neural impairments associated with MH. Relatedly, we have recently developed a robotic procedure⁹⁴ able to induce MH under robotically controlled conditions and further reported that patients with PD-MH are highly sensitive to the procedure versus healthy controls and patients with PD-nMH³¹. Applying such methods will allow it to be determined whether patients with PD with heightened sensitivity to robot-induced MH can already be detected by enhanced frontal theta oscillations, enabling even earlier identification of patients at risk of PD dementia before MH and frontal-subcortical impairments become symptomatic. Although MH were assessed using the 'hallucinations and psychosis' item of the MDS-UPDRS-I⁴⁸ and a semi-structured interview covering the different types of hallucinations associated with PD^{32,49}, further screening questionnaires should be developed, allowing the investigation of additional features of hallucinations (for example, frequency and severity). Finally, although our data showed that the occurrence of RBD does not differ between PD-MH and PD-nMH, these results were based on screening questionnaires^{57,58}, future study should include RBD diagnosis based on polysomnography.

Methods

Study design

Seventy-five individuals participated in this study. All those fulfilling MDS new criteria for PD-MH—sense of presence, passage hallucinations, visual illusions and/or pareidolias ($n = 31$)—and PD-nMH ($n = 44$) were prospectively recruited from a sample of outpatients regularly attending the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau, Barcelona. Individuals were diagnosed with PD by a neurologist with expertise in movement disorders. Each individual was interviewed regarding disease onset, medication history, current medications, and dosage (levodopa daily dose and dopaminergic agonist-equivalent daily dose). Motor status and stage of illness were assessed by the MDS-UPDRS-III scale. The two subgroups of patients were comparable in sex, age, disease duration, dopaminergic doses, dopaminergic agonists, motor severity, sleep disturbances, and cognition.

Exclusion criteria included a history of major psychiatric disorders, cerebrovascular disease, conditions known to impair mental status other than PD, and the presence of factors that prevented magnetic resonance imaging (MRI) scanning (for example, claustrophobia, MRI incompatible prosthesis). Patients with focal abnormalities in MRI or non-compensated systemic diseases (that is, diabetes and hypertension) were also excluded. In patients with motor fluctuations, cognition was examined during the best 'on' state. All participants were on stable doses of dopaminergic drugs during the 4 weeks before inclusion. Patients were included if the hallucinations remained stable during the 3 months before inclusion in the study. No participant had used or was using antipsychotic medication. All subjects had normal or corrected-to-normal vision. Informed consent to participate in the study was obtained from all participants according to the Declaration of Helsinki. The study was approved by the local ethics committee (Sant Pau Institute for Biomedical Research IIBSP-PAR-2019-17).

Resting-state EEG data were collected using a 19-channel EEG system. Resting-state EEG data were collected with eyes open for 5 minutes.

Neuropsychiatric, neuropsychological, and EEG data were collected during the best ON-state for each patient. The EEG recordings were always performed between 9:00 and 14:00. To assess changes over time of the cognitive functions, and how they might be associated to MH (measured at baseline), PD-CRS was administered to patients 24 months (year 2) and 60 months (year 5) after the first assessment. From the 75 patients, 67 were tested at 24 months and 53 at the third assessment.

Hallucinations and cognitive functions assessments

Presence and type of MH were assessed using the hallucinations and psychosis item of the MDS-UPDRS-1⁴⁸, and a semi-structured interview covering the different types of MH associated with PD. The hallucinations and psychosis item is a clinical scale from 0 to 4: 0 corresponds to absence of hallucinations; 1 (slight): illusions or non-formed hallucinations, but patient recognizes them without loss of insight; 2 (mild): formed hallucinations independent of environmental stimuli. No loss of insight; 3 (moderate): formed hallucinations with loss of insight; and 4 (severe): patient has delusions or paranoia. The semi-structured interview used in this study has been used and published previously (ref. 49 see mds26432-sup-0001-suppappendix.doc and ref. 32 see mds27557-sup-0001-Supinfo.docx), and is used for the identification and characterization of different psychotic phenomena associated with PD. We categorize minor hallucinators as those participants with a score of 1 in the hallucinations and psychosis item of the MDS-UPDRS-1, and reported a sense of presence, passage hallucinations, and/or visual illusions using the semi-structured interview, at least weekly during the previous month. In summary, patients were included in the PD-MH group if they had had a sense of presence (presence hallucinations), passage hallucinations, visual illusions, and/or pareidolias at least

monthly, and if these phenomena were present during the three months before inclusion in the study. Cognition was assessed by the PD-CRS⁸⁸, a cognitive scale specifically designed to capture the whole spectrum of cognitive functions impaired over the course of PD. This battery comprises nine tasks explicitly designed for a brief and separate scoring procedure including frontal-subcortical tasks (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate and delayed free recall verbal memory) as well as posterior cortical tasks (confrontation naming, clock copying). The frontal-subcortical assessment score ranges from 0 to 114 points, the posterior assessment score from 0 to 20 points. The sum of the two scores is added to give the total score of the PD-CRS (0–134). Lower scores indicate lower cognitive functions. MCI has been associated with a total PD-CRS score of ≤ 81 (ref. 59). To assess cognitive changes due to the disease and the presence of MH, cognitive functions were screened (PD-CRS) 24 and 60 months after the initial visit. During those follow-up assessments no EEG was recorded.

RBD was assessed with two screening questionnaires, RBDIQ, which is a single-question (yes/no) screening tool for dream enactment behaviors (was available for all patients except 1)⁵⁷ and RBDSQ, which is a 10-item patient self-rating questionnaire (yes/no; maximum total score 13 points) covering the clinical features of RBD⁵⁸. RBDSQ was available for 43 of 75 patients.

EEG acquisition preprocessing

Continuous EEG was acquired at 250 Hz from 19 standard scalp sites (Fp1-2, F3-4, C3-4, T3-4, T5-6, P3-4, O1-2, F7-8, Fz, Cz, Pz) using passive tin electrodes mounted in an elastic cap and referenced to the two mastoid leads. Vertical eye movements were monitored using a bipolar montage with two electrodes linked together and placed below each eye referenced to a third electrode placed centrally above the eyes. Horizontal eye movements were monitored using two electrodes placed on the external canthi of each eye. Electrode impedances were kept below 5 k Ω . The electrophysiological signals were filtered with a bandpass of 0.1–35 Hz and digitized at a rate of 250 Hz. EEG acquisition was done using the Brain Vision Recorder and BrainAMP system (Brain Products GmbH; Germany). Data were analyzed off-line with the EEGLAB toolbox⁹⁵ for MATLAB (<http://sccn.ucsd.edu/wiki/EEGLAB>). After importing, data were low-pass-filtered at 45 Hz, and high-pass filtered at 1 Hz with a conventional FIR filter. After removing the electrodes and epochs contaminated by artifacts, data were re-referenced to the average reference.

The resting-state period was divided into 2-second epochs. Artifacts were removed in four steps: (1) channels and then trials were rejected if their value exceeded 2.5 times the global variance (from all channels and trials, respectively). Frontal electrodes (Fp1 and Fp2) and EOG channels were excluded from this step to avoid biases (from possible eye blinks) in the variance definition, and (2) independent component analysis (ICA) was applied to the remaining trials. ICA components reflecting eye blinks, saccades, or noise were identified and removed using SASICA⁹⁶. Noisy electrodes rejected at step (1) were replaced by interpolating neighboring channels after the ICA procedure; (3) all epochs were inspected again for remaining ambient noise not removed by the ICA and rejected if artifacts had remained.

Estimating oscillatory power and aperiodic signals

The power spectrum was estimated with the Fourier transform using Hanning as tapers, in the frequency 1 Hz to 50 Hz, with a frequency resolution of 0.5 Hz. The power spectrum was calculated for each trial and then averaged. Power spectrum estimation was computed for each electrode and participant independently.

Electrophysiological data in humans are characterized by a prominent $1/f$ power distribution, often referred to as 'background noise'⁹⁷. This $1/f$ -like power distribution (also defined as aperiodic signal), captures the phenomenon whereby the power at low frequencies is greater,

conversely power is progressively lower at higher frequencies. This pattern results in overall negatively sloped power spectrum across a wide range of frequencies. Most methods and, therefore, most of the research used to analyze oscillatory power, neglect the role of this aperiodic signal. This introduces a possible confound, in which the identified neural oscillations contain a superposition of periodic and aperiodic signals. To avoid this confounding in our analyses we used a recent method that estimates both aperiodic and periodic signals⁴⁷.

We used the open-source, Python-based Fitting Oscillations and One-Over-F (FOOOF) (version 1.0) toolbox⁴⁷ to estimate both the periodic and aperiodic signals. We restricted the FOOOF algorithm to eight oscillatory peaks within the 2–45 Hz range and constrained the peak width between 2–10 Hz. We restricted the number of oscillatory peaks estimated by FOOOF to peaks, in order to reduce the risk of overfitting (see refs. 98,99). In addition, a threshold (a peak was greater than the noise floor of at least one standard deviation above the residuals) was used to label the peak as a genuine neural oscillation. All the other parameters were used as indicated by default⁴⁷. More details on the procedure can be found here⁴⁷. The Python code to fit the model was run in R Studio using the reticulate package¹⁰⁰, and as implemented previously¹⁰¹. The model was applied to every electrode and patient. With this approach a power value (or other parameter of the periodic signal) is not necessarily identified for every frequency band and/or electrode (due to the minimal threshold to identify a peak). Missing values were excluded.

Data preprocessing was performed using statistical thresholds, independent of the patients' groups labeling, to avoid confounds. Group labeling (PD-PH; PD-nMH) was only used for the statistical models. Therefore, data analyses cannot be considered as blinded, which can be considered as a possible limitation.

Statistical analysis

Clinical–demographic variables. Statistical difference between PD-MH and PD-nMH on the measured clinical and demographic variables was assessed using the Welch test, Fisher Exact test, or Mann–Whitney *U* test, based on normality of the data. Normality was assessed with the Shapiro–Wilk test: when the *P* value for a specific variable was greater than 0.05 the distribution of the given data was assumed to not differ significantly from normal distribution (Table 1). For the PD-CRS frontal–subcortical the Shapiro–Wilk test, *P* > 0.05, but not for the posterior cognitive functions; we decided to use the Mann–Whitney *U* test for both cognitive tests to avoid confounds due to using different statistical tests.

Periodic and aperiodic EEG signals. To investigate modulations of the signals as a function of MH and cognitive functions, models were performed with the periodic (that is, power and center) or aperiodic signals (slope and offset) as the dependent variable, and with group (PD-MH and PD-nMH) and cognitive functions (PDCRS; either for the frontal–subcortical sub-score or the posterior sub-score) as covariates (UPDRS-III scores were used instead of the cognitive functions of the control analyses). An interaction term between the two covariates was used in the model. Models were independently applied to each electrode and frequency band of interest (theta, alpha, beta, gamma). The significance was estimated based on two-tailed permutation marginal tests for linear models (5,000 iterations; permuco R package¹⁰²). Correction for multiple comparisons for the number of electrodes tested was obtained with FDR¹⁰³, applied to each frequency band independently. Patient's electrodes for which a peak in a determined frequency was not observed/measured were excluded from the statistical models.

Longitudinal data

Progression of the cognitive functions. To assess changes in cognitive functions measured at baseline (year 0), 24 months (year 2), and 60 months (year 5), frontal–subcortical and posterior cognitive functions were analyzed with linear mixed-effects models (Afex R package¹⁰⁴).

Patient drop-out in the longitudinal data was due to either personal and/or clinical reasons. Two distinct models were performed for the two PD-CRS sub-scores. The statistical models assessing cognitive decline over the years used subgroups and the measures time-points as a fixed effect (interaction between subgroups of patients and years) and with random intercepts for each participant. *P* values were calculated using parametric bootstrap.

EEG activity at baseline (year 0) anticipates cognitive decline (at year 5). Based on the results of the cognitive decline over the year, frontal–subcortical cognitive decline was quantified by calculating the difference in score between the two points (year 0 – year 5) and normalized by dividing by the sum of the two scores (year 0 + year 5). To investigate whether the cognitive decline was associated with the theta power over the frontal electrodes (that is mean of the frontal cluster observed at the first assessment; see Fig. 3b) and was differently modulated between subgroups of patients, we conducted two-tailed permutation marginal tests for linear models (5,000 iterations; permuco R package¹⁰²), with theta (but also alpha, beta, and gamma) power and subgroups as independent variables (and with an interaction term between the two), and cognitive decline as the dependent variable.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data are available here: https://gitlab.epfl.ch/fbernasc/pd_mh_eeg_cognition.git.

Code availability

Codes for the analyses are available here: https://gitlab.epfl.ch/fbernasc/pd_mh_eeg_cognition.git.

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Author contributions

F.B. conceptualized idea, analyzed the data and wrote paper, J.P., H.B-K, S.M-H collected data and wrote paper, J.K, O.B wrote paper. J.M. and A.H-B. collected data. All authors approved the definitive version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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