

BRAIN COMMUNICATIONS

Memory deficits in Parkinson's disease are associated with reduced beta power modulation

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There is an increasing recognition of the significant non-motor symptoms that burden people with Parkinson's disease. As such, there is a pressing need to better understand and investigate the mechanisms underpinning these non-motor deficits. The electrical activity within the brains of people with Parkinson's disease is known to exhibit excessive power within the beta range (12–30 Hz), compared with healthy controls. The weight of evidence suggests that this abnormally high level of beta power is the cause of bradykinesia and rigidity in Parkinson's disease. However, less is known about how the abnormal beta rhythms seen in Parkinson's disease impact on non-motor symptoms. In healthy adults, beta power decreases are necessary for successful episodic memory formation, with greater power decreases during the encoding phase predicting which words will subsequently be remembered. Given the raised levels of beta activity in people with Parkinson's disease, we hypothesized that the necessary decrease in power during memory encoding would be diminished and that this would interfere with episodic memory formation. Accordingly, we conducted a cross-sectional, laboratory-based experimental study to investigate whether there was a direct relationship between decreased beta modulation and memory formation in Parkinson's disease. Electroencephalography recordings were made during an established memory-encoding paradigm to examine brain activity in a cohort of adults with Parkinson's disease ($N=28$, 20 males) and age-matched controls ($N=31$, 18 males). The participants with Parkinson's disease were aged 65 ± 6 years, with an average disease duration of 6 ± 4 years, and tested on their normal medications to avoid the confound of exacerbated motor symptoms. Parkinson's disease participants showed impaired memory strength ($P=0.023$) and reduced beta power decreases ($P=0.014$) relative to controls. Longer disease duration was correlated with a larger reduction in beta modulation during encoding, and a concomitant reduction in memory performance. The inability to sufficiently decrease beta activity during semantic processing makes it a likely candidate to be the central neural mechanism underlying this type of memory deficit in Parkinson's disease. These novel results extend the notion that pathological beta activity is causally implicated in the motor and (lesser appreciated) non-motor deficits inherent to Parkinson's disease. These findings provide important empirical evidence that should be considered in the development of intelligent next-generation therapies.

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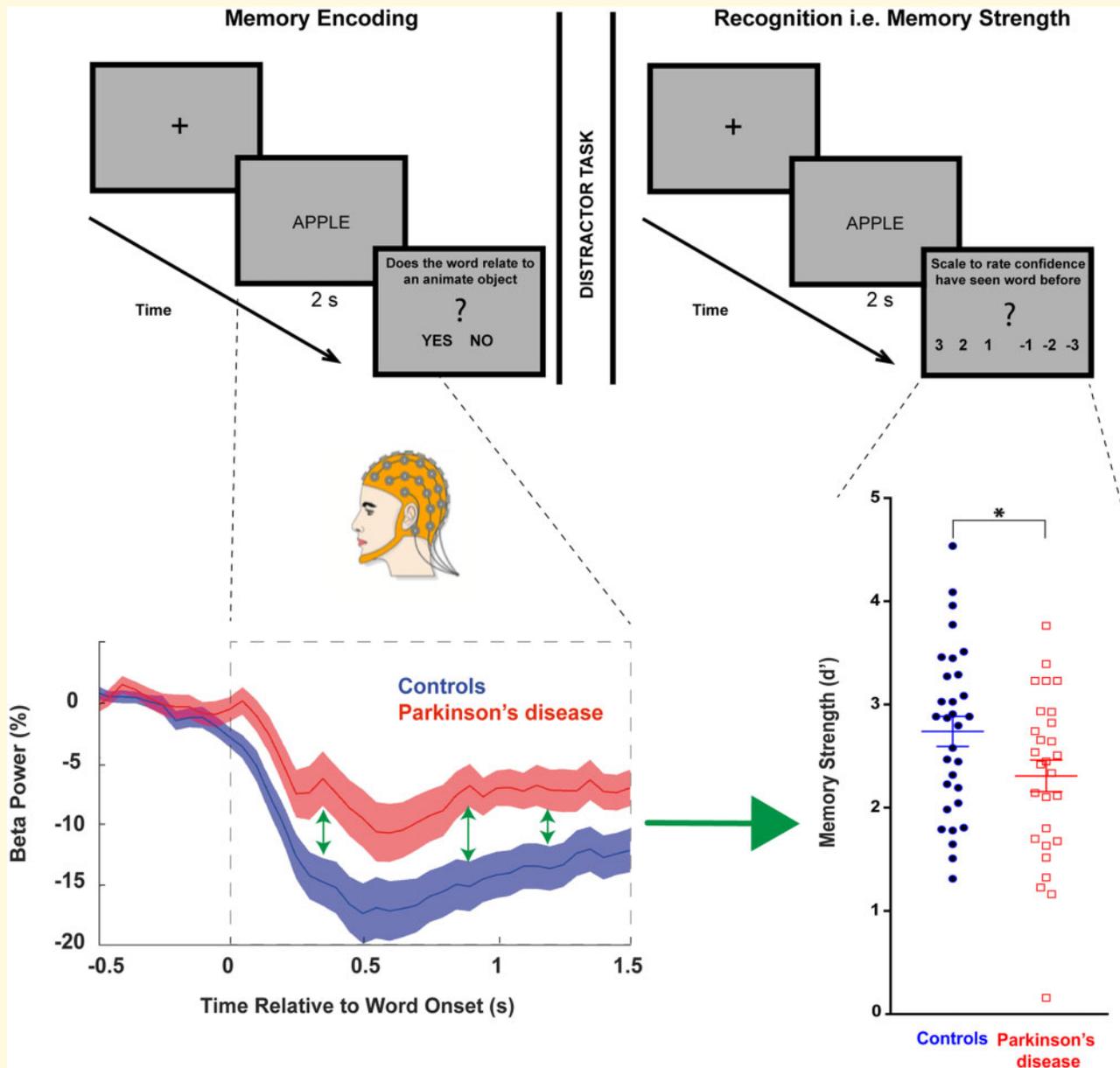
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Abbreviations: ANOVA = analysis of variance; BG = basal ganglia; EEG = electroencephalography; HH = high confidence hit; IFC = inferior frontal cortex; LH = low confidence hit; M = Miss; RM = repeated measures; SME = subsequent-memory effect

Graphical Abstract



Introduction

Parkinson's disease is classified as a movement disorder. However, there is growing recognition that non-motor burdens also significantly impact those suffering with the condition. Non-demented Parkinson's disease patients can experience cognitive difficulties, including long-term memory deficits (for a review see [Raskin *et al.*, 1990](#); [Zgaljardic *et al.*, 2003](#)) and specifically the ability to

recall verbal memory ([Cohn *et al.*, 2010](#); [Dujardin *et al.*, 2015](#); [Edelstyn *et al.*, 2015](#)).

One striking feature of Parkinson's disease demonstrated repeatedly over the last 20 years is that the electrical activity recorded from basal ganglia (BG) networks in people with Parkinson's disease exhibits excessively high levels of activity within the beta frequency range (12–30 Hz) compared with healthy controls. Under normal circumstances, beta activity is modulated with

voluntary movement, where the amplitude of oscillations (power) in the beta range drops at the onset of movement and rises again at the end. It is suggested that elevated beta is associated with tonic motor state and an event-related power decrease within BG networks 'allows' movement to take place (Joundi *et al.*, 2013; Brittain and Brown, 2014), and as such the excessively high beta activity seen in Parkinson's disease prevents decreases in power and thus interferes with voluntary movement (Jenkinson and Brown, 2011). Indeed, therapies that reduce beta activity, such as dopamine replacement therapy (Ray *et al.*, 2008) or deep brain stimulation (Eusebio *et al.*, 2011), also proportionately improve bradykinesia and rigidity (Ray *et al.*, 2008). Interestingly, decreases in beta power can also occur in the absence of motor output during imagined voluntary movements (McFarland *et al.*, 2000; Miller *et al.*, 2010). However, to date the link between exaggerated beta activity and motor symptoms in Parkinson's disease remains circumstantial and correlative. It therefore remains an unresolved question as to whether pathological beta activity is causal or an epiphenomenon.

Given that beta power is elevated throughout the BG–thalamocortical circuitry in Parkinson's disease and that this elevation has been observed over broad areas of frontal cortex (Litvak *et al.*, 2011), we postulated that the excessive beta power seen in Parkinson's disease should interfere with other neural mechanisms that normally operate within this spatial domain. Identifying such beta dependent processes and demonstrating a deficit of function in Parkinson's disease would provide further evidence that increased beta power is responsible for the motor and non-motor symptoms of the disease. Recent experimental evidence suggests a role for beta oscillations in the encoding of explicit long-term memory. Specifically, a greater reduction of beta power occurs in the left inferior frontal cortex (IFC) during memory formation of words that are subsequently remembered compared with those that are not (Sederberg *et al.*, 2003; Hanslmayr *et al.*, 2009, 2011; Meeuwissen *et al.*, 2011; Meconi *et al.*, 2016). This relationship is especially strong if the explicit memory strategy requires semantic processing (Hanslmayr *et al.*, 2009). Memory strategies utilizing semantic processing are examples of deep encoding; when people engage with the meaning of the words, e.g. put them into the context of a sentence or make a judgement about whether they relate to living/nonliving entities. Conversely, in shallow encoding an individual only engages with the presented items on a superficial and more perceptual level, as opposed to a cognitive level (Craik and Lockhart, 1972). Examples are detecting whether a presented word contains a specific letter, or whether the first and last letters of the word are in alphabetical order (Otten *et al.*, 2001). Unlike in deep encoding, decreases in beta power during shallow encoding are not predictive of memory performance (Hanslmayr *et al.*, 2009). Furthermore, a decrease in beta

power is not seen when similar words are deeply encoded but using non-semantic strategies (Fellner *et al.*, 2013). Therefore, it appears that decreases in beta power are specifically driven by the semantic nature of the encoding task. If the explicit motor deficits in Parkinson's disease are a result of increased beta power in motor areas of the brain, it stands-to-reason that the memory deficits may well be the result of the elevated levels of beta activity, which prevent the encoding driven decrease in beta power required for semantic processing, and memory formation as a result thereof.

Employing a semantic-encoding memory task to investigate the role of pathological beta in Parkinson's disease has several advantages. First, it removes the confound of movement during the window for beta power decreases. Therefore, if a relationship exists between behaviour and beta power, this would argue against impaired beta decreases seen in the motor system being an epiphenomenon that merely reflects the paucity of movement in people with Parkinson's disease. Second, semantic processing (Gabrieli *et al.*, 1998) and episodic memory formation (Otten and Rugg, 2001) recruit the 'left' IFC. This is important since dynamic modulation of beta has already been shown to be compromised in Parkinson's disease within the cortical–BG network including 'right' IFC and subthalamic nucleus (Swann *et al.*, 2009, 2011; Brittain *et al.*, 2012). Given the coherent beta activity within cortico–BG circuitry (Hirschmann *et al.*, 2011; Litvak *et al.*, 2011) and bidirectional communication (Lalo *et al.*, 2008; Horschig *et al.*, 2015) within these circuits, we would predict that pathological beta would equally affect 'left' IFC beta power and therefore impair episodic memory that recruits semantic-encoding strategies. Intriguingly, it has been demonstrated behaviourally that Parkinson's disease patients do show a specific memory deficit when recollecting deep-encoded words but no deficit in shallow-non-semantic encoding (Cohn *et al.*, 2010). If this specific deficit can be shown to be associated with the inability to sufficiently decrease beta activity, it would demonstrate that impaired modulation of beta might underlie at least some of the higher cognitive symptoms associated with the disease. Finally, we have demonstrated a causal relationship between beta power decreases in left inferior prefrontal cortex and memory performance in young healthy adults (Hanslmayr *et al.*, 2014). Elucidating a direct relationship between beta power and episodic memory performance in Parkinson's disease would therefore strongly argue for a causal role of exaggerated beta oscillations in the symptoms of Parkinson's disease.

Given this background, the current study aimed to determine whether there is a direct relationship between impaired decreases in beta power and the long-term memory deficits observed in non-demented Parkinson's disease. The study design, hypotheses and analyses were preregistered (MacDonald *et al.*, 2016). We recorded surface electroencephalography (EEG) during an established

memory-encoding paradigm to examine beta oscillations in Parkinson's disease patients and healthy controls during deep-semantic and shallow-non-semantic encoding. We hypothesized that Parkinson's disease patients would exhibit impaired memory performance compared with healthy controls following deep-semantic encoding but that there would be no difference in memory performance between groups following shallow-non-semantic encoding. We further hypothesized that Parkinson's disease patients would show reduced beta power decreases during deep-semantic encoding compared with healthy controls but that there would be no difference in beta power between groups during shallow-non-semantic encoding.

Materials and methods

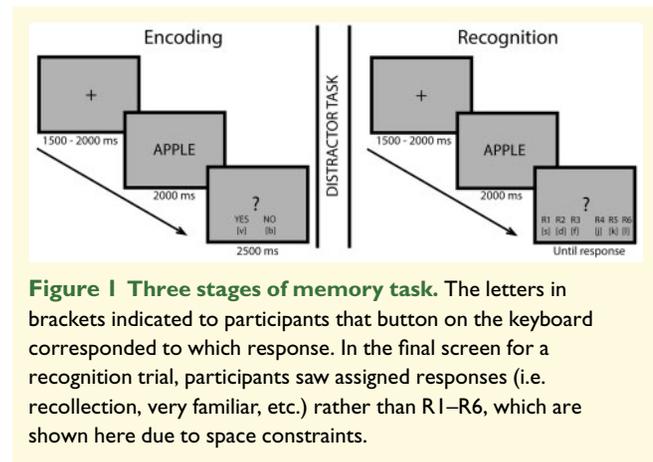
The study was approved by the University of Birmingham Research Ethics Committee (ERN_09-528AP20), and written informed consent was obtained from each participant. Data collection was carried out during a single laboratory session for each participant at the University of Birmingham.

Behavioural task

Participants were seated ~1 m from a 19-in computer monitor. Stimuli were presented in black text against a grey background using the Psychophysics Toolbox extension of MATLAB (Brainard, 1997). The task was divided into eight blocks, and each block was divided into three stages (Fig. 1).

First, there was an 'encoding stage' that required either deep-semantic encoding or shallow-non-semantic encoding of 30 words presented on the screen one at a time. All participants completed four blocks of trials of each encoding condition (i.e. encoding blocks). The order of presentation of each encoding type was counterbalanced across participants. In the deep-semantic-encoding blocks, participants judged whether the presented word was animate, i.e. whether it referred to the property of a living entity. In the shallow-non-semantic-encoding blocks, participants judged whether the first and last letters of the word were in alphabetical order. These encoding instructions have been used previously to investigate subsequent-memory effects (SME) (Otten and Rugg, 2001; Hanslmayr et al., 2009). Participants responded on each trial by pressing one of two response buttons ('yes' or 'no') on the keyboard using their index and middle finger. Parkinson's disease patients used fingers on their less affected hand, and hand assignment was randomized (regardless of hand dominance) across healthy participants for comparison with patients. Button assignment was counterbalanced across patients and participants.

The encoding stimuli were taken from a pool of 240 English words, with a list of 120 per encoding condition selected from the Medical Research Council (MRC)



psycholinguistic database (Coltheart, 1981). Encoding lists were matched according to word frequency (10–93 per million), concreteness (252–593), imageability (452–615), number of syllables (1–4) and number of letters (3–10). Words were randomly drawn from the first encoding list for the first four encoding blocks, and the second list for the last four blocks. The order of encoding instructions rather than encoding lists was counterbalanced across participants. A single trial began with a fixation cross for a variable duration of between 1500 and 2000 ms, followed by word presentation for 2000 ms and ended with a question mark to prompt the participant to respond (for which they were given 2500 ms). Participants were instructed not to react during word presentation but give their response during presentation of the question mark.

The second stage in each block consisted of a distracter task during which 20 faces of famous and non-famous people were presented to the participant one at a time. The participant was required to rate the attractiveness of each face using a 6-point rating scale. The distracter stage was intended to prevent the participants rehearsing the word lists and also to familiarize participants with the 6-button ratings, which were to be used in the subsequent recognition stage.

In the final 'recognition stage' of each block, the 30 previously encoded words and 15 novel stimuli words drawn from the same pool of English database words were presented to participants one at a time. The lists of encoded and novel words were kept consistent between participants. The order of words was randomized, and participants were required to rate their confidence as to whether the word was one encountered in the 'encoding stage', or was a new word. Ratings were given using the 6-point rating scale where response options were R1: recollect, R2: very familiar, R3: familiar, R4: unsure new, R5 sure new, R6: very sure new, using buttons pressed with the index, middle and ring fingers on both hands. The assignment of the buttons was counterbalanced across participants (i.e. R1–R6 versus R6–R1), and participants were explicitly instructed to use the full range of

confidence ratings. The list of new words was matched to encoding lists for word frequency, concreteness, imageability, number of syllables and number of letters. A trial progressed in the same order and with the same timings as during the 'encoding stage', except that the question mark and button prompts remained on-screen until the participant responded.

Electroencephalography recording

Continuous EEG data were recorded using a 128-channel BioSemi ActiveTwo system (BioSemi) with electrodes positioned at the 128 standard equidistant BioSemi sites. Data were digitized using the BioSemi ActiView software, with a sampling rate of 1024 Hz and filtered between 0.1 and 100 Hz.

Behavioural data analysis

Reaction times and response accuracies were recorded during the 'encoding stage'. Response times were calculated from the onset of the question mark, which prompted the participant to respond until button press. Accuracy was calculated as the number of correct 'yes' or 'no' responses during each type of encoding expressed as a percentage of all words presented for that encoding condition. All other behavioural analysis and presented data are from the 'recognition stage'. Trials in the recognition stage were grouped into high confidence hit (HH), low confidence hit (LH) and Miss (M) categories, depending on the participant's response and their individualized receiver operating characteristic curves (Hanslmayr *et al.*, 2009). Using receiver operating characteristic curves enabled objective quantification of individual response biases and corrected for participants' tendencies to use single buttons of the rating scale differently (Fig. 2). There was an average of 101 (minimum 66/maximum 118) of these remembered (HH and LH) trials for controls and 98 trials (minimum 66/maximum 118) for Parkinson's disease participants in deep-semantic encoding and 71 trials for both controls (minimum 33/maximum 98) and Parkinson's disease participants (minimum 25/maximum 103) in shallow-non-semantic encoding. For M trials, there were an average of 19 (minimum 2/maximum 54) for controls and 22 (minimum 2/maximum 54) for Parkinson's disease participants in deep-semantic encoding and an average of 49 trials for both controls (minimum 22/maximum 87) and Parkinson's disease participants (minimum 17/maximum 95) in shallow-non-semantic encoding. The primary dependent variable, memory strength (d'), was calculated from recognition responses using the following equation:

$$d' = Z[\% \text{ Hits}] - Z[\% \text{ false alarms}].$$

Z scores were calculated for each individual using MATLAB (The Mathworks). Hits refer to combined HH

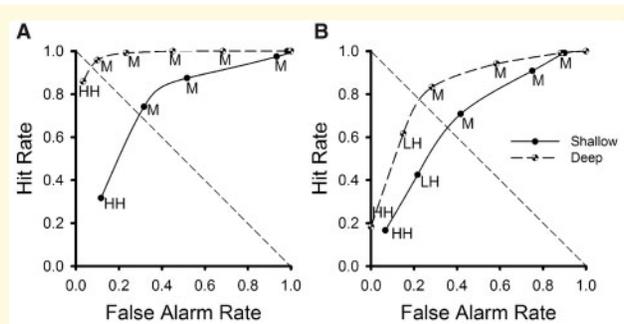


Figure 2 Receiver operating characteristic curves for a representative control (A) and Parkinson's disease participant (B) in deep-semantic- and shallow-non-semantic-encoding conditions. The false alarm rate is cumulative. The responses given on the 6-point rating scale are grouped into the following conditions: HH, LH and M.

and LH responses when a word is correctly remembered. False alarms are responses where the participant has incorrectly identified a new word as remembered.

EEG data analysis

All EEG analysis and presented data are from the 'encoding stage'. Offline analysis was performed in MATLAB using the open-source FieldTrip toolbox (Oostenveld *et al.*, 2011) and in-house MATLAB functions. Raw EEG data were high-pass (1 Hz) and low-pass filtered (40 Hz) with finite impulse response filters, re-referenced to the average reference, down-sampled to 500 Hz and epoched into 7000 ms segments around word presentation (3000 ms pre-stimulus onset to 4000 ms post-stimulus onset) for preprocessing. Independent component analysis allowed components related to ocular artefacts to be visually identified and removed before subsequent visual inspection and manual removal of remaining artefacts. If any channels had been removed during artefact rejection (mean 0.6 channels removed, minimum: 0, maximum: 3), sensor data were interpolated via triangulation of nearest neighbour and then finally re-referenced to the average reference.

The EEG recording epochs extracted from individual encoding trials were grouped into HH, LH and M categories, depending on the participant's subsequent response in the 'recognition stage'. Epochs were further segmented from 750 ms pre-stimulus to 2000 ms post-stimulus after filtering for the time-frequency analysis (shorter segmentation at this stage is to remove edge artefacts from filtering). The entire power spectrum was corrected for $1/f$ (Podvalny *et al.*, 2015; Voytek *et al.*, 2015) by fitting a linear function to the log-transformed data for every time point and then subtracting the linear fit. The 2.75-s epochs were then subjected to a Morlet wavelet transformation (width of 7 cycles) as implemented in Fieldtrip to extract time-frequency characteristics at frequencies 2–40 Hz in steps of 1 Hz. Average power values

were calculated for each trial type (HH, LH and M) and baseline corrected (relative change, baseline -750 to -250 ms). This baseline duration is common to examine beta power modulation in memory paradigms (e.g. Hanslmayr et al., 2009; Meconi et al., 2016) and the timing avoids filter smearing from post-stimulus effects into the baseline period. The primary dependent measure was beta power decrease for words that were subsequently successfully remembered, regardless of confidence level (i.e. during successful encoding of a memory resulting in a HH or LH trial in the ‘recognition stage’). The secondary dependent measure was the SME in beta power which compared power between Hit (i.e. subsequently remembered with high or low confidence) and M (i.e. subsequently forgotten) trials (Brewer et al., 1998; Otten et al., 2001; Hanslmayr et al., 2009). All analyses of beta power between and within groups used the same number of trials (adding to a total of 120 Hits/M) as the behavioural analysis except for trials that were removed before being categorized as Hit/M due to EEG artefact (controls: average of two trials removed, range 0–30 for deep-semantic condition; average of four trials removed, range 0–31 for shallow-non-semantic condition; Parkinson’s disease: average of two trials removed, range 0–7 for deep-semantic condition; average of one trial removed, range 0–5 for shallow-non-semantic condition). A minimum of five trials for Hits and/or M was required for a participant to be included in the beta power analyses.

Statistical analysis

For memory strength (d'), participants who had values outside 3 SD of the group mean were removed using the median absolute deviation method. The Shapiro–Wilk test ensured normality before using a mixed-effects repeated-measures (RM) 2×2 analysis of variance (ANOVA) with factors group (controls, Parkinson’s disease) and encoding (deep, shallow) as per our preregistered protocol expecting a group \times encoding interaction (MacDonald et al., 2016). *Post hoc* and planned comparisons were performed using *t*-tests. A least absolute shrinkage and selection operator regression was performed for the Parkinson’s disease group to determine the capacity of age and/or disease duration to predict memory strength following deep-semantic and shallow-non-semantic encoding, accounting for collinearity between age and disease duration. A mixed-effects RM 2×2 ANOVA with factors group (controls, Parkinson’s disease) and encoding (deep, shallow) tested for differences between groups in encoding accuracy and reaction time for the two encoding conditions.

In alignment with previous EEG studies, and as per our preregistered protocol, post-stimulus beta power decreases are expected to be associated with successful memory formation in healthy (Hanslmayr et al., 2009, 2011) and patient populations (Meconi et al., 2016).

Therefore, lower beta from 12 to 20 Hz was the main frequency range of interest for all dependent measures (see <https://osf.io/vb64n/>). We did, however, conduct additional between group analyses within the alpha (8–11 Hz) and theta range (4–7 Hz) using the same steps as for beta power to rule out widespread frequency changes and confirm that our results were specific to beta.

Only negative clusters in the beta frequency range were expected so comparisons of scalp-wide group averaged data were subjected to one-tailed cluster-based permutation testing (2000 iterations) using the Monte-Carlo ‘maxsum’ method (Meconi et al., 2016), averaged over 12–20 Hz and 0–1.5 s relative to encoding stimulus onset. The time window of 0–1.5 s post-stimulus onset was chosen based on findings from previous studies investigating beta power modulation using the same or similar memory paradigm (Hanslmayr et al., 2009; Meconi et al., 2016) and to avoid capturing any motor-related beta activity prior to the cue for a motor response (Pfurtscheller and Lopes da Silva, 1999), which appeared at the end of the encoding period (2 s after encoding stimulus). Data from all 128 electrodes are included in all EEG analyses. The only exception is for the additional correlational analyses in Parkinson’s disease patients to further investigate the effect of encoding on their beta power modulation at an individual level, when a subset of only left frontal electrodes was used based on a literature-driven prior hypothesis (Hanslmayr et al., 2009, 2011; Meeuwissen et al., 2011). This subset consisted of the front left quadrant taken from left sagittal to vertex (D23–A1 on BioSemi cap) and vertex down to mid frontal (A1–C17). A 2×2 mixed-effects RM ANOVA also tested for an encoding (shallow, deep) \times group (Controls, Parkinson’s disease) interaction of beta power and SME averaged for each participant over 0–1.5 s, 12–20 Hz and significant cluster electrodes. Linear regression tested for a relationship between each Parkinson’s disease individual’s maximum levels of beta power decrease over left frontal electrodes during deep-semantic encoding and (i) memory strength and (ii) disease duration.

The criterion for all statistical significance was $\alpha = 0.05$. Greenhouse–Geisser *P*-values are reported for non-spherical data.

Data availability

Anonymized data, not published in the article, will be shared on reasonable request from a qualified investigator.

Results

Participants

Twenty-nine adults with Parkinson’s disease and 34 healthy control adults with no known neurological

Table 1 Participant demographics and global cognitive function

	HC	Parkinson's disease
Age (years)	67 (9)	65 (6)
Education	3.8 (0.4)	3.9 (0.4)
Gender	13F/18M	8F/20M
Disease duration (years)	N/A	6 (4)
Handedness	3L/28R	5L/23R
OCS-Plus	9.7 (0.5)	9.7 (0.5)

Values are mean (SD) unless otherwise specified. F = female; HC = healthy controls; M = male; OCS-Plus = Oxford Cognitive Screen Plus questionnaire (maximum 10); L = left-handed; R = right-handed; N/A = not applicable. Education is grouped into 1 = no formal education; 2 = primary school; 3 = secondary school; and 4 = tertiary level.

impairment were recruited into the study from local Parkinson's disease community groups and research volunteer databases. This preregistered recruitment target (see <https://osf.io/vb64n/>) was calculated to account for 10% drop out and that some participants might be unable to adequately perform the memory task (e.g. insufficient number of remembered items) while still being sufficient to detect a large behavioural effect size (Cohn *et al.*, 2010: Experiment 1) and obtain a power of 0.9. Data for three control participants were removed due to not being able to perform the memory task correctly (i.e. responding to all words in the same way without discrimination), and data for one Parkinson's disease participant were removed due to a change in diagnosis. Demographic information for the remaining 31 control and 28 Parkinson's disease participants is provided in Table 1. Patients were at an average disease duration of 6 ± 4 years (range 0.3–14) and tested on their normal medications to avoid the confound of exacerbated motor symptoms (see Table 2 for demographic and clinical data for each individual Parkinson's disease participant). All participants were native English speakers, had completed education at secondary or tertiary level, had no history of dementia, had normal or corrected-to-normal vision and completed the Oxford Cognitive Screen Plus questionnaire (Demeyere *et al.*, 2016) as an assessment of global cognitive function. The two groups did not differ with respect to age, global cognitive function or level of education (all $P > 0.254$). All results are shown as group means \pm standard error.

Behavioural

Memory strength

Normal distributions were confirmed for all behavioural data sets (all $P > 0.423$). A mixed-effects RM ANOVA on memory strength (d') revealed no main effect of group ($F_{1, 57} = 2.494$, $P = 0.120$) but a main effect of encoding ($F_{1, 57} = 183.499$, $P < 0.001$). Memory performance improved in both groups with the semantic processing strategy associated with deep encoding (2.524 ± 0.105) leading to greater memory strength (d') during

recognition testing compared with shallow encoding (1.249 ± 0.057). There was a group \times encoding interaction ($F_{1, 57} = 4.885$, $P = 0.031$, Fig. 3A). One-tailed *post hoc* *t*-tests revealed no difference in memory strength between groups following shallow-non-semantic encoding ($t_{57} = 0.130$, $P = 0.500$), but deep-semantic encoding lead to greater memory strength in control participants (2.739 ± 0.145) compared with Parkinson's disease (2.309 ± 0.153 ; $t_{57} = 2.042$, $P = 0.023$). Although both groups demonstrated memory benefits from the semantic processing required during deep encoding, controls benefited to a greater degree than Parkinson's disease participants.

When controlling for age, disease duration had a specific detrimental effect on mechanisms underlying memory formation when semantic processing was required in deep encoding. A least absolute shrinkage and selection operator regression was run for Parkinson's disease participants to correlate disease duration with deep-semantic and shallow-non-semantic memory strength as well as age. Only memory strength in the deep-semantic-encoding condition was significantly negatively correlated with disease duration (Fig. 3B, $F_{1, 27} = 11.533$, $P = 0.002$, other $P > 0.242$). A similar regression analysis to correlate age and memory strength in controls was not performed as the assumption of normality was violated for age.

Encoding reaction time and accuracy

For reaction time, a mixed-effects RM ANOVA produced a main effect of encoding ($F_{1, 55} = 6.430$, $P = 0.014$) but no effect of group ($F_{1, 55} = 1.289$, $P = 0.261$) or encoding \times group interaction ($F_{1, 55} = 0.764$, $P = 0.386$). For both groups, reaction time was faster in shallow-non-semantic encoding (1.12 ± 0.03 s) compared with deep-semantic encoding (1.17 ± 0.03 s) by an average of 50 ms. Similarly, for accuracy, there was a main effect of encoding ($F_{1, 55} = 139.156$, $P < 0.001$) but no effect of group ($F_{1, 55} = 0.044$, $P = 0.834$) or encoding \times group interaction ($F_{1, 55} = 0.119$, $P = 0.732$). Accuracy was higher in shallow-non-semantic encoding ($90.9 \pm 1.0\%$) compared with deep-semantic encoding ($75.2 \pm 1.1\%$) for both groups as expected. The lack of any main effects or interactions with group indicate the significant difference in memory strength between groups in the deep-semantic condition is therefore unlikely to be driven by perceptual differences during encoding.

EEG

All EEG analysis and presented data are from the 'encoding stage'. EEG data from one control and two Parkinson's disease participants could not be used due to technical problems or large movements from dyskinesia, leaving 30 controls and 26 Parkinson's disease EEG data sets for analysis.

As hypothesized, the cluster-based permutation testing on all electrodes showed that controls demonstrated

Table 2 Demographic and clinical data for Parkinson's participants

Subject	Age (years)	Gender	Parkinson's disease medication	LEDD (mg)	Disease duration (years)	Side most affected
1	61	M	Stalevo: 375 mg levodopa (5 × 75 mg/18.75 mg/200 mg) Ropinirole 8 mg Rasagiline 1 mg	759	11	R
2	65	F	Rasagiline 1 mg Madopar: 800 mg levodopa (4 × 50 mg/200 mg)	900	8	L
3	76	F	Repinex 8 mg Sinemet: 500 mg levodopa (4 × 25 mg/100 mg, 1 × 25 mg/100 mg CR)	635	11	L
4	68	M	Sinemet: 300 mg levodopa (3 × 25 mg/100 mg)	300	5	R
5	62	M	Stalevo: 200 mg levodopa (4 × 50 mg/12.5 mg/200 mg) Rasagiline 1 mg Apomorphine 3 mg Repinex 4 mg	476	10	R
6	67	M	Madopar: 200 mg levodopa (4 × 12.5 mg/50 mg) Rasagiline 1 mg	300	2	L
7	68	M	Madopar: 400 mg levodopa (4 × 25 mg/100 mg) Rasagiline 1 mg Repinex 8 mg	660	8	L
8	58	F	Madopar: 300 mg levodopa (3 × 25 mg/100 mg) Mirapexin 0.26 mg	326	6	L
9	72	M	Selegiline 5 mg Sinemet: 500 mg levodopa (5 × 25 mg/100 mg) ReQuipXL 12 mg Amantadine 300 mg	1090	13	L
10	79	M	Rasagiline 1 mg Ropinirole 8 mg	260	6	R
11	74	M	Stalevo: 700 mg levodopa (3 × 200 mg/50 mg/200 mg, 1 × 100 mg/25 mg/200 mg) Amantadine 300 mg Rotigotine 16 mg	1711	14	L
12	64	M	Mirapexin 1.56 mg	156	3	L
13	67	M	Rotigotine 8 mg Rasagiline 1 mg Madopar: 400 mg levodopa (4 × 25 mg/100 mg) Entacapone 800 mg	1804	10	R
14	67	M	Rasagiline 1 mg Pramipexole 2.1 mg Sinemet: 300 mg levodopa (3 × 25 mg/100 mg)	610	4	R
15	61	F	None	N/A	3	L
16	59	M	Rasagiline 1 mg	100	1	R
17	56	F	Rasagiline 1 mg Sinemet: 100 mg levodopa (1 × 25 mg/100 mg) Stalevo: 250 mg levodopa (3 × 50 mg/12.5 mg/200 mg 1 × 100 mg/25 mg/200 mg) Ropinirole 12 mg Rotigotine 6 mg	773	5	L
18	75	M	Madopar: 500 mg levodopa (5 × 25 mg/100 mg)	680	3	L
19	62	F	Sinemet: 150 mg levodopa (3 × 12.5 mg/50 mg)	150	0.33	L
20	58	M	Sinemet: 150 mg levodopa (3 × 12.5 mg/50 mg)	150	1	L
21	70	M	Sinemet: 400 mg levodopa (4 × 25 mg/100 mg)	400	4	L
22	59	F	Ropinirole 12 mg Sinemet: 400 mg levodopa (4 × 25 mg/100 mg)	640	7	L
23	69	M	Madopar: 150 mg levodopa (3 × 12.5 mg/50 mg)	150	0.5	L
24	62	M	Madopar: 700 mg levodopa (6 × 25 mg/100 mg, 1 × 25 mg/100 mg CR) Ropinirole 16 mg	1020	6	R
25	63	M	Requip 10 mg	200	1	L
26	61	F	Ropinirole 8 mg Madopar: 400 mg levodopa (8 × 12.5 mg/50 mg)	560	4	L
27	54	M	Madopar: 400 mg levodopa (4 × 25 mg/100 mg) Selegiline 25 mg	650	1	L
28	73	M	Sinemet: 400 mg levodopa (4 × 25 mg/100 mg)	400	8	R

LEDD = levodopa equivalent daily dose; M = male; F = female; CR = continuous release; L = left; R = right; N/A = not applicable.

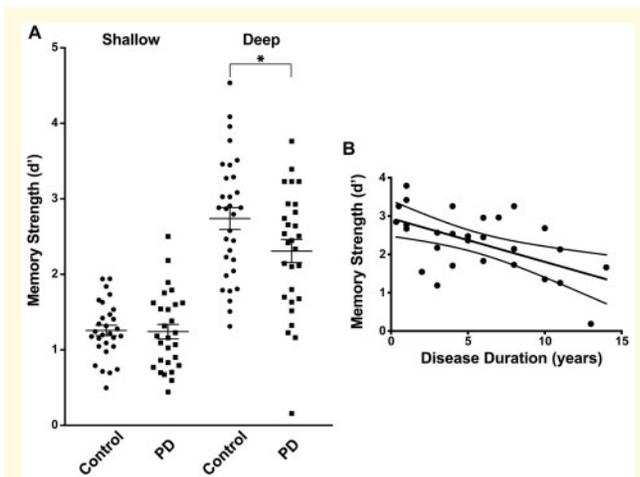


Figure 3 Memory performance. (A) Memory performance during encoding conditions illustrating greater memory strength during deep-semantic encoding for healthy controls ($N = 31$) compared with Parkinson's disease participants ($N = 28$). Error bars denote standard error of the mean. $*P < 0.05$. (B) Correlation between deep encoding memory performance and disease duration for Parkinson's disease participants ($P = 0.002$).

greater beta power decreases during deep-semantic encoding of subsequently remembered words (Hits) compared with Parkinson's disease participants (cluster stat = -150.1 , $P = 0.014$; Fig. 4A and B shows beta power decreases for electrodes in significant cluster); however, no difference between groups emerged during shallow-non-semantic encoding (cluster stat = -3.7 , $P = 0.326$; Fig. 4C and D shows beta power decreases for electrodes in largest cluster that did not reach significance). A mixed-effects RM ANOVA on averaged beta (over 0–1.5 s, 12–20 Hz) further supported this finding by producing a significant encoding \times group interaction ($F_{1, 54} = 6.959$, $P = 0.011$) that confirms the difference between groups in deep-semantic encoding ($t_{54} = 2.910$, $P = 0.005$) is significantly different to shallow-non-semantic encoding ($t_{54} = 1.030$, $P = 0.307$). There were no main effects of encoding ($F_{1, 54} = 0.612$, $P = 0.437$) or group ($F_{1, 54} = 3.946$, $P = 0.052$). Therefore, a difference between decreases in beta power across groups is seen only in the deep-semantic-encoding condition, indicating that there is a deficit when decreasing beta power in the Parkinson's disease group that occurs specifically during deep-semantic processing.

Cluster-based permutation testing on all electrodes in the alpha and theta frequency ranges showed no significant between-group differences in power (alpha: cluster stat = -8.9 , $P = 0.219$; theta: no significant clusters were identified). This confirms that our between-group differences detailed above are specific to the beta frequency range.

The relationship between decreases in beta power and the deep-semantic-encoding condition is reinforced by the

similar pattern of beta power seen during the encoding of words that were not successfully remembered (M). M in controls were associated with greater decreases in beta power during deep-semantic encoding when compared with Parkinson's disease participants (cluster stat = -54.1 , $P = 0.031$); however, no difference between groups emerged during shallow-non-semantic encoding (cluster stat = -3.8 , $P = 0.330$). A mixed-effects RM ANOVA similarly produced main effects of encoding ($F_{1, 54} = 5.450$, $P = 0.023$) and group ($F_{1, 54} = 6.155$, $P = 0.016$) and a significant encoding \times group interaction ($F_{1, 54} = 5.975$, $P = 0.018$). The interaction confirms the difference between groups in deep-semantic encoding ($t_{54} = 3.367$, $P = 0.001$) is significantly different to shallow-non-semantic encoding ($t_{54} = 0.919$, $P = 0.362$). The fact that a difference in beta power is seen between groups during encoding of both remembered and forgotten items implies the difference is related to deep-semantic processing in general. This overall reduction in beta power modulation and thereby impaired deep-semantic processing may lead to reduced memory performance in Parkinson's disease participants.

Successful memory formation specifically involving deep-semantic processing was associated with greater reductions in beta power. Within groups, controls demonstrated greater decreases in beta power for subsequently remembered words during deep-semantic compared with shallow-non-semantic encoding (cluster stat = -94.4 , $P = 0.012$; Fig. 4E and F shows beta power decreases for electrodes in significant cluster). Interestingly, at a group level, Parkinson's disease participants did not show significantly greater reductions in beta power in deep-semantic encoding compared with shallow-non-semantic (no significant clusters were identified), although they did show a behavioural benefit of deep-semantic encoding, albeit to a lesser extent than controls. Based on findings of left IFC beta being specifically linked to memory strength in healthy controls (Hanslmayr *et al.*, 2009, 2011; Meeuwissen *et al.*, 2011), we did an additional correlational analysis focusing on left frontal beta in Parkinson's disease patients. Despite no group-level effect, linear regressions illustrated that Parkinson's disease participants who showed greater beta power decreases over left frontal electrodes also had significantly greater memory strength during deep-semantic encoding ($P = 0.008$, $R^2 = 0.256$, Fig. 5A) but that disease duration negatively correlated with left frontal maximum decreases in beta power ($P = 0.007$, $R^2 = 0.263$, Fig. 5B). Parkinson's disease participants earlier in the disease who were able to achieve greater reductions in beta power in left frontal electrodes benefited more from deep-semantic-encoding strategies of memory formation.

The secondary dependent measure was the SME in beta power, which compared power between Hit (i.e. subsequently remembered with high or low confidence) and M (i.e. subsequently forgotten) trials (Brewer *et al.*, 1998; Otten *et al.*, 2001; Hanslmayr *et al.*, 2009). This

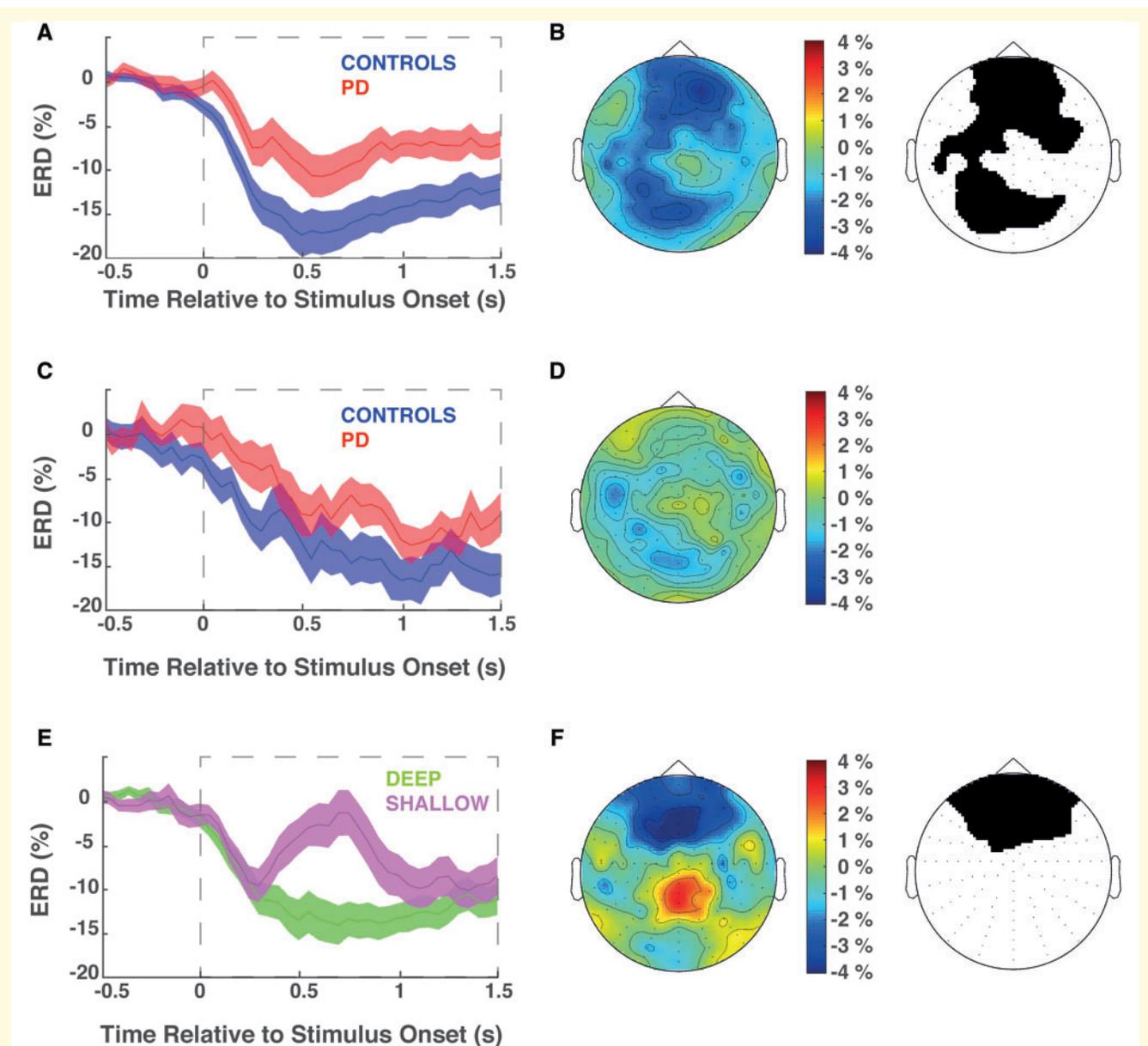
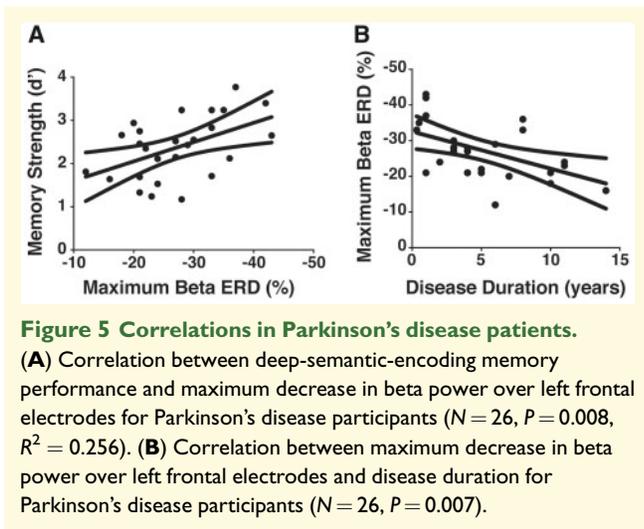


Figure 4 Event-related decreases in beta power. Average beta (12–20 Hz) event-related power decrease for electrodes in significant and/or largest cluster identified during cluster-based statistical analysis. *Top row*: between-group differences during deep-semantic encoding of remembered words; *middle row*: between-group differences during shallow-non-semantic encoding of remembered words; *bottom row*: differences within healthy participants between deep-semantic and shallow-non-semantic encoding of remembered words. Grey dashed squares indicate time window used in statistical analysis to identify significant electrode clusters over 12–20 Hz. Time course of decreases in beta power averaged over electrodes contributing to significant and/or largest cluster during encoding of subsequently successfully remembered words for controls (blue, $N = 30$) compared with Parkinson's disease participants (red, $N = 26$) in the deep-semantic-encoding (A) and shallow-non-semantic-encoding (C) conditions. A power decrease is denoted with negative values. Only deep-semantic encoding showed a significant difference between groups (electrodes contributing to significant cluster black in B). Topographical maps show the location of the differences in beta power decreases between groups in deep (B) and shallow (D) encoding, with colder colours indicating significantly greater decreases in beta power in controls compared with Parkinson's disease participants. Cluster shown for shallow-non-semantic encoding in C and D did not reach significance. (E) Time course of beta power decrease averaged over electrodes contributing to significant cluster during encoding of subsequently successfully remembered words for deep-semantic (green) compared with shallow-non-semantic encoding (magenta) in controls. A power decrease is denoted with negative values. Only controls showed a significant difference between encoding conditions (electrodes contributing to significant cluster black in F). Topographical map in F shows the location of differences in beta power decreases between encoding conditions, with colder colours indicating significantly greater reductions in beta power in deep-semantic compared with shallow-non-semantic encoding. No cluster identified between encoding conditions for Parkinson's disease patients.



categorization in the 'encoding stage' depended on the participant's response in the 'recognition stage' and their individualized receiver operating characteristic curves (Hanslmayr *et al.*, 2009). A minimum of five trials was required for Hits and M, resulting in $N = 27$ for controls and $N = 25$ for Parkinson's disease participants in the SME analysis. The SME results broadly replicated a number of previous findings (Hanslmayr *et al.*, 2009, 2011; Meconi *et al.*, 2016) and further support the importance of decreases in beta power as the mechanism underlying successful memory formation through deep-semantic-encoding strategies: there was a significant SME in deep-semantic encoding for controls (cluster stat = -39.8 , $P = 0.037$, Fig. 6A and B illustrates beta power decreases for electrodes in significant cluster) and Parkinson's disease participants (cluster stat = -78.7 , $P = 0.008$; Fig. 6C and D illustrates beta power decreases for electrodes in significant cluster). Importantly, there was no significant SME associated with shallow-non-semantic encoding (controls: cluster stat = -14.6 , $P = 0.182$; Fig. 6E and F illustrates beta power decreases for electrodes in largest cluster that did not reach significance; Parkinson's disease: cluster stat = -2.0 , $P = 0.755$; Fig. 6G and H illustrates beta power decreases for electrodes in largest cluster that did not reach significance). A mixed-effects RM ANOVA showed a main effect of encoding ($F_{1, 54} = 17.389$, $P < 0.001$), confirming that deep-semantic encoding produced a greater average SME ($-5 \pm 1\%$) compared with shallow-non-semantic encoding ($0.3 \pm 0.7\%$). There was no main effect of group ($F_{1, 54} = 0.221$, $P = 0.640$) or encoding \times group interaction ($F_{1, 54} = 0.073$, $P = 0.788$). The lack of an interaction indicates that, although Parkinson's disease participants remembered fewer items than controls following deep-semantic encoding, the remembered items in both groups were accompanied by similar electrophysiological signatures (i.e. SME) and, in both cases, they lead to the same

behavioural outcome—that of remembering (i.e. d' above zero).

Discussion

The study confirmed our preregistered hypotheses and produced several novel findings that provide the first evidence of impaired modulation of beta power being associated with a non-motor symptom of Parkinson's disease. Parkinson's disease participants showed impaired memory strength compared with healthy controls but only following deep-semantic encoding of words. This behavioural finding was mirrored by the EEG results which demonstrated that Parkinson's disease participants exhibited reduced beta power decreases compared with healthy controls but again only during deep-semantic processing. Furthermore, a correlation between disease duration and an increased deficit in deep-semantic encoding suggested that the neuropathology of Parkinson's disease has a specific detrimental effect on the mechanisms underlying deep-semantic information processing leading to both reduced beta power decreases and reduced memory strength. This is reinforced by that fact that participants with Parkinson's disease who showed greater beta power decreases over left frontal electrodes benefited to a greater extent from the deep-semantic-encoding memory strategy. There were no differences between the groups in age, global cognitive function, education or perception during encoding that could explain these behavioural or EEG results. Therefore, our results appear to be specific to deep-semantic processing. Overall, our findings strengthen the idea that dysfunctional beta oscillations are likely to be the cause of Parkinson's disease symptoms in both motor and non-motor domains.

Parkinson's disease did not cause impaired memory performance in general, but rather a specific deficit in deep-semantic encoding of memory. Deep-semantic encoding in the context of the current study utilized general knowledge about the word to form an abstract representation and evaluate the representation as animate or inanimate. Age-related memory decline is a widely acknowledged fact that is seen across several subdomains, including episodic memory (e.g. see Shing *et al.*, 2010). Over and above the aging-related decline, a further decline in episodic memory resulting from deep-semantic encoding appeared to be caused by the mechanisms underlying Parkinson's disease. Replicating previous findings, Parkinson's disease participants were able to employ the non-semantic-encoding strategy to build a memory trace of equivalent strength to controls (Cohn *et al.*, 2010). The difference in memory performance between groups was only elucidated following a deep-semantic-encoding instruction. In contrast to Cohn *et al.* (2010), the current Parkinson's disease participants still showed a behavioural benefit from the deep-semantic-encoding

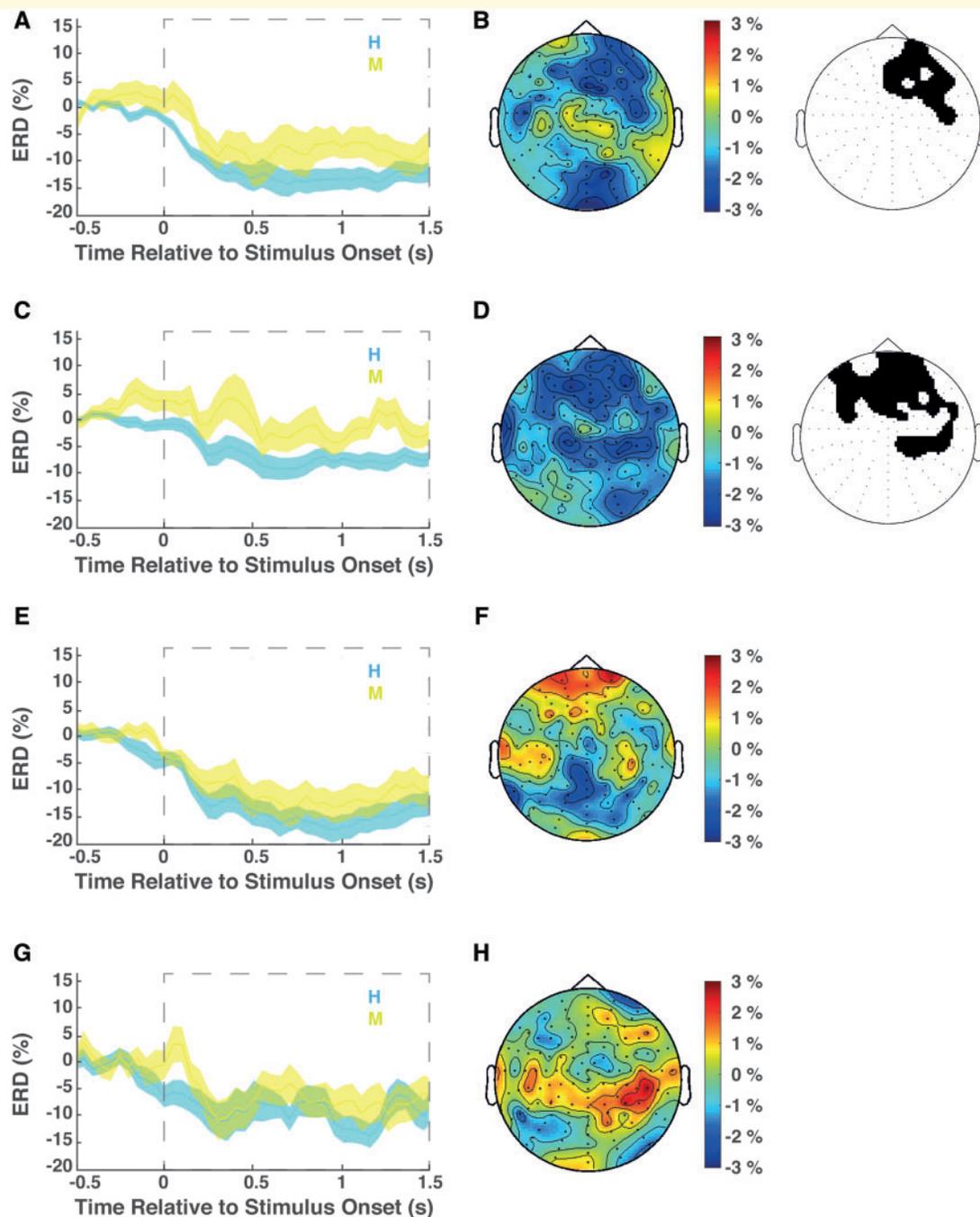


Figure 6 Subsequent-memory effects. Average beta (12–20 Hz) event-related power decreases for electrodes in significant and/or largest cluster identified during cluster-based statistical analysis. *Top row*: differences within healthy participants between remembered and forgotten words during deep-semantic encoding; *second row*: differences within Parkinson's disease participants between remembered and forgotten words during deep-semantic encoding; *third row*: differences within healthy participants between remembered and forgotten words during shallow-non-semantic encoding; *bottom row*: differences within Parkinson's disease participants between remembered and forgotten words during shallow-non-semantic encoding. Grey dashed squares indicate time window used in statistical analysis to identify significant electrode clusters over 12–20 Hz. Time course of decrease in beta power averaged over electrodes contributing to significant and/or largest cluster during Hit (H, cyan) compared with M (yellow) trials in deep encoding for controls (A, N = 27) and Parkinson's disease participants (C, N = 25). Both groups demonstrated greater reductions in beta power during encoding of subsequently remembered (H) compared with forgotten (M) words, but only the clusters in deep-semantic encoding reached significance (electrodes contributing to significant cluster black in B and D). Topographical maps show the location of differences in beta power decrease between words in deep-semantic encoding for controls (B) and Parkinson's disease patients (D), with colder colours indicating greater reductions in beta power for remembered compared with forgotten words. Time course and location of decreases in beta power averaged over electrodes contributing to largest, non-significant cluster during H (cyan) compared with M (yellow) trials in shallow-non-semantic encoding for controls (E and F, N = 27) and Parkinson's disease participants (G and H, N = 25).

memory strategy and those who were less progressed in the disease benefited to a greater degree. People with Parkinson's disease struggle to spontaneously implement the optimal memory encoding strategy (Knobe *et al.*, 1998). However, with explicit encoding instructions, Parkinson's disease participants managed to improve memory with the optimal deep-semantic-encoding strategy, albeit to a lesser degree than controls. This finding suggests that they are able to recruit the neural mechanisms to process semantic information about the words in the deep encoding condition, but something prevents the level of processing reaching that of controls and reduces memory strength. This finding is in line with other behavioural evidence of impaired semantic processing in Parkinson's disease (Cousins and Grossman, 2017). Overall, people with Parkinson's disease exhibited a limited deep-semantic processing capacity during memory encoding rather than a general deficit in recognition memory.

The deficit in episodic memory performance following a deep-semantic-encoding strategy displayed by Parkinson's disease participants was associated with a reduced dynamic range of beta power during encoding. Brain oscillations are considered one of the core neural mechanisms for the storage and retrieval of long-term memories (Buzsaki and Draguhn, 2004; Fell and Axmacher, 2011) and the extent of decreases in neural oscillations is thought to relate to the degree of information stored in the brain (Hanslmayr *et al.*, 2012). In the current study, the greater level of beta power decreases for deep-semantic versus shallow-non-semantic encoding and words that were subsequently remembered compared with those that were not further support the importance of decreases in beta power as the mechanism underlying successful deep-semantic memory formation (Sederberg *et al.*, 2006; Hanslmayr *et al.*, 2009, 2011; Meeuwissen *et al.*, 2011; Meconi *et al.*, 2016). As both groups displayed similar behavioural outcomes of deep-semantic encoding (i.e. d' values above zero, although Parkinson's disease participants remembered fewer items than controls), it is not surprising that both groups displayed similar electrophysiological differences between Hit and M trials (i.e. an SME). Importantly, however, overall decreases in beta power were significantly reduced in Parkinson's disease participants compared with controls during deep-semantic processing, but not for words encoded with a shallow-non-semantic strategy. This distinction implies that a reduced capacity to decrease beta power following stimulus presentation for Parkinson's disease participants reduced the effectiveness of semantic processing, leading to fewer successfully recognized words and a lower d' value.

It has been proposed that the relative change in pre- to post-stimulus power is most important for memory performance, rather than absolute power levels (Klimesch *et al.*, 2003; Klimesch *et al.*, 2006). Parkinson's disease participants demonstrated decreases in the reactivity of

their event-related beta power and therefore reduced encoding capacity. Parkinson's disease participants who were further progressed in the disease demonstrated further reductions in both beta reactivity and memory strength. A reduced dynamic range of BG–thalamocortical beta power in Parkinson's disease can therefore interfere with other neural mechanisms that operate in the beta frequency range apart from movement, including memory formation.

The neural changes causing episodic memory deficits in Parkinson's disease may be the same as those underlying motor symptoms. Memory formation recruits an extensive network of mainly left-lateralized regions for verbal material. This network includes the anterior temporal lobe for storage of conceptual representations and processing concepts at an abstract level (Jefferies and Lambon Ralph, 2006; Patterson *et al.*, 2007) and the IFC and temporoparietal region for strategic search and control processes that are necessary for semantic processing (Jefferies and Lambon Ralph, 2006; Binder *et al.*, 2009; Jefferies, 2013). The extent of beta power decreases in left prefrontal cortex, specifically IFC, has been linked to memory performance (Hanslmayr *et al.*, 2009, 2011). Function of the prefrontal cortex is heavily influenced by the integrity of dopaminergic input onto frontostriatal connections. Therefore, it is not surprising that dopaminergic dysfunction seen in Parkinson's disease leads to impaired IFC function, observed in motor tasks that recruit the right IFC as part of the response inhibition network (Gauggel *et al.*, 2004; Bokura *et al.*, 2005; Obeso *et al.*, 2011; Swann *et al.*, 2011). We have extended these findings to also show impairment during a memory task that has been shown to recruit the left IFC during deep-semantic encoding. Previous studies have highlighted the ability of BG oscillatory activity to influence cortical neuronal oscillations recorded with surface EEG (Horschig *et al.*, 2015; Chung *et al.*, 2018). We therefore propose that the same pathological BG beta mechanism causing the motor symptoms in Parkinson's disease is contributing to the deficit in deep-semantic encoding of memory seen in the current study. This would imply a common neural mechanism may underlie a variety of deficits in Parkinson's disease that involve cortico-BG processes, which operate predominantly in the beta frequency range.

Identifying a common neural mechanism behind the motor and non-motor symptoms of Parkinson's disease has implications for treatment and disease monitoring. There are currently no standard treatment options for mild memory and cognitive problems in Parkinson's disease (i.e. mild cognitive impairment). Applying interventions previously shown to decrease exaggerated beta activity such as deep brain stimulation or dopamine replacement therapy (Ray *et al.*, 2008; Eusebio *et al.*, 2011) should in theory also help with memory deficits caused by the same pathology. Considering the inverse relationship demonstrated in the current study between

disease progression and both memory performance and decreases in beta power, it is feasible that this memory paradigm could be developed as a useful surrogate to measure functional beta reactivity. As such, the paradigm could be used as a new and convenient behavioural test to monitor disease progression, with specific applications in telemedicine.

It is important to note that, while we present findings that the neural changes causing episodic memory deficits in Parkinson's disease may resemble those underlying motor symptoms, we do not posit that reduced beta reactivity is the sole deficit that emerges in Parkinson's disease. Nor, in fact, that there is a single source of beta that homogenizes symptomology across domains (Spitzer and Haegens, 2017). Instead, we extend the impact of a deficit that has been identified in the motor domain to other (cognitive) areas. This will likely explain some symptoms well, but not all, and should be a consideration when titrating medications to alleviate different aspects of motor and/or cognitive performance. It is important to make this distinction as we are not claiming that beta observed in the motor system directly influences memory encoding—but that beta in memory-relevant areas is also deficient and, while these rhythms are likely to serve a similar functional role, deficits may indeed be graded across functional areas. Hence, motor deficits and memory deficits may be differentially influenced depending on the underlying pathophysiological state.

There are a few limitations to the current study that should be considered. First, the relationship between beta power and the behavioural deficit in the Parkinson's disease group is correlational. However, it is the more parsimonious explanation that a common underlying neurological deficit (i.e. impaired modulation of beta power) causes both motor and memory problems than two unrelated behavioural symptoms producing the same epiphenomenon in the beta system. Furthermore, evidence exists for a causal relationship between the strength of beta power decreases in left prefrontal cortex and memory performance (Hanslmayr *et al.*, 2014) so the direct relationship shown in the current study would support a causal role of pathological beta in Parkinson's disease symptomology. Extending the findings from Hanslmayr and colleagues, future studies could use transcranial magnetic stimulation to modulate left prefrontal beta in people with Parkinson's disease and look for a causal influence on their episodic memory performance. Second, beta power modulation also plays a role in memory retrieval (Dujardin *et al.*, 1994; Duzel *et al.*, 2003) and people with Parkinson's disease are thought to use inefficient retrieval strategies (Zakzanis and Freedman, 1999). However using recognition, which is one of the simplest ways to test episodic memory, greatly reduced retrieval demands in our task, e.g. compared with free or cued recall. A retrieval based explanation for our behavioural findings is therefore rather unlikely. Nevertheless, we cannot completely discount the contribution of impaired beta

power decreases during retrieval to the reduced recognition memory performance in our study.

Despite displaying topographical maps in an effort to show the location of beta power differences between groups, the methods used in the current study cannot be used to form a robust conclusion about spatial differences in beta power modulation. The location of beta differences in deep-semantic encoding between patients and healthy participants seemed to indicate a widespread cortical deficit in beta power modulation in Parkinson's disease patients, which included the left frontal region. This widespread difference is in contrast to, for example more focal differences in beta power decreases for healthy participants between deep-semantic and shallow-non-semantic encoding. However, scalp-level EEG has limited spatial resolution. Subsequent studies using magnetoencephalography with a much higher spatial resolution would be needed to investigate these results further. Finally, when considering the generalizability of our results, it is worth noting that the Parkinson's disease patients in the current study were mild to moderately impaired in terms of disease severity. Our study therefore cannot directly speak to the relationship between memory impairments and beta oscillations in severely affected Parkinson's disease patients. However, our findings of an inverse relationship between disease duration and both memory performance and beta activity speaks to a general characterization that will likely extend (alongside other age-related factors) to those severely impaired patients.

Conclusion

This study provides the first evidence of impaired beta modulation being associated with a non-motor symptom of Parkinson's disease. Parkinson's disease participants showed impaired memory strength and decreases in beta power compared with healthy controls during deep-semantic encoding. The neuropathology of Parkinson's disease seemed to have a specific detrimental effect on the mechanisms underlying episodic memory formation in a deep-semantic-encoding task leading to both reduced memory strength and reduced beta modulation. We propose that the neural changes causing memory deficits in Parkinson's disease may be the same as those underlying motor symptoms, i.e. impaired modulation of beta activity within BG–thalamocortical circuitry. Importantly, the decrease in beta modulation shown in our study cannot be explained away as an epiphenomenon that scales with decreased movement in Parkinson's disease. Our findings strengthen the idea that dysfunctional beta oscillations are causal in Parkinson's disease symptomology and extend their implications to non-motor symptoms of the disease.

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Competing interests

The authors declare no competing financial interests or other conflicts of interest.

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