Different features of the cortical sensorimotor rhythms are uniquely linked to the severity of specific symptoms in Parkinson's disease

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Abstract

Parkinson's disease (PD) is associated with functional changes in the neural activity within the brain's sensorimotor network, which in turn are related to the characteristic motor symptoms in PD. The functional changes in PD are particularly prominent in terms of oscillatory neuronal activity in the characteristic sensorimotor alpha and beta rhythms. However, summaries in terms of alpha or beta power do not capture the full range of the complex dynamic nature of the signals from the somatosensory cortex. This raises the question of how to quantify and summarise the functional changes in such oscillatory features in a manner that captures the relevant disease- and symptom-related neural activity.

We investigated the role of spontaneous cortical somatosensory activity in the electrophysiological alpha and beta bands among a cohort of early- to mid-stage PD patients (N=78) and age- and gender-matched healthy controls (N=60) using source reconstructed resting-state magnetoencephalography (MEG) recordings. We quantified the oscillatory features of the neural time series by its oscillatory alpha power, beta power, and 1/f broadband characteristics using power spectral density, and additionally by characterising "burst" properties in the signals. We examined the relationship between the signal features and disease state, age, sex, and cortical thickness. Using multiple regression, we examined the relative contribution of the oscillatory features on the clinical manifestation of motor symptoms in the PD group.

Our results show that PD patients differ from healthy controls on several of the oscillatory features, showing higher beta-band power, higher burst amplitude, and steeper 1/f broadband characteristics compared to healthy controls, as well as a steeper age-related decrease in the bursts rate. While there was a high degree of correlation between some of the oscillatory features, several features also appeared functionally separated,
showing independent feature-to-symptom relationships. For instance, oscillatory beta power increased with the severity of midline function symptoms, while burst rate decreased with the severity of bradykinesia.

Our study shows that quantification of distinct features within the oscillatory sensorimotor neural time series in PD captures different underlying mechanisms related to disease progression and symptom severity, which in turn has a potential for a more individualised and precision-based approach to assessing functional neural changes in PD.
1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disease characterised by gradual death of dopaminergic neurons and loss of the neurotransmitter dopamine. The pathogenesis of PD begins long before the initial manifestation of symptoms and gradually deteriorates from the initial stages. Accumulation of Lewy bodies leads to lesions in the substantia nigra pars compacta, which typically spread to and affect the brain stem, basal ganglia and, in the final stages, the neocortex. The progressive structural and neurochemical changes in PD are accompanied by widespread functional changes in neuronal activity, which in turn lead to worsening clinical symptoms, commonly in the form of movement disorders such as tremor, rigidity, and bradykinesia with co-occurring non-motor systems like sleep disorders, depression, fatigue, and cognitive deficits.

The changes in brain function in PD are particularly prominent in the oscillatory activity of neurons. Spontaneous oscillatory beta band (13–30 Hz) activity in the sub-thalamic nucleus (STN) exhibits a systematic disease-related increase in synchronicity in PD that is related to the dopamine level and correlated with the severity of bradykinesia and rigidity. Changes in the beta band extend beyond the STN through the basal ganglia-thalamic cortical sensorimotor network. The cortical manifestation of the disease-related changes in the sensorimotor network can be measured non-invasively from the cortex, using electro- or magnetoencephalography (EEG or MEG). Non-invasive neural recordings can potentially provide prospective biomarkers of disease or symptom-related neural changes in PD. Increased oscillatory beta-band activity in the sensorimotor cortex has been linked to increased symptom severity, such as rigidity and bradykinesia. The cortical beta-band power has also been shown to increase by dopaminergic medication, though others have found no effect of medication on cortical beta-band power. Deep brain stimulation of the STN in PD patients has shown to lead to a decrease in the power of
spontaneous activity in the cortical sensorimotor beta and alpha (8-12Hz) bands\textsuperscript{18,19} (but see also\textsuperscript{13,20}). Importantly, there is evidence that the beta-band changes are not in the same direction across the different stages of PD. For example, there are reports of increased cortical beta-band power in the early stages of PD\textsuperscript{21}, whereas the later stages are associated with decreased beta-band power.\textsuperscript{22}

The beta-band power is not the only feature of the sensorimotor rhythms that is altered in PD. Several studies have found a shift in the beta-band centre frequency (the frequency at which the power spectrum density peaks in the beta-band) towards a lower frequency in PD patients compared to healthy controls.\textsuperscript{23–25} The shift towards lower beta-band centre frequency is more pronounced in PD patients with dementia\textsuperscript{26–29} and correlates with reduced cognitive ability.\textsuperscript{25,30} Notably, the centre frequency shift is detectable already in the early stages of PD\textsuperscript{24}, and dopaminergic medication does not appear to affect the centre frequency shift.\textsuperscript{31} The changes in beta band power and centre frequency in PD could indicate that different features of the oscillatory beta-band activity reflect different underlying neural functions expressed in the measured sensorimotor signals. Changes in beta-band power could be functionally related to sensorimotor disturbances, and changes in centre frequency could be related to cognitive function.

Notably, the characteristics of neuronal oscillatory activity may hold additional information of disease-related changes in PD. Both beta-band power and centre frequency reflect a quantification of power spectral density (PSD). While these features can provide valuable information about disease-related changes in PD, the quantification of a neural time series by the PSD provides a static summary of the oscillatory activity across the entire time series. PSD does not account for inherent dynamics in this activity or changes in the time series on shorter time scales—as is prevalent in neural time series. The beta-band exhibits a great degree of variation over time and contains characteristic high-amplitude "bursts" that last about 50-200 ms, both in the cortical and sub-cortical beta-band.\textsuperscript{32–35} Functionally, the transient bursts appear to play a pivotal role in sensorimotor processing through the basal ganglia-thalamic-cortical network. For instance, the presence of a beta burst in
the sensorimotor cortex close to a tactile stimulation decreased the likelihood of tactile detection\textsuperscript{36}, and the rate of beta bursts is shown to decrease in the time leading up to a movement both in STN\textsuperscript{37–39} and in the sensorimotor cortex.\textsuperscript{40}

In PD, quantification of beta-band burst activity from recordings in the STN has shown that beta-burst rate and duration are reduced by dopaminergic medication\textsuperscript{41,42} and deep brain stimulation.\textsuperscript{35} Furthermore, at the cortical level, PD patients exhibit a decrease in the rate of beta burst compared to healthy controls.\textsuperscript{17} This decrease in beta burst rate scale with increased severity of bradykinesia and postural-kinetic tremor symptoms but does not change as an effect of dopaminergic medication.\textsuperscript{17} Notably, the burst rate showed a higher sensitivity than PSD beta power for discriminating PD patients from healthy controls, demonstrating that the choice of method for beta-band characterisation directly influences the sensitivity of subsequent analyses.

In sum, there is solid evidence of functional changes in the oscillatory sensorimotor neural activity in PD—whether assessed as PSD band power, peak shift or burst rate. The measures differ between PD patients and healthy controls and scale with PD symptom severity. Sensorimotor activity measured non-invasively with MEG/EEG contains rich information about the functional state of the sensorimotor system and how this changes in PD. The central challenge is quantifying the measured neural signals to extract the disease's relevant features from the signals, be it the spectral power, centre frequencies, or burst-like features. This is further complicated by the fact that in addition to disease-related changes, these features likely differ with age, and the available data come from studies with small sizes—typically in the range of 5-30 participants.\textsuperscript{43}

In the current study, we aimed to compare how different oscillatory features of cortical sensorimotor activity change in PD to elucidate what oscillatory features in the neural time-series differ between PD patients and healthy controls and how these features are associated with different motor symptoms in PD. We extracted the sensorimotor neural resting-state activity from source reconstructed resting-state MEG signals in the sensorimotor cortex (Figure 1) and quantified the time-series in terms of the PSD in the canonical mu-band,
consisting of the sensorimotor alpha (8-12 Hz) and beta (13-30 Hz) bands. The two frequency components of the mu band are co-occurring in the sensorimotor areas but appear to be functionally independent.\textsuperscript{44,45} In addition to the band-specific analysis, we compared the 1/f broadband characteristics of the PSD.\textsuperscript{46,47} Finally, we compared features of the sensorimotor rhythm in terms of time-domain analysis of spontaneous transient bursts.\textsuperscript{17,36} We tested this hypothesis by analysing how these features differed between PD patients and healthy controls and how the difference interacted with age and sex. As ageing is associated with structural and functional changes in the sensorimotor cortex\textsuperscript{48,49}, we investigated if the potential changes in sensorimotor activity in PD differ across age. Since both healthy ageing and PD disease progression are linked to thinning of the cortex\textsuperscript{50}, we further included thickness of the sensorimotor cortex in the analysis.

The central hypothesis was that there would be differences in features of the sensorimotor signals, but different features may be related to different functional changes. We hypothesised that individual oscillatory features would reflect different underlying neural function in the sensorimotor system and thereby show different relationships to the clinical manifestations of specific motor symptoms in PD. We tested this hypothesis in two steps: first by examining the inter-relationship between all different measures, and subsequently by examining what feature—or combination of features—best explained the variation in severity within each motor symptoms.

To enable a sensitive assessment of disease-related oscillatory changes in PD, we aimed for a large cohort of PD patients (N=78) and healthy controls (N=60), balanced across gender and age, and with gender- and age-matched groups (Table 1).
Figure 1: Overview of the data processing pipeline from three minutes raw resting-state MEG, through source reconstruction and extracting the activity in the sensorimotor cortex. To compare features, we did a Fourier transformation of the signal to calculate the PSD and quantified sensorimotor bursts in the time series in the sensorimotor ROI.
2 Results

The main analyses tested the effect of group (PD patients/healthy controls; Table 1), age, sex, and cortical thickness in the sensorimotor cortex on the features explained in Table 2. Second, we tested for associations between the clinical rating of motor symptoms in the PD group by a multiple regression analysis including the sensorimotor signal features in Table 2 and age, sex, and cortical thickness to regress out the contribution hereof and estimate the relative effect size of each signal feature. Figure 2 displays the PSD of the sensorimotor signal.

Table 1: Group-level summary of the participants included in the analysis. Mean (standard deviation).

| Measure          | Parkinson's patients | Healthy controls | Statistics                  |
|------------------|----------------------|------------------|-----------------------------|
| N                | 78                   | 60               |                             |
| Sex (female/male)| 29/49                | 27/33            | χ² = 0.57, p = 0.45         |
| Age              | 65.6 (9.5)           | 63.93 (8.4)      | Welsh t(138.0) = 1.08, p = 0.28 |
| Disease duration | 4.4 (3.7) years      | -                | -                           |
| LEDD             | 548 (273) mg         | -                | -                           |
| MDS-UPDRS-III    | 18.9 (10.8)          | -                | -                           |
| MoCA             | 26.1 (2.8)           | 26.2 (2.1)       | Welsh t(136) = 0.10, p = 0.92 |
Table 2: Explanation of the main outcome variables in the analysis

| Variable Category | Variable          | Explanation                                                                 |
|-------------------|-------------------|-----------------------------------------------------------------------------|
| **PSD**           | Beta power        | The maximum peak in the 13-30 Hz band. Estimated as the height of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Beta centre frequency (Hz) | The dominant frequency bin in the 13-30 Hz band. Estimated as the mean of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Alpha power       | The maximum peak in the 8-12 Hz band. Estimated as the height of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Alpha centre frequency (Hz) | The dominant frequency bin in the 8-12 Hz band. Estimated as the mean of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | 1/f intercept     | The intercept of the log-linear regression estimated from the full PSD in the 0.5-40 Hz range. |
|                   | 1/f exponent      | The exponent of the log-linear regression—corresponding to the slope of the log-log transformed PSD—estimated from the full PSD in the 0.5-40 Hz range. |
| **Bursts**        | Rate              | The number of burst events in the sensorimotor time series divided by the length of time series. |
|                   | Duration (ms)     | Duration of the burst events defined as the time the time-series is above threshold until the next time-point it drops below the threshold. |
|                   | Interval (ms)     | Time from the mu/beta time-series drops below threshold until the next time-point it reaches threshold again. |
|                   | Amplitude         | The maximum amplitude of the mu/beta time-series within one burst event. |

2.1 Differences in PSD features between groups

For the first analysis, we wanted to examine if PSD features differed between PD patients and healthy controls and how this might interact with sex, age and cortical thickness. The model parameters and statistical significance of predictors in the regression analysis for all outcome measures are presented in Table 3.
Table 3: regression coefficients and 95% CI for the regression models of the sensorimotor signal features

(Table 2) with Group, Age, Sex, and Cortical Thickness. Values in red indicate coefficients of statistically significant factors in the model comparison (see main text). LL: lower limit, UL: upper limit.
Figure 2: Grand average PSD (mean+se) for the PD group (blue) and healthy control group (red).

2.1.1 Beta power

The PSD beta power showed significant effects of group ($\chi^2(1) = 5.42; p = 0.020$), age ($\chi^2(1) = 4.00; p=0.46$) and the three-way interaction between age, sex, and cortical thickness ($\chi^2(1) = 8.05; p = 0.005$). The relative effect of group corresponded to an increase in beta power of 23.8% [CI: 3.6:48.5] for PD patients. The relative effect of age corresponded to a relative change of -0.2% per year of age (Figure 3). The direction of interaction three-way interaction between age, sex, and cortical thickness indicated that higher cortical thickness was associated with a steeper decrease in beta power, with a larger decrease in beta power in older ages for males compared to females.

2.1.2 Beta centre frequency

There were no significant effects of any predictor on beta centre frequency.

2.1.3 Alpha power

There were no significant effects of any predictor on PSD alpha power.
2.1.4  Alpha centre frequency

The analysis of alpha centre frequency showed a significant interaction between group and age ($\chi^2(1) = 5.82; p = 0.016$) and a significant interaction between group and cortical thickness ($\chi^2(1) = 3.95; p = 0.047$). The age-related differences in alpha centre frequency increased by 0.05 Hz [CI: -0.03:0.12] per year of age for healthy controls. The difference was -0.02 Hz [CI: -0.11:0.08] per year of age for PD patients. Higher cortical thickness was associated with a 0.30 Hz [CI: -0.45:1.08] difference in alpha centre frequency per standardised unit increase in cortical thickness for healthy controls and a difference of -0.16 Hz [CI: -0.80:0.60] per standardised unit increase in cortical thickness for PD patients.

2.1.5  Broadband 1/f intercept

The 1/f intercept of the PSD spectrum showed a significant effect of group ($\chi^2(1) = 12.19; p = 0.0005$) and interaction between Group and Sex ($\chi^2(1) = 4.41; p = 0.036$). The 1/f intercept were 23.5% [CI: 10.5:35.3] higher for female PD patients compared to female healthy controls and 9.5% [CI: -2.0:26.1] higher for male PD patients compared to male healthy controls. Male PD patients had -12.1% [CI: -30.4:3.8] lower 1/f intercepts compared to female PD patients. Male healthy controls showed a slight increase in PSD intercept of 5.3% [CI: -8.1:16.4] compared to female healthy controls.

2.1.6  Broadband 1/f exponent

The analysis of the 1/f exponent or the PSD showed a significant effect of group ($\chi^2(1) = 8.48; p = 0.003$) and a significant effect of cortical thickness ($\chi^2(1) = 6.02; p = 0.014$). PD patients had relative steeper decay with 11.9% [CI: 1.0:26.1] higher 1/f exponent than healthy controls. Higher cortical thickness was associated with a -3.6% [CI: -12.8:5.5] difference in 1/f exponent per standardised unit increase in cortical thickness (Figure 3).
2.2 Differences in burst features between groups

2.2.1 Burst rate

The analysis of burst per minute showed main effects of age ($\chi^2(1) = 5.10; p = 0.024$) and sex ($\chi^2(1) = 7.86; p = 0.038$) as well as interactions between group and age ($\chi^2(1) = 11.74; p = 0.001$), age and sex ($\chi^2(1) = 5.39; p = 0.020$), age and cortical thickness ($\chi^2(1) = 6.55; p = 0.010$), and sex and cortical thickness ($\chi^2(1) = 4.35; p = 0.037$).

The age-related effect corresponded to a lower burst rate of -0.7% [CI: -1.5:0.3] per year for female PD patients and -0.9% [CI: -1.4:-0.4] lower rate per year for male PD patients, whereas female controls had a relative increase in burst rate of 0.9% [CI: 0.1:1.6] per year and male controls had a stable trend of -0.2% [CI: -0.9:0.6] per year. The interaction between sex and cortical thickness showed a relative difference of -8.0% [CI: -14.4:-1.7] per standardised unit increase in cortical thickness for females but did not vary across age for men with an estimated relative difference of -0.8% [CI: -8.1:6.7] per standardised unit increase in cortical thickness (Figure 3). The direction of the interaction between age and cortical thickness meant that thicker cortex was associated with an additional relative difference in burst rate per year of age of -7.1% [CI: -13.5:-0.7] per standardised unit increase in cortical thickness.

2.2.2 Burst duration

The mixed-model analysis of burst duration revealed a group-level main effect of age ($\chi^2(1) = 7.83; p = 0.005$) and sex ($\chi^2(1) = 4.32; p = 0.038$) and an effect of the interaction between age and cortical thickness $\chi^2(1) = 4.10; p = 0.043$). The relative effect of sex showed that men had an overall 9.8% [CI: -18.3:-1.1] shorter burst duration than females. The age-related difference in burst duration corresponded to a difference of 0.14% [-0.9:0.7] per year of age. The age-related difference was further modified by -2.1% [CI: -13.5:-0.7] per standardised unit increase in cortical thickness.
2.2.3 Burst interval

The mixed-model analysis of the burst interval only showed significant main effect of age ($\chi^2(1) = 6.52; p = 0.011$) and interaction between age and sex ($\chi^2(1) = 4.41; p = 0.036$). The model predicted a relative difference in interval per year of age of -0.6% [CI: -2.1:0.9] for females and difference of 1.0% [CI: -0.6:2.5] per year of age for males.

2.2.4 Burst amplitude

The mixed-model analysis of burst amplitudes showed a significant main effect of group ($\chi^2(1) = 10.94; p = 0.0009$) and interaction between group and sex ($\chi^2(1) = 6.35; p = 0.012$). Female PD patients had on average 41.0% [CI: 18.0:68.3] higher burst amplitude than female controls, while male PD patients had 15.6% [CI: 2.2:35.7] higher burst amplitude than male controls. Male PD patients had a relative lower burst amplitude than female PD patients of -18.0% [CI: -29.8:-3.3] compared to a negligible relative amplitude difference of 5.3% [CI: -10.1:22.8] between male and females healthy controls.
2.3 Clinical symptoms and sensorimotor oscillatory features

The analysis of axial symptoms (midline function rating in MDS-UPDRS-III) showed a positive significant effect of median burst duration ($\chi^2(1) = 5.00; p = 0.025$) and a marginally significant effect PSD beta power ($\chi^2(1) = 3.86; p = 0.049$) showing that longer burst duration and higher beta power was associated with an increase in midline function symptoms. In addition, there were significant effects of covariates age ($\chi^2(1) = 7.12; p = 0.005$) and sex ($\chi^2(1) = 8.25; p = 0.004$) on midline function.

Upper limbs bradykinesia showed significant effects of burst rate ($\chi^2(1) = 9.29; p = 0.002$) and alpha centre frequency ($\chi^2(1) = 6.14; p = 0.013$) as well as a significant effect of the covariate cortical thickness ($\chi^2(1) = 6.09; p = 0.014$). The negative effect of burst rate means that reduced burst rate was associated with increased symptom rating.

There were no significant effects of the main predictors on symptom rating for rest tremor, rigidity, postural/kinetic tremor, nor lower limb bradykinesia, though there was a significant effect of sex on rest...
tremor ($\chi^2(1) = 7.81; p = 0.005$). The standardised regression coefficients of each predictor variable on the motor symptoms measured with MDS-UPDRS-III are presented in Table 4.
Table 4: Standardised regression coefficients (95% CI) for the six regression models on motor symptoms measured with the MDS-UPDRS-III. Values in bold indicate significant factors in the model comparison.

| Variable category | Variable | Midline function | Rest tremor | Rigidity | Bradykinesia upper extremity | Postural and kinetic tremors | Bradykinesia lower limb |
|-------------------|----------|------------------|-------------|----------|-----------------------------|-----------------------------|-------------------------|
| Intercept         |          | -0.42            | -0.52       | -0.33    | 0.02                        | -0.26                       | 0.12                    |
|                   |          | LL: -0.80        | LL: -0.93   | LL: -0.80| LL: -0.40                   | LL: -0.71                   | LL: -0.71               |
|                   |          | UL: -0.04        | UL: -0.13   | UL: 0.13 | UL: 0.40                    | UL: 0.16                    | UL: 0.19                |
| Beta power        |          | 0.33             | 0.24        | 0.33     | -0.18                       | 0.00                        | -0.22                   |
|                   |          | LL: -0.06        | LL: -0.16   | LL: -0.12| LL: -0.57                   | LL: -0.41                   | LL: -0.43               |
|                   |          | UL: 0.70         | UL: 0.64    | UL: 0.78 | UL: 0.17                    | UL: 0.42                    | UL: 0.44                |
| Beta centre frequency |      | 0.02             | -0.20       | 0.03     | -0.11                       | -0.13                       | 0.01                    |
|                   |          | LL: -0.27        | LL: -0.50   | LL: -0.32| LL: -0.38                   | LL: -0.46                   | LL: -0.45               |
|                   |          | UL: 0.30         | UL: 0.10    | UL: 0.36 | UL: 0.20                    | UL: 0.20                    | UL: 0.19                |
| Alpha power       |          | -0.11            | -0.22       | -0.12    | 0.24                        | 0.11                        | 0.02                    |
|                   |          | LL: -0.50        | LL: -0.61   | LL: -0.58| LL: -0.14                   | LL: -0.34                   | LL: -0.34               |
|                   |          | UL: 0.28         | UL: 0.21    | UL: 0.35 | UL: 0.66                    | UL: 0.57                    | UL: 0.54                |
| PSD               |          | 0.01             | 0.13        | 0.12     | **0.29**                    | 0.08                        | 0.22                    |
| Alpha centre frequency |    | -0.24            | -0.16       | -0.16    | 0.01                        | -0.21                       | LL: -0.22               |
|                   |          | LL: -0.66        | LL: -0.86   | LL: -1.63| LL: -0.84                   | LL: -0.89                   |                         |
|                   |          | UL: 0.89         | UL: 1.54    | UL: 1.70 | UL: 0.42                    | UL: 1.51                    | UL: 1.50                |
| 1/f intercept     |          | -0.13            | 0.47        | 0.45     | -0.59                       | 0.35                        | -0.98                   |
|                   |          | LL: -1.11        | LL: -0.66   | LL: -0.86| LL: -1.63                   | LL: -0.84                   | LL: -0.89               |
|                   |          | UL: 0.89         | UL: 1.54    | UL: 1.70 | UL: 0.42                    | UL: 1.51                    | UL: 1.50                |
| 1/f exponent      |          | -0.05            | -0.26       | -0.16    | 0.17                        | -0.02                       | 0.46                    |
|                   |          | LL: -0.67        | LL: -0.87   | LL: -0.86| LL: -0.47                   | LL: -0.74                   | LL: -0.73               |
|                   |          | UL: 0.56         | UL: 0.39    | UL: 0.63 | UL: 0.81                    | UL: 0.70                    | UL: 0.68                |
| Rate              |          | 0.13             | 0.05        | 0.06     | **-0.60**                   | -0.08                       | 0.15                    |
|                   |          | LL: -0.28        | LL: -0.40   | LL: -0.48| LL: -1.01                   | LL: -0.59                   | LL: -0.57               |
|                   |          | UL: 0.56         | UL: 0.53    | UL: 0.61 | UL: -0.17                   | UL: 0.43                    | UL: 0.40                |
| Length            |          | **0.31**         | -0.15       | 0.07     | 0.09                        | -0.07                       | 0.27                    |
|                   |          | LL: 0.00         | LL: -0.46   | LL: -0.32| LL: -0.22                   | LL: -0.42                   | LL: -0.42               |
|                   |          | UL: 0.60         | UL: 0.16    | UL: 0.45 | UL: 0.42                    | UL: 0.29                    | UL: 0.29                |
| Burst             |          | 0.29             | 0.12        | 0.18     | -0.21                       | -0.01                       | 0.35                    |
| Interval          |          | LL: -0.07        | LL: -0.31   | LL: -0.31| LL: -0.58                   | LL: -0.44                   | LL: -0.46               |
|                   |          | UL: 0.66         | UL: 0.55    | UL: 0.64 | UL: 0.20                    | UL: 0.43                    | UL: 0.44                |
| Amplitude         |          | 0.04             | -0.19       | -0.30    | 0.67                        | -0.15                       | 0.64                    |
|                   |          | LL: -0.83        | LL: -1.12   | LL: -1.34| LL: -0.20                   | LL: -1.10                   | LL: -1.19               |
|                   |          | UL: 0.88         | UL: 0.72    | UL: 0.78 | UL: 1.59                    | UL: 0.88                    | UL: 0.84                |
| Age               |          | **0.03**         | 0.00        | 0.00     | 0.01                        | 0.01                        | 0.01                    |
|                   |          | LL: 0.01         | LL: -0.03   | LL: -0.03| LL: -0.02                   | LL: -0.02                   | LL: -0.02               |
|                   |          | UL: 0.06         | UL: 0.03    | UL: 0.03 | UL: 0.04                    | UL: 0.04                    | UL: 0.04                |
| Sex               |          | **0.70**         | **0.74**    | 0.55     | -0.14                       | 0.33                        | -0.25                   |
|                   |          | LL: 0.17         | LL: 0.17    | LL: -0.04| LL: -0.70                   | LL: -0.31                   | LL: -0.31               |
|                   |          | UL: 1.18         | UL: 1.32    | UL: 1.22 | UL: 0.45                    | UL: 0.97                    | UL: 0.94                |
| Cortical thickness |        | -0.17            | -0.05       | -0.05    | **-0.27**                   | -0.18                       | -0.10                   |
|                   |          | LL: -0.41        | LL: -0.29   | LL: -0.34| LL: -0.51                   | LL: -0.48                   | LL: -0.46               |
|                   |          | UL: 0.07         | UL: 0.22    | UL: 0.25 | UL: -0.03                   | UL: 0.11                    | UL: 0.11                |
| Multiple R-squared|         | **0.441**        | 0.277       | 0.156    | 0.375                       | 0.193                       | 0.173                   |

Multiple R-squared: 0.441, 0.277, 0.156, 0.375, 0.193, 0.173
2.4 Correlation between variables

Table 5 presents the significant correlations between the PSD summaries, burst features, age, cortical thickness and clinical rating scales. There was generally high correlations between the PSD features and burst features. The PSD beta power correlated with the burst rate ($r=0.26$, $p=0.002$), burst duration ($r=0.20$, $p=0.022$), burst amplitude ($r=0.52$, $p<0.001$), and correlated negatively with the burst interval ($r=-0.24$, $p=0.005$). The PSD alpha power also correlated with the burst rate ($r=0.26$, $p<0.001$), burst amplitude ($r=0.32$, $p<0.001$) and showed a negative correlation with the bursts interval ($r=-0.23$, $p=0.011$). The PSD centre frequencies in neither the beta-band nor alpha-band showed any significant correlation with burst features.

The 1/f broadband characteristic of the PSD showed high degree of correlation with the measures of the oscillatory peaks in the PSD for both the 1/f intercept (beta power: $r=0.52$, $p<0.001$; beta centre frequency: $r=-0.18$, $p=0.035$; alpha power: $r=0.41$, $p<0.001$; alpha centre frequency: $r=-0.19$, $p=0.035$) and 1/f exponent (beta power: $r=0.57$, $p<0.001$; beta centre frequency: $r=-0.30$, $p<0.001$; alpha power: $r=0.40$, $p<0.001$; alpha centre frequency: $r=-0.43$, $p<0.001$). The 1/f intercept further showed a high degree of correlation with all four burst features (burst rate: $r=0.55$, $p<0.001$; burst duration: $r=0.31$, $p<0.001$; bursts interval: $r=-0.48$, $p<0.001$; burst amplitude: $r=0.91$, $p<0.001$), though the 1/f exponent only correlated with the burst amplitude ($r=0.30$, $p<0.001$).
Table 5: Statistically significant correlation coefficients between all main variables. Green colours indicate a positive correlation between variables, and red colours indicate a negative correlation between variables—the intensity of the colour scales with the correlation coefficient.

| Variable category | Beta power | Beta centre frequency | Alpha power | Alpha centre frequency | 1/f intercept | 1/f exponent | Rate | Duration | Interval | Amplitude | Age | Cortical thickness | MoCA | Midline function | Rest tremor | Rigidity | Bradykinesia upper extremity | Postural and kinetic tremors | Bradykinesia lower limb | UPDRS |
|-------------------|------------|-----------------------|------------|------------------------|---------------|--------------|------|----------|----------|-----------|----|-------------------|------|------------------|-----------|----------|---------------------|-------------------------|----------------|-------|
| Beta power        | -0.35      | 0.63                  | -0.32      | 0.52                   | 0.57          | 0.26         | 0.2  | 0.24     | 0.52     | 0.18      | -0.21| 0.28              | 0.24 |
| Beta centre freq. | -0.35      | -0.34                 | 0.22       | -0.18                  | -0.3          | -0.17        |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Alpha power       | 0.63       | -0.34                 | -0.36      | 0.41                   | 0.32          | -0.23        | 0.45 | -0.2     |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Alpha centre freq.|-0.32       | 0.22                  | -0.38      | -0.19                  | -0.43         | 0.18          |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| 1/f intercept     | 0.52       | -0.18                 | 0.41       | -0.29                  | 0.56          | 0.31         | -0.44| 0.91     | 0.18     | -0.25     | -0.15|                   |     |                   |           |          |                      |                         |                |       |
| 1/f exponent      | 0.57       | -0.3                  | 0.4        | -0.43                  | 0.56          | 0.3          |      | 0.21     |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Rate              | 0.26       | 0.32                  | 0.55       | 0.55                   | 0.55          | -0.39        | 0.56 |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Duration          | 0.2        | 0.31                  | 0.55       | -0.61                  | -0.29         | 0.2          |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Interval          | -0.24      | -0.23                 | -0.48      | -0.61                  | -0.44         | 0.2          |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Amplitude         | 0.52       | 0.45                  | 0.91       | 0.3                    | 0.55          | 0.29        | -0.44|          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Age               | 0.18       | -0.17                 | 0.18       | 0.2                    | -0.19         | -0.22        | 0.37 | 0.26     |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Cortical thickness| 0.18       | 0.25                  | -0.25      | -0.38                  | -0.38         | -0.38        | 0.38 | 0.38     |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| MoCA              | -0.21      | -0.2                  | -0.21      | -0.19                  | -0.21         | -0.22        | -0.19| -0.37    | -0.26    | -0.23    |     |                   |     |                   |           |          |                      |                         |                |       |
| Midline function  | 0.28       |                      |            |                        | 0.37          | -0.38        | -0.37| 0.38     | 0.38     | 0.38     | 0.4  | 0.28              | 0.32 |
| Rest tremor       | 0.38       |                      |            |                        | 0.38          | 0.37         | -0.28| 0.28     | 0.28     | 0.28     | 0.32 | 0.32              | 0.49 |
| Rigidity          | 0.38       | 0.37                  | 0.28       | 0.28                   | 0.53          | 0.23         |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Bradykinesia upper extremity | 0.23       | 0.26                  | 0.26       | 0.26                   | 0.4           | 0.4          | 0.28 | 0.49     |          |           |     |                   |     |                   |           |          |                      |                         |                |       |
| Postural and kinetic tremors | 0.24       | 0.26                  | 0.28       | 0.53                   | 0.32          | 0.32         | 0.28 | 0.32     | 0.25     | 0.49     |     |                   |     |                   |           |          |                      |                         |                |       |
| Bradykinesia lower limb | 0.32       | 0.25                  | 0.23       | 0.49                   |              |             |      |          |          |           |     |                   |     |                   |           |          |                      |                         |                |       |

3 Discussion
In this study, we aimed to explore how different features of somatosensory oscillatory neuronal activity differed between PD patients and healthy controls across age and gender, and how these features relate to motor symptoms in PD. In agreement with our primary hypothesis, the PD patients differed from healthy controls on several oscillatory features as expected, showing higher beta-band power, higher burst amplitude, a steeper broadband 1/f slope and exponent compared to healthy controls. Furthermore, the analysis of bursts showed that the burst rate was reduced in PD patients compared to healthy controls, confirming previous results on bursts and PD from our group—here on a cohort with three times as many participants. Notably, our current results show that the reduced burst rate in PD is not a static group-level difference but interacts with age, gender and cortical thickness and results in a steeper reduction in burst rate in PD with age compared to healthy controls.

Following our secondary hypothesis, we expected that different oscillatory features would reflect distinct underlying functional neural properties and manifest as different motor symptoms in PD. Examining the inter-relationship between the features, we observed significant correlations between most oscillatory features, indicating that we had some redundancy among our measures. For instance, the 1/f intercept showed a significant positive correlation with the 1/f slope and beta-band PSD and a high correlation with burst amplitude. We did, however, also see evidence of independent features. Using regression models to examine which oscillatory features were associated with different symptoms, our results showed that the oscillatory features had distinctive relationships with specific symptom scales: bradykinesia severity was related to the burst rate, and alpha centre frequency (and also to cortical thickness) but midline symptoms were related to burst duration and beta power.

While we did see correlations between the band-specific oscillatory power in the PSD and the burst rate and burst amplitude—as expected since increased rate and amplitude would necessarily lead to higher PSD—it was, unexpectedly, the intercept of the broadband 1/f regression that showed the highest correlation with the
burst features. This study adds to the growing evidence that a narrow-band focus—e.g. the beta-band in isolation—could potentially miss essential aspects of the neural signals. Quantifying only the peaks in the PSD misrepresents the actual oscillatory response at those frequencies as the peaks are influenced by the broadband offset and 1/f decay exponent, so any unaccounted-for systematic differences in either PSD offset or decay exponent can lead to a false conclusion that there is a difference in the oscillatory response.46,47

These results show that the different features capture different neural processes, reflecting that a neural time series obtained by electrophysiological recordings differs along various dimensions. In the time domain, increased oscillatory power can reflect both increased burst duration and change in burst amplitude and an expression of "true" sustained oscillations in the signal.34,51 The presence of more sustained oscillation in the sensorimotor rhythm, particularly the beta band, might reflect a higher level of inhibition of sensorimotor information as is seen in recordings from STN5 and, to some extent, at the cortical level.36,52 However, sustained oscillations are not in contrast to the bursting properties of the sensorimotor rhythm. The neural time-series can express both a degree of sustained oscillations while also exhibiting variation in the degree of transient bursts—e.g. a signal of steady oscillation with transient high-amplitude bursts.

The observed disease-related changes in spontaneous cortical bursts in the form of increased burst power and a more rapid decrease in rate over age for PD patients could reflect inhibited projections along the thalamic-cortical pathways caused by disturbances in the dopamine-dependent structures projecting to the cortex. The bursting properties of the cortical sensorimotor neural activity are proposed to occur due to long-range input through the ascending thalamic-cortical connection to the cortex, leading to an increase in the local neural excitation and resulting in a burst of synchronous activity.34 Interestingly, we did not find significant group differences in burst duration in the current study, supporting the view that the central mechanisms of the cortical bursts are not primarily affected in PD. The sub-cortical beta-band activity is directly influenced by the activity of dopamine-responding neurons, as there is a high density of dopamine-dependent neurons in these
subcortical brain structures in contrast to the cortex, where the density of dopamine-receptive neurons is low.

Any effect of dopamine and dopaminergic medication on the cortical beta-band is likely an indirect effect mediated by neural connectivity in the direct and indirect neural pathways between basal ganglia, thalamus, and cortex. The differences in the cortical sensorimotor burst rate in PD might be an indirect effect of the loss of dopamine and changes in the beta band in the sub-cortical structures projecting to the sensorimotor cortex. The notion that the cortical sensorimotor activity is indirectly related to dopamine depletion in PD is further supported by findings from animals studies showing that hydroxydopamine injections lead to exaggerated beta-band oscillations only after several days had passed, suggesting that oscillatory changes occurred as an effect after dopamine depletion rather than a direct consequence of the depletion itself.\(^7\) The indirect influence of dopamine on the cortical beta-band might also explain the often weak or even absent effect of dopaminergic medication on cortical beta-band activity.\(^{11,16,17,53}\) However, the current study cannot directly address the role of dopamine on cortical oscillations since all patients in the study were tested on their regular dose of medication.

We explored how age-related differences in cortical sensorimotor neural activity might interact with disease-related changes in PD within the current study. Age-related effects on spontaneous sensorimotor activity are commonly dealt with by matching the age distributions of the patient group and the healthy control group—usually within a narrow age span. The analysis showed, as expected, age-related differences in the sensorimotor activity—most notably in the beta PSD and for the burst duration, burst interval, and burst rate. The age-related differences in burst rate differed between PD patients and healthy controls, with PD patients showing a more considerable reduction of burst as a function of age than healthy controls. The steeper reduction in burst rate with age in PD seems in accordance with the fact that higher age at PD onset is associated with a faster disease progression and more rapid decline in motor function\(^{54}\), though a longitudinal design is needed to confirm the relation between disease progression, reduction in burst rate, and age.
We did not see a significant "slowing" of the beta PSD centre frequency between groups, as reported in several previous studies. An explanation might be that such slowing is more pronounced in PD patients with dementia and correlates with cognitive ability. The PD patients in the current study were cognitively well-functioning and did not differ in their cognitive ability from the healthy controls. Another explanation is that we focused on the activity in the sensorimotor cortex, whereas the slowing of alpha and beta PSD is usually found in frontal areas and globally throughout the brain.

We included measures of cortical thickness within the same region of interest (ROI) from which we extracted the function time-series, as we hypothesised that age-related effects upon the functional measures might be mediated through the age-related structural changes in the cortex. However, despite the negative correlation between age and cortical thickness (as expected), we did not find pervasive evidence that cortical thickness affected the functional measures. Cortical thickness did show an effect on the burst rate through interaction on the age-related effect. The only measure that showed a group-specific difference in cortical thickness was the alpha centre frequency, where a higher cortical thickness was associated with a lower alpha PSD peak.

We also included sex to explore if disease-related changes in sensorimotor oscillatory activity differed between males and females, as there are well-documented sex differences in the manifestation of PD. Male sex is a risk factor for developing PD, with average incidence ratios of approximately 2:1 male-female ratio across all stages of the disease. The disease debuts on average two years earlier in males than females and differs in the initial manifestation of symptoms, with women more likely to develop tremor specific symptoms and men more likely to develop rigidity. We are not aware of any previous studies that explicitly included sex as a factor in analysing neural oscillations in PD.

We found significant differences between males and females in the bursting properties in the sensorimotor signal. The burst amplitude was more prominent for female PD patients than for male PD patients, and the age-related differences in both burst rate and burst intervals differed between males and females. These
finding clearly illustrate the need for further studies into the sex-specific changes in neural function and how they manifest and relate to PD.

A possible factor behind the sex differences in PD is the contribution of sex hormones on the nigrostriatal pathway and linked to the deterioration of the dopaminergic system, where testosterone levels appear to enhance dopamine loss while estrogen has been identified as a neuroprotective agent for PD. Estrogen has been demonstrated by how it generally influences incidence levels and how menopause-related variations in estrogen levels are linked to variations in symptom severity. If this influences oscillations in the sensorimotor cortex is unclear at the current stage.

The present study quantified the neural time series from the sensorimotor cortex based on pre-defined summary measures of the PSD and burst properties. Our study is a broader approach with more sensorimotor rhythm features than other studies more focused on specific signal features, and we also included more PD patients and healthy controls than similar functional studies. However, focusing the analysis on different features within a narrow ROI potentially ignores other types of measurements that might be relevant to understanding the development of PD and motor symptoms; for example, the long-range connectivity between the sensorimotor cortex and other cortical areas and the connections between the sensorimotor cortex and the basal ganglia and thalamus (though the subcortical structures are practically invisible in MEG). Treating the activity in the sensorimotor cortex as single time series also means that we remove the sensitivity to spatial features of the signals, e.g. focal versus spatially blurred activity in one group or the other. If the oscillatory activity extends over a larger cortical surface area, then that signal will also manifest as power differences in the measured signal. There are potentially many more features to be uncovered, and future studies may explore how the PSD- and burst features further interact with other aspects of brain activity in the global function of the brain to fully understand the interaction between functional and structural changes in PD.
We investigated a relatively large cohort of PD patients and healthy controls (for a neuroimaging study) to make meaningful inferences about how age and sex interact with the group level difference between PD patients and healthy controls, but a limitation is that our study is cross-sectional. We aim to follow this cohort longitudinally to estimate the development trajectories of the sensorimotor oscillatory activity in PD compared to healthy ageing.

There are myriad ways to quantify brain dynamics, and finding features of neural signals that can explain disease mechanism or symptoms, even if extracted along with a reduced number of dimensions, will be helpful if they provide adequate information about the disease- or symptom-state. Further characterisation of the association between features in the non-invasive brain signals and motor symptoms can potentially be a valuable tool to aid in the diagnosis and evaluation of treatments. Understanding how features in the neural time series are related to motor symptoms in PD will also help develop non-invasive neural stimulation that can potentially relieve motor symptoms. 35,59
4 Methods

4.1 Participants

80 PD patients (age 44-85; 32 female) and 71 healthy controls (age 46–78; 46 female) participated in the study. The study was approved by the regional ethics committee (Etikprövningsnämnden Stockholm, DNR 2019-00542) and followed the Declaration of Helsinki. All participants gave written informed consent before participation.

The PD patients were recruited from the Parkinson's Outpatient Clinic, Department of Neurology, Karolinska University Hospital, Stockholm, Sweden. The healthy controls were recruited by advertising or amongst spouses of PD patients. 22 participants (18 patients, 4 healthy controls) were included from a previous study17 who were qualified based on the recruitment criteria of the present study and had done the same MEG and MRI procedures as in the present study. All data were reanalysed following the procedure described below.

The inclusion criteria for the PD group were a diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria with Hoehn and Yahr stage 1-3.60 Inclusion criteria for the control group were not having a diagnosis of PD, no form of movement disorder, and no history of neurological disorders, epilepsy, or psychiatric disorders.

Exclusion criteria for both groups were a diagnosis of major depression, dementia, history or presence of schizophrenia, bipolar disorder, epilepsy, or history of alcoholism or drug addiction according to the Diagnostic and Statistical Manual of Mental Disorders.61

One participant declined to do the MRI scanning, one participant had a scanner malfunction during MRI acquisition, and eleven participants had their MRI scans cancelled and were not included in the analysis. Two PD patients and 11 healthy controls were excluded. Table 1 is a summary of the participants included in the analysis.
The PD patients participated in the study while they were on their regular prescribed dose of medication. The Levodopa equivalent daily dose (LEDD) was calculated according to Tomlinson et al.\textsuperscript{62} Motor symptoms in the PD group were assessed using the Movement-Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III).\textsuperscript{59} Global cognition was assessed with the Montreal Cognitive Assessment battery (MoCA).\textsuperscript{64}

### 4.2 MEG recordings

MEG data were recorded with a Neuromag TRIUX 306-channel MEG system, with 102 magnetometers and 102 pairs of planar gradiometers. Data were sampled at 1000 Hz with an online 0.1 Hz high-pass filter and 330 Hz low-pass filter. The MEG scanner was located inside a two-layer magnetically shielded room (Vacuumschmelze GmbH) with internal active shielding active to suppress electromagnetic artefacts. The subjects' head position and head movements inside the MEG scanner were measured during recordings with head-position indicator coils (HPI) attached to subjects' heads. The HPI location and additional points sampled uniformly across the subjects' head shape were digitized with a Polhemus Fastrak motion tracker before the measurements. Horizontal and vertical electrooculogram (EOG) and electrocardiogram (ECG) were recorded simultaneously with the MEG.

We recorded three minutes of resting-state MEG while the participants sat with their eyes closed. The participants were instructed to close their eyes and relax for three minutes. The recordings began after assuring the participant sat still with their eyes closed.

### 4.3 MRI acquisition

3D T1-weighted magnetisation-prepared rapid gradient-echo (MPRAGE) sequence structural images (voxel size: $1 \times 0.94 \times 0.94$ mm) were obtained on a GE Discovery 3.0 T MR scanner for morphological analysis and creating source spaces for MEG source reconstruction. Multi-echo "FLASH"\textsuperscript{65} images were obtained to create volumetric headmodels for MEG source reconstruction (see below).
4.4 MRI processing

The MRI images were processed with Freesurfer\(^66\) (v. 5.3) to get surface reconstructions of the cortical mantle. The surfaces were obtained with the automatic routine for extracting cortical surfaces in Freesurfer from the individual T1-weighted MRI.

We defined the cortical sensorimotor area by segmenting the cortical surface using the anatomical labels provided by Freesurfer automatic labelling.\(^67\) The analysis focused on a region of interest (ROI) consisting of the left pre- and post-central gyri and central sulcus. The pre/postcentral gyri were combined because a biomagnetic source on either sulci wall will leave a trance on the other side due to the close distance and the field spread of MEG signals. The ROI was defined for each subject based on the individual cortical reconstructions. The average cortical thickness in the ROI was estimated with Freesurfer.\(^68\)

4.5 MEG pre-processing

The MEG was processed by applying temporal signal space separation (tSSS) to suppress artefacts from outside the scanner helmet and correct head movement during the recording.\(^69\) The tSSS had a buffer length of 10 s and a cut-off correlation coefficient of 0.95. Movement correction was done by shifting the head position to a position based on the median of the continuous head position during the three-minute recording.

The MEG data processing and source reconstruction was done with MNE-Python\(^70\) in Python 3.8. First, we marked data segments containing muscle artefacts and SQUID jumps (marked by the automatic artefact detection in MNE-Python). The data was filtered with a 48 Hz low-pass filter and 50 Hz notch filter to remove line noise. The continuous data were cut into 1.0 s epochs. Epochs marked with muscle artefacts or extreme values (above 5000 fT for magnetometers and 4000 fT/cm for gradiometers) were rejected. Between 0-65 % (median: 6.0 %) of data was rejected resulting in 63.0-180 s (median: 174.0 s) useful MEG data per participant. The remaining data length was not significantly different between groups (Wilcoxon rank sum test, \(p = 0.98\)).
We then used independent component analysis (ICA) using the fastica algorithm. Components representing artefacts from blinks and heartbeats were identified based on their correlation with the EOG and ECG, respectively and removed from the raw data. Between 0-5 (median 3) components were removed per participant. The number of removed ICA components was not significantly different between groups (Wilcoxon rank sum test, p = 0.71).

We then applied source reconstruction using noise weighted minimum-norm estimates. The noise covariance matrix was estimated from two minutes of empty room data recorded before each session. The source space consisted of 5124 evenly spaced points sampled across the white matter surfaces per participant. The inner skull boundary was estimated from the multi-echo MRI to create a single shell volume conductor model. The time series from the sensorimotor ROI was then extracted from the estimated source time series by singular value decomposition of all source points within the ROI.

4.6 Power spectral analysis

We analysed the spectral properties of the sensorimotor activity by calculating the PSD from 0.5 to 40 Hz across the entire ROI time series using Welch's method by segmenting the continuous data into 3.072 s epochs with 50% overlap and averaging the PSD across the segments.

Since the narrow-band beta power in the PSD is dependent on the broader features of the broadband spectrum, we further analysed the 1/f broadband characterises of the sensorimotor activity as this could play a role in the functional properties of the beta-band and has been shown to differ between healthy control and PD patients. We used the fitting oscillations & one over f (FOOOF) toolbox to analyse the 1/f broadband characteristic of the PSD (intercept and exponent) and the oscillatory peaks in the canonically defined beta band (13-30 Hz) and alpha band (8-12 Hz). A log-linear regression is fitted to the PSD and subtracted before fitting Gaussian functions to the peaks in the PSD. The midpoint of the Gaussians corresponds to the centre
frequency (i.e. peak frequency) and the height represents the signal power. A new log-linear function is fitted to the PSD after subtracting the Gaussian function to estimate the $1/f$ characteristic.

All participants showed a discernable beta peak in the PSD. Nine PD patients and nine healthy controls did not show a peak in the PSD alpha band (no difference between groups, $\chi^2(1) = 0.12; p = 0.73$).

4.7 Burst analysis

To calculate the burst properties of the sensorimotor activity in the time domain, we band-pass filtered the time-series with an 8-30 Hz band-pass filter using FieldTrip$^{73}$ in MATLAB (R2016b; MathWorks Inc.) and calculated the Hilbert envelope of the signal (Fig. 1). The burst threshold was defined as three times the median of the signal. The burst onset was defined as the time-point where the signal first reached half the max amplitude of the burst and ending at the time-point where the signal again dropped below half the max amplitude of the burst. The burst amplitude was defined as the maximum value of the burst. The burst duration was defined as the time from burst onset to burst end. The burst interval was defined as the time from the end of a burst to the time-point where the next burst began.

4.8 Statistics

4.8.1 Analysis of sensorimotor rhythm features

The main analyses tested the effect of group (PD patients/healthy controls), age, sex, and ROI cortical thickness on the features listed in Table 2 to describe how these factors might influence the features. For the PSD features, we modelled the outcomes as a linear function of group (PD patients/healthy controls), age, sex, and cortical thickness with linear regression in R (v. 4.0.2)$^{74}$ The regression models were fit to the data for each participant with all factors and up to their three-way interactions between the four predictors. One regression model was estimated per PSD feature. The burst rate (burst per minute) was modelled with Poisson regression using the same predictor variables.
4.8.2 Relation between clinical scores and sensorimotor oscillatory features

The MDS-UPDRS-III scores were divided into subscales based on symptoms: midline function, rest tremor, rigidity, upper-body bradykinesia, postural and kinetic tremor, and lower limb bradykinesia; according to Goetz et al., with the exception that left- and right-side upper-body bradykinesia were combined into a single factor. Each symptom score was analysed by multiple regression and modelled as a function of the burst rate, median burst duration, median bursts interval, median burst amplitude, PSD 1/f intercept, PSD 1/f exponent, PSD beta power, PSD beta centre frequency, PSD alpha power, and PSD alpha centre frequency for each PD patient. The models further included the age, sex, and cortical thickness to regress out the contribution hereof and estimate the relative effect size of each signal feature. All symptom ratings and continuous predictor variables, except age, were z-transformed to get the standardised effect size from the regression models. Significance testing was done by removing one predictor from the model and comparing the variance explained between the full model and the model with a predictor removed by log-likelihood ratio tests.

4.8.3 Correlation between variables

Since the features analysed in the main analysis are all extracted from the same signal, we wanted to explore the mutual relation between variables. We computed the Pearson correlation between the signal features in Table 2, age, cortical thickness, MoCA, and MDS-UPDRS-III subscales for all pairwise complete cases.

4.9 Data Availability

Parts of the data used in this analysis will be made available at a public data repository. Scripts for running the analysis presented in the paper are available at www.github.com/mcvinding/PD_beta_bursts2.
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Figure and table legends

Figure 1
Overview of the data processing pipeline from three minutes raw resting-state MEG, through source reconstruction and extracting the activity in the sensorimotor cortex. To compare features, we did a Fourier transformation of the signal to calculate the PSD and quantified sensorimotor bursts in the time series in the sensorimotor ROI.

Figure 2
Grand average PSD (mean+se) for the PD group (blue) and healthy control group (red).

Figure 3
Scatterplots of the individual measures and model predictions over age for (A) PSD beta power, (B) burst rate, and (C) PSD broadband 1/f exponent, split between PD patients (blue) and healthy controls (red), and female (solid) and male (dashed).
Tables

Table 1

Group-level summary of the participants included in the analysis. Mean (standard deviation).

| Measure            | Parkinson’s patients | Healthy controls | Statistics         |
|--------------------|----------------------|------------------|--------------------|
| N                  | 78                   | 60               |                    |
| Sex (female/male)  | 29/49                | 27/33            | χ² = 0.57, p = 0.45|
| Age                | 65.6 (9.5)           | 63.93 (8.4)      | Welsh t(138.0) = 1.08, p = 0.28 |
| Disease duration   | 4.4 (3.7) years      | -                | -                  |
| LEDD               | 548 (273) mg         | -                | -                  |
| MDS-UPDRS-III      | 18.9 (10.8)          | -                | -                  |
| MoCA               | 26.1 (2.8)           | 26.2 (2.1)       | Welsh t(136) = 0.10, p = 0.92 |

Table 2

Table 2: Explanation of the main outcome variables in the analysis
Table 3

Regression coefficients and 95% CI for the regression models of the sensorimotor signal features (Table 2) with Group, Age, Sex, and Cortical Thickness. Values in red indicate coefficients of statistically significant factors in the model comparison. LL: lower limit, UL: upper limit.

| Variable Category | Variable                  | Explanation                                                                 |
|-------------------|---------------------------|------------------------------------------------------------------------------|
| PSD               | Beta power                | The maximum peak in the 13-30 Hz band. Estimated as the height of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Beta centre frequency (Hz)| The dominant frequency bin in the 13-30 Hz band. Estimated as the mean of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Alpha power               | The maximum peak in the 8-12 Hz band. Estimated as the height of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | Alpha centre frequency (Hz)| The dominant frequency bin in the 8-12 Hz band. Estimated as the mean of the Gaussian function fitted to the PSD after regressing out the 1/f regression line. |
|                   | 1/f intercept             | The intercept of the log-linear regression estimated from the full PSD in the 0.5-40 Hz range. |
|                   | 1/f exponent              | The exponent of the log-linear regression—corresponding to the slope of the log-log transformed PSD—estimated from the full PSD in the 0.5-40 Hz range. |
| Bursts            | Rate                      | The number of burst events in the sensorimotor time series divided by the length of time series. |
|                   | Duration (ms)             | Duration of the burst events defined as the time the time-series is above threshold until the next time-point it drops below the threshold. |
|                   | Interval (ms)             | Time from the mu/beta time-series drops below threshold until the next time-point it reaches threshold again. |
|                   | Amplitude                 | The maximum amplitude of the mu/beta time-series within one burst event. |
| Variable category | Variable       | Midline function | Rest tremor | Rigidity | Bradykinesia upper extremity | Bradykinesia lower limb | Postural and kinetic tremors |
|-------------------|----------------|------------------|-------------|----------|-----------------------------|-------------------------|-----------------------------|
|                   | Intercept      | -0.42            | -0.52      | -0.33    | 0.02                        | -0.26                   | 0.12                        |
|                   |                 | LL: -0.80        | LL: -0.93  | LL: -0.80| LL: -0.40                   | LL: -0.71               | LL: -0.71                   |
|                   |                 | UL: -0.04        | UL: -0.13  | UL: 0.13 | UL: 0.40                    | UL: 0.16                | UL: 0.19                    |
|                   | Beta power      | 0.33             | 0.24       | 0.33     | -0.18                       | 0.00                   | -0.22                       |
|                   |                 | LL: -0.06        | LL: -0.16  | LL: -0.12| LL: -0.57                   | LL: -0.41               | LL: -0.43                   |
|                   |                 | UL: 0.70         | UL: 0.64   | UL: 0.78 | UL: 0.17                    | UL: 0.42                | UL: 0.44                    |
|                   | Beta centre frequency | 0.02         | -0.20      | 0.03     | -0.11                       | -0.13                  | 0.01                        |
|                   |                 | LL: -0.27        | LL: -0.50  | LL: -0.32| LL: -0.38                   | LL: -0.46               | LL: -0.45                   |
|                   |                 | UL: 0.30         | UL: 0.10   | UL: 0.36 | UL: 0.20                    | UL: 0.20                | UL: 0.19                    |
|                   | Alpha power     | -0.11            | -0.22      | -0.12    | 0.24                        | 0.11                   | 0.02                        |
|                   |                 | LL: -0.50        | LL: -0.61  | LL: -0.58| LL: -0.14                   | LL: -0.34               | LL: -0.34                   |
|                   |                 | UL: 0.28         | UL: 0.21   | UL: 0.35 | UL: 0.66                    | UL: 0.57                | UL: 0.54                    |
|                   | Alpha centre frequency | 0.01         | 0.13       | 0.12     | 0.29                        | 0.08                   | 0.22                        |
|                   |                 | LL: -0.24        | LL: -0.16  | LL: -0.16| LL: 0.01                    | LL: -0.21               | LL: -0.22                   |
|                   |                 | UL: 0.24         | UL: 0.40   | UL: 0.43 | UL: 0.56                    | UL: 0.38                | UL: 0.38                    |
|                   | 1/f intercept   | -0.13            | 0.47       | 0.45     | -0.59                       | 0.35                   | -0.98                       |
|                   |                 | LL: -1.11        | LL: 0.66   | LL: -0.86| LL: 1.63                    | LL: -0.84               | LL: -0.89                   |
|                   |                 | UL: 0.89         | UL: 1.54   | UL: 1.70 | UL: 0.42                    | UL: 1.51                | UL: 1.50                    |
|                   | 1/f exponent    | -0.05            | -0.26      | -0.16    | 0.17                        | -0.02                  | 0.46                        |
|                   |                 | LL: -0.67        | LL: -0.87  | LL: -0.86| LL: -0.47                   | LL: -0.74               | LL: -0.73                   |
|                   |                 | UL: 0.56         | UL: 0.39   | UL: 0.63 | UL: 0.81                    | UL: 0.70                | UL: 0.68                    |
|                   | Rate            | 0.13             | 0.05       | 0.06     | -0.60                       | -0.08                  | 0.15                        |
|                   |                 | LL: -0.28        | LL: 0.40   | LL: -0.48| LL: 1.01                    | LL: -0.59               | LL: -0.57                   |
|                   |                 | UL: 0.56         | UL: 0.53   | UL: 0.61 | UL: 0.17                    | UL: 0.43                | UL: 0.40                    |
|                   | Length          | 0.31             | -0.15      | 0.07     | 0.09                        | -0.07                  | 0.27                        |
|                   |                 | LL: 0.00         | LL: -0.46  | LL: -0.32| LL: 0.22                    | LL: -0.42               | LL: -0.42                   |
|                   |                 | UL: 0.60         | UL: 0.16   | UL: 0.45 | UL: 0.42                    | UL: 0.29                | UL: 0.29                    |
|                   | Burst           | 0.29             | 0.12       | 0.18     | -0.21                       | -0.01                  | 0.35                        |
|                   | Interval        | 0.29             | 0.12       | 0.18     | -0.21                       | -0.01                  | 0.35                        |
|                   |                 | LL: -0.07        | LL: -0.31  | LL: -0.31| LL: -0.58                   | LL: -0.44               | LL: -0.46                   |
|                   |                 | UL: 0.66         | UL: 0.55   | UL: 0.64 | UL: 0.20                    | UL: 0.43                | UL: 0.44                    |
|                   | Amplitude       | 0.04             | -0.19      | -0.30    | 0.67                        | -0.15                  | 0.64                        |
|                   |                 | LL: -0.83        | LL: -1.12  | LL: -1.34| LL: -0.20                   | LL: -1.10               | LL: -1.19                   |
|                   |                 | UL: 0.88         | UL: 0.72   | UL: 0.78 | UL: 1.59                    | UL: 0.88                | UL: 0.84                    |
|                   | Age             | 0.03             | 0.00       | 0.00     | 0.01                        | 0.01                   | 0.01                        |
|                   |                 | LL: -0.01        | LL: -0.03  | LL: -0.03| LL: -0.02                   | LL: -0.02               | LL: -0.02                   |
|                   |                 | UL: 0.06         | UL: 0.03   | UL: 0.03 | UL: 0.04                    | UL: 0.04                | UL: 0.04                    |
|                   | Sex             | 0.70             | 0.74       | 0.55     | -0.14                       | 0.33                   | -0.25                       |
|                   |                 | LL: 0.17         | LL: 0.17   | LL: -0.04| LL: -0.70                   | LL: -0.31               | LL: -0.31                   |
|                   |                 | UL: 1.18         | UL: 1.32   | UL: 1.22 | UL: 0.45                    | UL: 0.97                | UL: 0.94                    |
|                   | Other           | -0.17            | -0.05      | -0.05    | -0.27                       | -0.18                  | -0.10                       |
|                   | Cortical thickness| -0.17           | -0.05      | -0.05    | -0.27                       | -0.18                  | -0.10                       |
|                   |                 | LL: -0.41        | LL: -0.29  | LL: -0.34| LL: -0.51                   | LL: -0.48               | LL: -0.46                   |
|                   |                 | UL: 0.07         | UL: 0.22   | UL: 0.25 | UL: 0.03                    | UL: 0.11                | UL: 0.11                    |
|                   | Multiple R-squared | 0.441          | 0.277      | 0.156    | 0.375                       | 0.193                  | 0.173                       |
Table 4

Standardised regression coefficients (95% CI) for the six regression models on motor symptoms measured with the MDS-UPDRS-III. Values in bold indicate significant factors in the model comparison.
| Variable category | Variable | Midline function | Rest tremor | Rigidity | Bradykinesia upper extremity | Postural and kinetic tremors | Bradykinesia lower limb |
|-------------------|----------|------------------|-------------|----------|----------------------------|----------------------------|--------------------------|
| **Intercept**     |          | -0.42            | -0.52       | -0.33    | 0.02                       | -0.26                      | 0.12                     |
|                   |          | LL: -0.80        | LL: -0.93   | LL: -0.80| LL: -0.40                  | LL: -0.71                  | LL: -0.71                |
|                   |          | UL: -0.04        | UL: -0.13   | UL: 0.13 | UL: 0.40                   | UL: 0.16                   | UL: 0.19                 |
| **Beta power**    |          | **0.33**         | 0.24        | 0.33     | -0.18                      | 0.00                       | -0.22                    |
|                   |          | LL: -0.06        | LL: -0.16   | LL: -0.12| LL: -0.57                  | LL: -0.41                  | LL: -0.43                |
|                   |          | UL: 0.70         | UL: 0.64    | UL: 0.78 | UL: 0.17                   | UL: 0.42                   | UL: 0.44                 |
| **Beta centre frequency** |        | 0.02             | -0.20       | 0.03     | -0.11                      | -0.13                      | 0.01                     |
|                   |          | LL: -0.27        | LL: -0.50   | LL: -0.32| LL: -0.38                  | LL: -0.46                  | LL: -0.45                |
|                   |          | UL: 0.30         | UL: 0.10    | UL: 0.36 | UL: 0.20                   | UL: 0.20                   | UL: 0.19                 |
| **Alpha power**   |          | -0.11            | -0.22       | -0.12    | 0.24                       | 0.11                       | 0.02                     |
|                   |          | LL: -0.50        | LL: -0.61   | LL: -0.58| LL: -0.14                  | LL: -0.34                  | LL: -0.34                |
|                   |          | UL: 0.28         | UL: 0.21    | UL: 0.35 | UL: 0.66                   | UL: 0.57                   | UL: 0.54                 |
| **PSD Alpha centre frequency** |      | 0.01             | 0.13        | 0.12     | **0.29**                   | 0.08                       | 0.22                     |
|                   |          | LL: -0.24        | LL: -0.16   | LL: -0.16| LL: 0.01                   | LL: -0.21                  | LL: -0.22                |
|                   |          | UL: 0.24         | UL: 0.40    | UL: 0.43 | UL: 0.56                   | UL: 0.38                   | UL: 0.38                 |
| **1/f intercept** |          | -0.13            | 0.47        | 0.45     | -0.59                      | 0.35                       | -0.98                    |
|                   |          | LL: -1.11        | LL: 0.66    | LL: 0.86 | LL: -1.63                  | LL: -0.84                  | LL: -0.89                |
|                   |          | UL: 0.89         | UL: 0.54    | UL: 1.70 | UL: 0.42                   | UL: 1.51                   | UL: 1.50                 |
| **1/f exponent**  |          | -0.05            | -0.26       | -0.16    | 0.17                       | -0.02                      | 0.46                     |
|                   |          | LL: -0.67        | LL: -0.87   | LL: -0.86| LL: -0.47                  | LL: -0.74                  | LL: -0.73                |
|                   |          | UL: 0.56         | UL: 0.39    | UL: 0.63 | UL: 0.81                   | UL: 0.70                   | UL: 0.68                 |
| **Rate**          |          | 0.13             | 0.05        | 0.06     | **-0.60**                  | -0.08                      | 0.15                     |
|                   |          | LL: -0.28        | LL: -0.40   | LL: -0.48| LL: -1.01                  | LL: -0.59                  | LL: -0.57                |
|                   |          | UL: 0.56         | UL: 0.53    | UL: 0.61 | UL: -0.17                  | UL: 0.43                   | UL: 0.40                 |
| **Length**        |          | **0.31**         | -0.15       | 0.07     | 0.09                       | -0.07                      | 0.27                     |
|                   |          | LL: 0.00         | LL: -0.46   | LL: -0.32| LL: -0.22                  | LL: -0.42                  | LL: -0.42                |
|                   |          | UL: 0.60         | UL: 0.16    | UL: 0.45 | UL: 0.42                   | UL: 0.29                   | UL: 0.29                 |
| **Burst Interval** |          | 0.29             | 0.12        | 0.18     | -0.21                      | -0.01                      | 0.35                     |
|                   |          | LL: -0.07        | LL: -0.31   | LL: -0.31| LL: -0.58                  | LL: -0.44                  | LL: -0.46                |
|                   |          | UL: 0.66         | UL: 0.55    | UL: 0.64 | UL: 0.20                   | UL: 0.43                   | UL: 0.44                 |
| **Amplitude**     |          | 0.04             | -0.19       | -0.30    | 0.67                       | -0.15                      | 0.64                     |
|                   |          | LL: -0.83        | LL: -1.12   | LL: -1.34| LL: -0.20                  | LL: -1.10                  | LL: -1.19                |
|                   |          | UL: 0.88         | UL: 0.72    | UL: 0.78 | UL: 1.59                   | UL: 0.88                   | UL: 0.84                 |
| **Age**           |          | **0.03**         | 0.00        | 0.00     | 0.01                       | 0.01                       | 0.01                     |
|                   |          | LL: 0.01         | LL: -0.03   | LL: -0.03| LL: -0.02                  | LL: -0.02                  | LL: -0.02                |
|                   |          | UL: 0.06         | UL: 0.03    | UL: 0.03 | UL: 0.04                   | UL: 0.04                   | UL: 0.04                 |
| **Sex**           |          | **0.70**         | 0.74        | 0.55     | -0.14                      | 0.33                       | -0.25                    |
|                   |          | LL: 0.17         | LL: 0.17    | LL: -0.04| LL: -0.70                  | LL: -0.31                  | LL: -0.31                |
|                   |          | UL: 1.18         | UL: 1.32    | UL: 1.22 | UL: 0.45                   | UL: 0.97                   | UL: 0.94                 |
| **Other Cortical thickness** |       | -0.17            | -0.05       | -0.05   | **-0.27**                  | -0.18                      | -0.10                    |
|                   |          | LL: -0.41        | LL: -0.29   | LL: -0.34| LL: -0.51                  | LL: -0.48                  | LL: -0.46                |
|                   |          | UL: 0.07         | UL: 0.22    | UL: 0.25 | UL: -0.03                  | UL: 0.11                   | UL: 0.11                 |
| **Multiple R-squared** |       | **0.441**         | 0.277       | 0.156   | 0.375                      | 0.193                      | 0.173                    |
Table 5

Statistically significant correlation coefficients between all main variables. Green colors indicate a positive correlation between variables and red colors indicate a negative correlation between variables. The intensity of the color scales with the correlation coefficient.

| Variable category | Beta power | Beta centre frequency | Alpha power | Alpha centre frequency | 1/f intercept | 1/f exponent | Rate | Duration | Inteval | Amplitude | Age | Midline function | Rest tremor | Rigidity | Bradykinesia upper extremity | Postural and kinetic tremors | Bradykinesia lower limb |
|-------------------|------------|-----------------------|-------------|------------------------|---------------|-------------|------|----------|---------|-----------|-----|-----------------|-------------|---------|----------------------|----------------------|---------------------|
| Beta power        | -0.35      | 0.63                  | -0.32       | 0.52                   | 0.57          | 0.26        | 0.2  | -0.24    | 0.52    | 0.18      | -0.21 | -0.28          | 0.24        |         |                      |                      |                     |
| Beta centre frequency | -0.35     | 0.34                  | 0.22        | -0.18                  | -0.3          | -0.17       |      |          |         |           |       |                |             |         |                      |                      |                     |
| Alpha power       | -0.63      | -0.34                 | -0.41       | 0.4                    | 0.32          | -0.23       | 0.45 |          |         |           |       |                |             |         |                      |                      |                     |
| Alpha centre frequency | -0.32   | 0.22                  | -0.36       | -0.19                  | -0.43         | -0.18       |      |          |         |           |       |                |             |         |                      |                      |                     |
| 1/f intercept     | 0.52       | 0.31                  | 0.41        | -0.19                  | 0.56          | 0.31        | -0.48 | -0.91    |         |           |       |                |             |         |                      |                      |                     |
| 1/f exponent      | 0.57       | 0.3                   | 0.4         | -0.43                  | 0.56          | 0.3         |      |          |         |           |       |                |             |         |                      |                      |                     |
| Rate              | -0.26      | 0.32                  | 0.55        | 0.55                   | -0.8          | 0.55        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Duration          | 0.2        | 0.31                  | 0.55        | 0.55                   | -0.61         | 0.29        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Inteval           | -0.24      | -0.23                 | -0.48       | 0.4                    | 0.6           | 0.64        | -0.44 | 0.2      |         |           |       |                |             |         |                      |                      |                     |
| Amplitude         | 0.52       | 0.45                  | 0.95        | 0.3                    | 0.55          | 0.29        | -0.44 | 0.2      |         |           |       |                |             |         |                      |                      |                     |
| Age               | 0.18       | -0.17                 | 0.18        | 0.2                    | -0.19         | -0.22       |      |          |         |           |       |                |             |         |                      |                      |                     |
| Cortical thickness| 0.18       | -0.25                 | 0.18        | 0.2                    | -0.19         | 0.19        |      |          |         |           |       |                |             |         |                      |                      |                     |
| MoCA              | -0.21      | 0.2                   | -0.21       | -0.19                  | -0.21         | 0.22        | 0.19 | -0.22    | 0.37    | 0.26      | -0.37 | -0.26         | 0.23        |         |                      |                      |                     |
| Midline function  | 0.28       | 0.3                   | 0.3         | 0.37                   | -0.38         | -0.38       |      |          |         |           |       |                |             |         |                      |                      |                     |
| Rest tremor       | 0.37       | -0.38                 | 0.38        | 0.4                    | 0.28          | 0.38        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Rigidity          | 0.38       | 0.37                  | 0.38        | 0.37                   | 0.28          | 0.38        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Bradykinesia upper extremity | 0.28   | 0.38                 | 0.37         | 0.28                   | 0.38          | 0.38        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Postural and kinetic tremors | 0.28 | 0.32           | 0.33         | 0.32                   | 0.38          | 0.38        |      |          |         |           |       |                |             |         |                      |                      |                     |
| Bradykinesia lower limb | 0.24 | 0.32           | 0.32         | 0.4                    | 0.28          | 0.33        |      |          |         |           |       |                |             |         |                      |                      |                     |

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