NEURAL SIGNATURES OF PREDICTIVE LANGUAGE PROCESSING IN PARKINSON'S DISEASE WITH AND WITHOUT MILD COGNITIVE IMPAIRMENT

RUNNING TITLE: PREDICTIVE LANGUAGE PROCESSING IN PARKINSON'S DISEASE

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Abstract

Cognitive deficits are common in Parkinson's disease (PD), with some PD patients meeting criteria for mild cognitive impairment (MCI). An unaddressed question is whether linguistic prediction is preserved in PD. This ability is nowadays deemed crucial in achieving fast and efficient comprehension, and it may be negatively impacted by cognitive deterioration. To fill this gap of knowledge, we used event-related potentials (ERPs) to evaluate mechanisms of linguistic prediction in a sample of PD patients (on dopamine compensation) with and without MCI. To this end, participants read sentence contexts that were predictive or not about a sentence-final word. The final word appeared after 1 second, matching or mismatching the prediction. The introduction of the interval allowed to capture neural responses both before and after sentence-final words, reflecting semantic anticipation and processing. PD patients with normal cognition (N = 58) showed ERP responses comparable to those of matched controls. Specifically, in predictive contexts, a slow negative potential developed prior to sentence-final words, reflecting semantic anticipation. Later, expected words elicited reduced N400 responses (compared to unexpected words), indicating facilitated semantic processing. PD patients with MCI (N = 20) showed, in addition, a prolongation of the N400 congruency effect (compared to matched PD patients without MCI), indicating that further cognitive decline impacts semantic processing. Finally, lower verbal fluency scores correlated with prolonged N400 congruency effects and with reduced pre-word differences in all PD patients (N = 78). This relevantly points to a role of deficits in temporal-dependent mechanisms in PD, besides prototypical frontal dysfunction, in altered semantic anticipation and semantic processing during sentence comprehension.

1. Introduction

Parkinson's disease (PD) is a chronic, neurodegenerative disorder that, in addition to motor defects, involves difficulties in a variety of cognitive domains, including executive functions, visuospatial skills, memory or language (Kudlicka, Clare & Hindle, 2011; Muslimovic, Post, Speelman, & Schmand, 2005, Pell & Monetta, 2008). These deficits tend to progress in severity and meet criteria for mild cognitive impairment (PD-MCI) in up to 40% of patients within the first 5 years of disease (Aarsland et al., 2010; Litvan et al., 2011). The development of PD-MCI is a robust predictor of further conversion to dementia (PDD). However, the pattern of progression of PD-MCI and the rate of conversion to PDD is highly variable between patients. Among the several cognitive phenotypes characterizing PD-MCI, changes in visuoperceptive skills, language production and comprehension, and semantic and episodic memory have been highlighted to better predict conversion to PDD than deficits mostly ascribed to frontal-executive dysfunction (Horta-Barba et al., 2020; Martínez-Horta & Kulisevsky, 2019; Lang et al., 2019). Yet, the mechanisms underlying deficits in language comprehension in PD and PD-MCI have been scarcely studied.

An aspect of language comprehension that has not been evaluated in PD is predictive language processing, which plays an important role in achieving fast and efficient language processing (Kutas & Federmeier, 2011). Accordingly, readers and listeners probabilistically infer and pre-activate different aspects of upcoming words (e.g., van Berkum, Brown, Zwitzerlood, Kooijman & Hagoort, 2005; Wicha, Bates, Moreno & Kutas, 2003). Much evidence of language prediction has been derived from the N400 event-related potential (ERP) component, an index of semantic processing (Kutas & Hillyard, 1980). The N400, a negativity peaking ~400 ms after word onset, is reduced for words that are more predictable in a given context (N400 context effect) (Kutas & Hillyard, 1984), which is considered to reflect facilitated semantic processing owing to the prediction of the word or some of its semantic features (Federmeier & Kutas, 1999). Most relevantly, recent research has shown that processing differences arise even before the word is presented. In particular, prediction negative potentials (PNP) – sustained, slow cortical potentials consistent with semantic anticipation – precede sentence-final words in predictive contexts, eliciting larger amplitudes before words that are strongly expected in a given context (e.g., before "ball" in "The goalkeeper managed to catch the… ball") (León-Cabrera, Rodríguez-Fornells &

Morís, 2017; León-Cabrera, Flores, Rodríguez-Fornells & Morís, 2019; Grisoni, Miller & Pulvermüller, 2017; for a review, see Pullvermüller & Grisoni, 2020).

Importantly, prior research suggests that linguistic prediction is reduced in populations with limited cognitive resources (Federmeier, McLennan, De Ochoa & Kutas, 2002; Federmeier & Kutas, 2005; Federmeier, Kutas & Schul, 2010; Payne & Federmeier, 2008; Wlotko & Federmeier, 2012; for reviews, see Payne & Silcox, 2019; Huettig, 2015). For instance, older adults seem to take less advantage of semantically rich contexts to facilitate subsequent processing (Federmeier & Kutas, 2005) and those with lower verbal fluency scores exhibit diminished or absent ERP effects associated with prediction, suggesting the adoption of a 'wait-and-see', incremental processing strategy instead (Federmeier et al., 2002). As previously stated, PD involves significant impairments in cognitive capacities including executive functions and working memory (WM), which may secondarily impact language comprehension in these patients (Grossman et al., 2002). Thus, we hypothesized that predictive language processing could be impaired in PD, especially in those individuals with worse cognitive status, as is the case of those with PD-MCI. In addition, there is behavioral evidence suggesting that PD patients have difficulties using lexical and sentential information to selectively activate appropriate meanings (Copland, Chenery & Murdoch, 2000a; Copland, Chenery & Murdoch, 2000b; Copland, Chenery & Murdoch, 2001; Copland, Sefe, Ashley, Hudson & Chenery, 2009). Also, several studies have pointed to slower or delayed lexical and semantic activation in PD (Arnott, Chenery, Murdoch & Silburn, 2001; Angwin, Chenery, Copland, Murdoch, & Silburn, 2005), including research focused upon N400 effects (Angwin et al., 2017a; but see, Friederici, Kotz, Werheid, Hein & von Cramon, 2003; Angwin, Dissanayaka, McMahon, Silburn, Copland, 2017b). These deficits in lexical and semantic processing could also hinder the ability to appropriately use sentence contexts to guide and activate representations ahead of time during sentence comprehension.

To address this, the current study investigated ERP signatures of semantic prediction and semantic processing in PD with normal cognition (PD-NC) and in PD with MCI, as well as in a group of control participants matched in age, gender and education. We presented sentence contexts that were predictive or not of a sentence-final word that was delayed by 1 s (see **Table 2**), thus allowing to capture the abovementioned ERP signatures in the anticipatory and processing

stages of prediction. In predictive contexts, half of the final words were semantically incongruent, thus representing a prediction mismatch.

Following previous studies in healthy adult population (León-Cabrera et al., 2017; 2019), we hypothesized that controls would anticipate the final word after predictive contexts, as indexed by the development of a PNP in the anticipatory stage. In PD-NC and PD-MCI, potential failure to anticipate would be reflected in a comparatively reduced or absent PNP. In the processing stage, after the presentation of the final word, we expected controls to exhibit canonical N400 context effects, consistent with facilitated processing of congruent words due to prediction (Kutas & Federmeier, 2011). On the other hand, if PD patients adopt a more incremental strategy for comprehension, they might still exhibit N400 context effects because, even in the absence of prediction, congruent words are easier to integrate than incongruent words. However, compared to controls, the magnitude of the effect or its onset latency might be delayed, reflecting more difficult or slower semantic processing compared to controls, who would benefit from prediction. Lastly, following prior findings in older adults (Federmeier et al., 2002), we explored whether the targeted ERP signatures of linguistic prediction were reduced or diminished in PD patients with lower verbal fluency scores.

2. Materials and Methods

No part of the study procedures or analyses was pre-registered prior to the research being conducted. In the following sections, we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1.Participants

Participants were prospectively recruited from a sample of outpatients regularly attending the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau (Barcelona, Spain). They were invited to participate in a longitudinal study involving comprehensive neuropsychological testing and two EEG recording sessions (one at baseline and a follow-up after 1 year). Healthy adults were also invited to participate in the study to serve as controls. The current study focused on the data collected in the baseline session. The project was approved by the research ethics committee of

the Hospital de la Santa Creu i Sant Pau. Before inclusion, written informed consent was obtained from all the participants.

The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author. Access can be granted only to qualified researchers under a collaboration agreement with the corresponding author and in accordance with ethical procedures governing the reuse of clinical data, including the completion of a formal data sharing agreement and approval of the local ethics committee.

2.2.Clinical and cognitive testing

PD patients had been diagnosed by a neurologist with expertise in movement disorders. All patients accomplished steps 1 and 2 of the UKPDSBB criteria, and three or more of the four first supportive positive criteria of step 3 (Hughes et al., 1992). Motor status and stage of illness were assessed by the MDS-UPDRS-III and Hoehn & Yahr scales (Goetz et al., 2008). Demographic variables including age, gender, years of formal education, disease onset, medication history, as well as the levodopa equivalent daily dosage (LDD) (Tomlinson et al., 2010) were collected for all patients (**Table 1**). All participants were classified as having either normal cognition or MCI based on their score in the Parkinson's Disease - Cognitive Rating Scale (PD-CRS) (Pagonabarraga et al. 2008). A cut-off score of ≤ 83 was used to classify patients as PD-MCI (Fernández de Bobadilla et al. 2013). Participants with dementia were excluded according to the MDS diagnostic criteria for PD with dementia (Emre et al., 2007). In PD patients, cognition was examined during the 'on' state, and all participants were on stable doses of dopaminergic drugs during the 4 weeks before inclusion.

In addition, all participants completed standardized semantic and phonological verbal fluency tests (Peña-Casanova et al., 2009). In these tests, they were asked to name as many animals (semantic verbal fluency) or words beginning with the letter P (phonological verbal fluency) as possible in 1 minute. For each participant, total verbal fluency scores were obtained by averaging the direct scores in the semantic and phonological fluency tests (for another study using total verbal fluency scores, see Federmeier et al., 2002).

Legal copyright restrictions prevent public archiving of the neuropsychological tests used, which can be obtained from the copyright holders in the cited references.

2.3.Final samples.

A total of 135 participants completed the baseline EEG recording session. Of those participants, 102 were PD patients and 33 were healthy controls. The data of some participants were excluded because the files were corrupt (n = 3) or their recordings were excessively noisy (n = 4) as determined by visual inspection of the raw data, leaving 128 participants available for analyses. From the remaining participants, 97 were PD patients and 31 were controls. Controls were excluded if they had mild cognitive impairment (n = 3) or their cognitive status was not available (n = 2). Lastly, participants with less than 20 available trials in any condition after EEG preprocessing (n = 9) were also excluded from the analyses (see EEG preprocessing section for more information about the artefact detection and rejection procedure).

The final pool of data consisted of 88 PD patients and 26 controls, from which matched samples were subsequently obtained to perform the following comparisons according to the goals of the present study: 1) PD patients with normal cognition (PD-NC) (N = 58) with an age-, gender- and education-matched Control group (N = 24), and 2) a subsample of Parkinson's disease patients with normal cognition (sPD-NC) (N = 19) with an age-, gender-, education- and years of disease's evolution-matched PD patients with mild cognitive impairment (PD-MCI) (N = 20). To avoid the comparison of patients classified as sPD-NC and PD-MCI but having similar PD-CRS total score, we selected participants with PD-CRS scores of < 75 for the PD-MCI group and of > 85 for the sPD-NC.

The demographic and clinical features of the final samples are reported in Table 1. Controls and PD-NC patients did not differ in age ($t(1,80) = –0.90$, $p = .37$, 95% CI [–5.19, 1.95]), education ($t(1,80) = 1.20$, $p = .23$, 95% CI [–0.84, 3.43]), gender ($X^2(1, 82) = .853$, $p = .35$), or verbal fluency scores ($t(1,80) = 1.73$, $p = .08$, 95% CI [–0.23, 3.53]). They differed in PD-CRS total score ($t(1,80) = –2.57$, $p = .01$, 95% CI [–11.41, –1.46]), but both groups were above the established score cut-off of 83 for PD-MCI diagnosis. Likewise, sPD-NC and PD-MCI patients did not differ in age ($t(1,37) = –1.23$, $p = 0.22$, 95% CI [–3.89, .94]), education ($t(1,37) = –1.30$, $p = 0.22$, 95% CI [–1.30, 5.34]), gender ($X^2(1, 39) = .033$, $p = .855$), disease's duration ($t(1,37) = –0.53$, $p = .59$, 95% CI [–2.84, 1.65]) or levodopa equivalent daily dose ($t(1,37) = –1.74$, $p = .09$, 95% CI [–293.94, 22.64]), but differed in PD-CRS total score ($t(1,37) = 12.96$, $p < .001$, 95% CI [26.2, 35.91]) and

total verbal fluency scores (t(1,37) = 6.59, p <.001, 95% CI [4.92, 9.29]). For all comparisons, equal variances were assumed based on null results in Levene's test.

Table 1. Demographics and clinical features of the patient and control samples.

	Control	**PD-NC**	P	**sPD-NC**	**PD-MCI**	P
N	24	58		19	20	
Age (years)	62.85 (6.82) [59.9, 65.7]	64.47 (7.61) [62.4, 66.4]	.37	70.75 (2.70) [69.4, 72]	72.22 (4.48) [70.1, 74.3]	.22
Education (years)	14.5 (4.04) [12.7, 16.2]	13.2 (4.57) [12, 14.4]	.23	12.42 (5.08) [9.9, 14.8]	10.4 (5.16) [7.9, 12.8]	.22
Women (%)	41.6	31	.35	42.1	45	.85
Disease duration (years)	n/a	5.26 (3.00) [4.4, 6]	-	5.68 (3.06) [4.2, 7.1]	6.28 (3.8) [4.4, 8]	.59
Levodopa dose (mg/d)	n/a	265.25 (249.58)	-	252.87 (293.74)	384.4 (215.04)	.12
LEDD (mg/d)	n/a	456.04 (230.68)	-	397.18 (236.08)	532.83 (209.70)	.09
PD-CRS total score [≤ 83 cutoff]	106.16 (8.74) [102.4, 109.85]	99.72 (10.86) [96.8, 102.5]	.01	98.2 (9.17) [93.7, 102.6]	67.15 (5.39) [64.6, 69.6]	<.001
Total verbal fluency score (DS)	19.66 (3.12)	18.01 (4.18)	.08	17.63 (4.32)	10.52 (2.08)	<.001

The values correspond to means, standard deviations (in round brackets) and 95% mean confidence intervals (CI) (in square brackets). For simplicity, CI are shown only for the relevant variables in the group comparisons.

P-values were determined with independent samples t-tests between groups for continuous and ordinal variables and with Pearson Chi-Square for nominal variables (Gender).

n/a = not applicable; LEDD = Total levodopa equivalent daily dosage; PD-CRS = Parkinson's Disease Cognitive Rating Scale; DS = Direct score.

2.4. Materials

We used the materials from León-Cabrera et al. (2019) consisting of high (HC) or low (LC) constraining sentence contexts, establishing a stronger or weaker expectation for an upcoming word (see Table 2 for sentence examples). A total of 312 sentences were included, of which 208 had HC sentence contexts (66.6 %) and 104 had LC sentence contexts (33.3 %). The sentences were originally created and categorized as either HC (mean cloze probability = 76%, SD ± 17.7%) or LC (mean cloze probability = 6.1%, SD ± 10.3%) (Mestres-Missé, Rodríguez-Fornells & Münte, 2007). Within the HC condition, half of the sentences ended with a congruent word and half with a semantically incongruent word. For the sake of task brevity to avoid fatigue, we decided to include this contrast (congruent vs. incongruent contrast) only in the HC condition. Sentences were further divided in two lists of 156 sentences, each list containing half of the sentences of each condition, and the use of one or another list was pseudorandomized across participants. In sum, each participant read the following sentences: 52 HC with congruent endings (HC congruent), 52 HC with incongruent endings (HC incongruent), and 52 LC with congruent endings (LC congruent) (**Table 2**). All final words were nouns. Congruent ones were the best completions – the word with the highest cloze-probability (i.e. percentage of individuals that supply that word as a continuation for that sentence) (Taylor, 1953) – and incongruent words were selected from the ESPAL database (Duchon et al., 2013) so that they matched the congruent endings in the variables of mean word length, mean number of syllables, word frequency, familiarity, imaginability and concreteness. The stimuli and task presentation code can be downloaded at https://osf.io/3FSP9/.

Table 2. Example sentences of each condition (original sentences in Spanish in brackets).

Condition	**Sentence context**	**Final word**
HC congruent	*The goalkeeper managed to catch the*	*ball*
	(El portero fue capaz de atrapar la)	(pelota)
HC incongruent	*The goalkeeper managed to catch the*	*shore*
	(El portero fue capaz de atrapar la)	(orilla)
LC congruent	*As a present she gave her son a*	*ball*
	(Le ha regalado a su hijo una)	(pelota)

2.5.Procedure

Participants were tested individually. After external electrodes and the EEG cap were placed, electrode impedances were checked. Participants were instructed to keep fixation on the center of the screen and to blink only during the blinking interval. After completing a short training block (4 sentences), the proper experiment started. They were instructed to read attentively and silently the words that would appear at the center of the screen.

The experiment consisted of 26 blocks of 6 trials each (2 HC congruent, 2 HC incongruent, 2 LC congruent). The order of the sentences within each block was randomized. Words were white on black background (font type: Arial; font size: 24 points). On each trial, a fixation point (a cross) appeared at the center of the screen (800 ms). Then, a sentence was presented word-by-word (300 ms per word, followed by a 200 ms blank screen). Between the penultimate and the final word, the blank screen remained for a period of 1 s (pre-word interval). After the final word (300 ms duration), a blank screen was presented (1000 ms) before the blinking signal (1 s; depiction of an eye at the center of the screen). The next trial began after the offset of the blinking signal (see **Figure 1** for a simplified display of the trial structure).

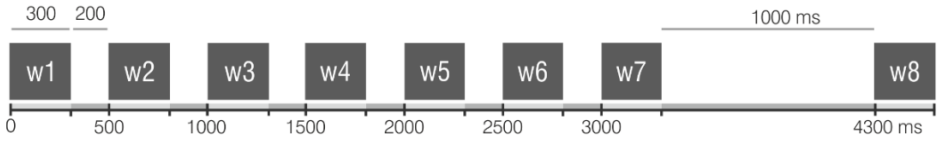

Figure 1. Depiction of the structure of a trial. Sentences were presented one word a time. Each word of the sentence context (w1 to w7) was displayed for 300 ms followed by a 200 ms inter-word interval, except for the last word (w7), which was followed by a 1000 ms interval (pre-word interval) leading up to the presentation of the final word (w8).

To ensure that participants were reading attentively, after every 2 blocks they were asked to judge whether the previous sentence was congruent or not ("did the previous sentence make sense?"). The question remained on the screen until they answered (yes/no) using the keyboard. The next block started immediately after the test except for even-numbered blocks, which were followed by a resting period that could be resumed anytime by the participant. All groups performed above chance in the congruency probe task (see Supplementary Materials for the accuracy of each group).

2.6. EEG recording

2.6.1. EEG acquisition.

Continuous electroencephalogram (EEG; sampling rate = 250 Hz) was recorded from 19 electrodes (FP1/2, F3/4, F7/8, Fz, C3/4, Cz, P3/4, Pz, T3/4, T5/6, O1/2) mounted on a cap following the international 10–20 system positions. The EEG signal was amplified on-line (band-pass filter = 0.016 – 1000 Hz) with Brain Vision. To monitor ocular artefacts, electrooculogram (EOG) electrodes were recorded with electrodes at bipolar vertical (supraorbital and suborbital ridge of the right eye) and horizontal (external ocular canthus of the left and right eyes) placements. All electrode impedances were kept below 5 kΩ. An on-line notch filter (50 Hz) was applied to attenuate high-frequency electrical noise and data were referenced to the mean activity of the left and right mastoid electrodes.

2.6.2. EEG preprocessing.

EEG data were preprocessed using ERPlab v7.0.0 (López-Calderón & Luck, 2014) of the EEGlab toolbox v14.0.0 (Delorme & Makeig, 2004), FieldTrip version 20181231 (Oostenweld, Fries, Maris & Schoffelen, 2011), and custom scripts programmed in MATLAB R2017b. For each participant and condition, the continuous data were segmented into the following epochs of interest: 1) from –100 to 1300 ms from the onset of the penultimate word (pre-word interval), and 2) from –100 to 1000 ms from the target word onset (word interval). Of note, in a previous study with healthy adult population (León-Cabrera et al., 2019), we used a larger pre-word interval that also included the sentence context (from the onset of the sentence until the offset of the delay), which importantly revealed that differences accrue early and gradually during sentence processing. However, we discarded this possibility in the current study because the EEG signal in the sentence context intervals contained many artifacts, as preliminarily assessed through visual inspection. It was not unlikely that participants, especially PD patients and older adults, had greater difficulties in refraining from blinking or from moving for a relatively long interval (4.3 seconds). We therefore opted to restrict the analysis of the anticipatory stage to the delay interval following previous reports (León-Cabrera et al., 2017; 2019).

Artefact detection and rejection were applied on the epoched data. To facilitate artefact rejection, we computed the vertical (vEOG) and horizontal (hEOG) bipolar EOG channels by subtracting

the inferior from the superior vertical EOG channels and the right from the left horizontal EOG channels, respectively. For the pre-word interval, all epochs with activity ± 85 µV in the ocular channels or ± 200 µV in any other channel were automatically removed and the remaining epochs were visually inspected and excluded if they contained blinks, muscle activity or large drifts. For the word interval, the concatenated epochs were first subjected to independent component analysis (ICA) decomposition to correct blinks because preliminary visual inspection revealed that many participants had difficulties refraining from blinking until the blinking signal, leading to a large loss of trials in this interval. ICA was run using the "runica" algorithm as implemented in EEGlab toolbox v14.0.0, excluding the ocular channels from the decomposition. The ocular components were detected and rejected based on visual inspection. After artifact-correction, epochs with activity ± 200 µV in any but ocular channels were automatically rejected, and those that remained were visually screened for any previously unnoticed artefacts (e.g. muscle activity or large drifts).

For the Control with PD-NC comparison, an average of 89.8 % trials per condition were available for analysis (HC = 85.7 trials; LC = 41.9 trials; HC congruent = 49.6 trials; HC incongruent = 49.6 trials; LC congruent = 49.7 trials; overall average = 46 trials per condition), with no significant differences in the percentage of available trials between groups (all p-values > 0.3). For the sPD-NC with PD-MCI comparison, an average of 87.4% trials per condition were included (HC = 79.2 trials; LC = 39.2 trials; HC congruent = 49.3 trials; HC incongruent = 49.5 trials; LC congruent = 49.6 trials; overall average = 45 trials per condition), with no significant differences in the percentage of remaining trials between groups (all p-values > 0.1).

2.7.Statistical analyses

2.7.1. Event-related potential analyses

Before performing statistical analyses, the data was baseline-corrected to the 100 ms pre-stimulus period and data were low-pass filtered (as implemented in ERPlab v7.0.0). For the pre-word interval, a 5 Hz low-pass Butterworth filter (12 dB/oct roll-off) was applied to the data to focus exclusively on slow activity (Brunia, Hackley, van Boxtel, Kotani & Ohgami, 2011). For the word interval, in which the N40 component was targeted, a 30 Hz low-pass Butterworth filter (12 dB/oct roll-off) was used. For the figures presented, the data were filtered using a 12 Hz low-pass filter (roll-off of 12 dB/oct).

2.7.2. Cluster-based permutation analyses

Non-parametrical cluster-based permutation tests were used to assess the differences (Maris and Oostenveld, 2007) (as implemented in Fieldtrip version 20181231 under MATLAB R2017b), a method that exerts proper control for the increased probability of false positives in the context of many comparisons. Broadly, it identifies adjacent time points and channels with similar differences between conditions. The test worked as follows in the present study. For within-subject comparisons, every sample (channel x time) was compared between two conditions (e.g., HC vs. LC) through a dependent *t*-test. For between-subject comparisons, an independent *t*-test compared the effect (e.g., HC minus LC) between groups at each sample (channel x time). Next, adjacent samples were clustered based on a *t*-value threshold (pre-determined from a one-tailed *t*-distribution with an alpha level of .05 and N-1 degrees of freedom) and the cluster with the largest sum of t-values was selected (cluster-level *t*-value). To determine whether effects were significant, the Monte Carlo method was used to construct a null distribution from the cluster-level *t*-values of random partitions obtained by randomly swapping the samples (between conditions and within participants for within-subject comparisons; and between conditions and between groups for between-subject comparisons) (5000 randomizations). Only observed clusters with cluster-level *t*-values within the 2.5th percentiles (alpha level of .05) of the null distribution were considered significant.

Choosing one-tailed testing is an optimal methodological decision when there are a priori hypotheses about the direction of the differences (Lakens, 2016). It allows to improve statistical sensitivity, which is particularly important when working with clinical samples. Following this, we chose one-tailed testing for the within-subject comparisons, as we had a priori hypotheses both for the pre- and post-word intervals. In the pre-word interval, we expected more negative amplitudes for HC than LC (León-Cabrera et al., 2017; 2019) In the post-word interval, where N400 context effects were targeted, we expected more negative amplitudes (larger N400 response) for unexpected that for expected words, that is, for HC incongruent than for HC congruent, as well as for LC congruent relative to HC congruent (Kutas & Federmeier, 2011). In turn, we chose two-tailed testing for the between-subject comparisons, as we did not have a priori hypotheses of the direction of the effects in this case.

2.7.3. Correlations between ERP effects and verbal fluency

After examining ERP effects, we conducted non-parametrical Spearman-Brown correlations to evaluate a potential linear relationship between the ERP effects and verbal fluency performance. All PD patients were included in this analysis (N = 78), that is, PD patients with normal cognition (N = 58) as well as PD patients with MCI (N = 20). For each participant, the total verbal fluency score was obtained by averaging the direct scores in semantic and phonological fluency subtests (see *Supplementary Materials* for correlations with each subtest individually). ERP measures were labeled and quantified as follows: 1) *PNP* (LC minus HC mean amplitude difference in the 600 ms before pre-word onset at a left anterior cluster including electrodes FP1, F3, Fz, F7); 2) *N400 congruency effect* (HC congruent minus HC incongruent mean amplitude difference from 300 to 500 ms post-word onset); 3) *N400 constraint effect* (LC congruent minus HC congruent mean amplitude difference from 300 to 500 ms post-word onset); and, based on the ERP results, 4) *prolonged N400 congruency effect* (HC congruent minus HC incongruent mean amplitude difference from 600 to 800 ms post-word onset). All effects tied to the N400 were tested on a centrally distributed cluster (averaged electrodes: Cz, C3, C4, Pz, P3, P4). All values were normalized before performing correlations. All *p*-values were corrected with the Holm-Bonferroni correction (Holm, 1979).

3. Results

3.1. Event-related potentials

3.1.1. Controls vs. PD patients with normal cognition

Figures 2A and **2B** show the grand-average ERPs at the F7 electrode during the pre-word interval in the Control group and the group of PD patients with normal cognition, respectively. The ERPs were computed in the interval from the onset of the penultimate word to the onset of the final word (1300 ms duration, the first 300 ms correspond to the penultimate word, and the last 1000 ms to the delay interval), with a 100 ms pre-stimulus baseline.

Both groups exhibited similar patterns, namely, an N100 associated with the processing of the penultimate word, followed by a positivity, and the later development of a negativity that became progressively larger as the presentation of the final word approached. As expected, based on previous findings in healthy adult population (León-Cabrera et al., 2019), the negativity was more prominent in the HC condition (relative to the LC condition), that is, when the final word

could be strongly predicted from the prior context. This difference was confirmed by a significant cluster in the Controls (p = 0.01) (**Fig. 2A**) as well as in PD individuals with normal cognition (p = 0.01) (**Fig. 2B**). The cluster showed a similar temporal profile in both groups. It started approximately 800 ms before the final word and went on until the word appeared. In regard to the spatial distribution, the cluster encompassed mainly frontal electrodes, with a slight left lateralization. There were no significant differences between groups.

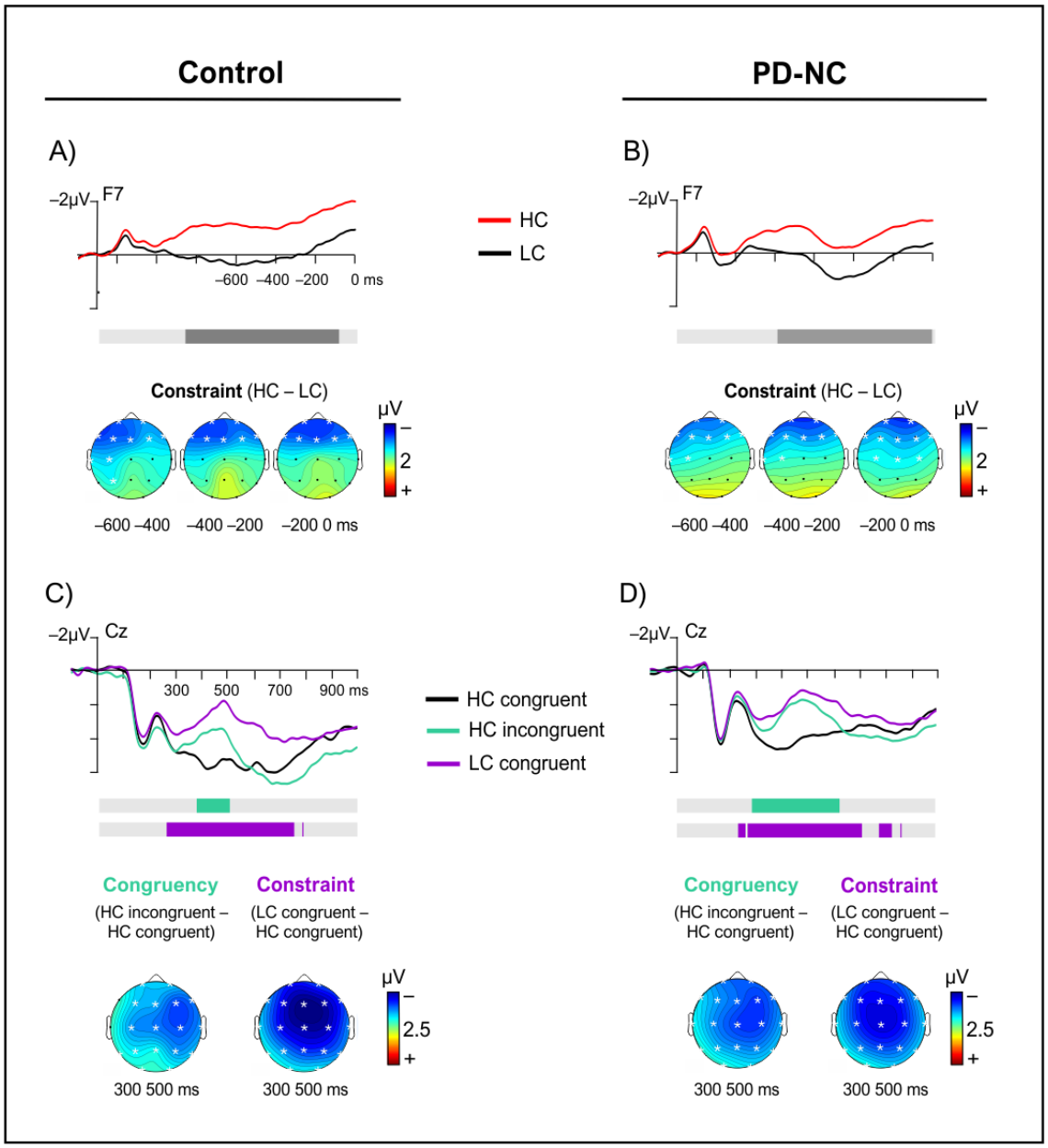

Figure 2. ERP results for the Control and the PD group. **A and B)** Grand-averaged ERPs at the F7 electrode during the pre-word interval for both conditions for (A) Controls and (B) PD patients. ERPs are time-locked to the presentation of the penultimate word (100 pre-stimulus baseline). The horizontal bar highlights (grey) the time interval in which significant differences were obtained. Below the ERPs, topographical maps indicating the electrodes (white asterisks) that showed a significant effect of constraint (HC minus LC) in the 600 ms prior to the critical word (in steps of 200 ms). **C and D)** Grand-averaged ERPs at Cz electrode after the presentation of the sentence-final word (100 pre-stimulus baseline) for (C) Control and (D) PD. The horizontal bars highlight the time interval of the N400 effect of Congruency (green) and Constraint (purple). Topographical maps with electrodes (white asterisks) that showed effects in the time interval in which N400 effects were expected to be maximal (300 to 500 ms post-word onset).

We then turned to the interval after word presentation. As can be observed in **Figures 2C** and **2D**, for both groups, unexpected words (HC incongruent and LC congruent) elicited a larger negativity peaking about 400 to 600 ms (relative to expected words; HC congruent) that is consistent with the canonical features of the N400. These differences were reflected in the significant clusters described below.

The effect of constraint (HC congruent versus LC congruent) was captured by significant clusters in the Control group ($p = .001$) (**Fig. 2C**) and in the PD group ($p < .001$) (**Fig. 2D**), whereby words presented in less predictive contexts (LC congruent) showed more negative amplitudes than words in strongly predictive contexts (HC congruent). There were no differences between groups. The cluster started about 250-300 ms after word onset and resolved at 700 ms, and it exhibited a widespread distribution over the scalp. In fact, the cluster was significant at all sites. On the other hand, the effect of congruency (HC congruent versus HC incongruent) was reflected in a shorter-lived cluster in the Control group ($p = .007$) (**Fig. 2C**) and in the PD group ($p<.001$) (**Fig. 2D**), in this case, confirming more negative amplitudes for incongruent than congruent words in strongly predictive contexts. Again, there were no significant differences between groups. The effect was widespread with a seemingly slight rightward focus in magnitude.

3.1.2. Subset of PD patients with normal cognition vs. PD with MCI

The mean voltage pattern elicited during the pre-word interval (**Fig. 3A** and **Fig. 3B**) exhibited the normative N100 component, followed by a transient positivity and a subsequent negativity in the last part of the interval that evidenced the hypothesized tendency towards more negative

amplitudes for HC than LC. However, in this case, there were no statistically significant differences between conditions, nor any differences between the two groups.

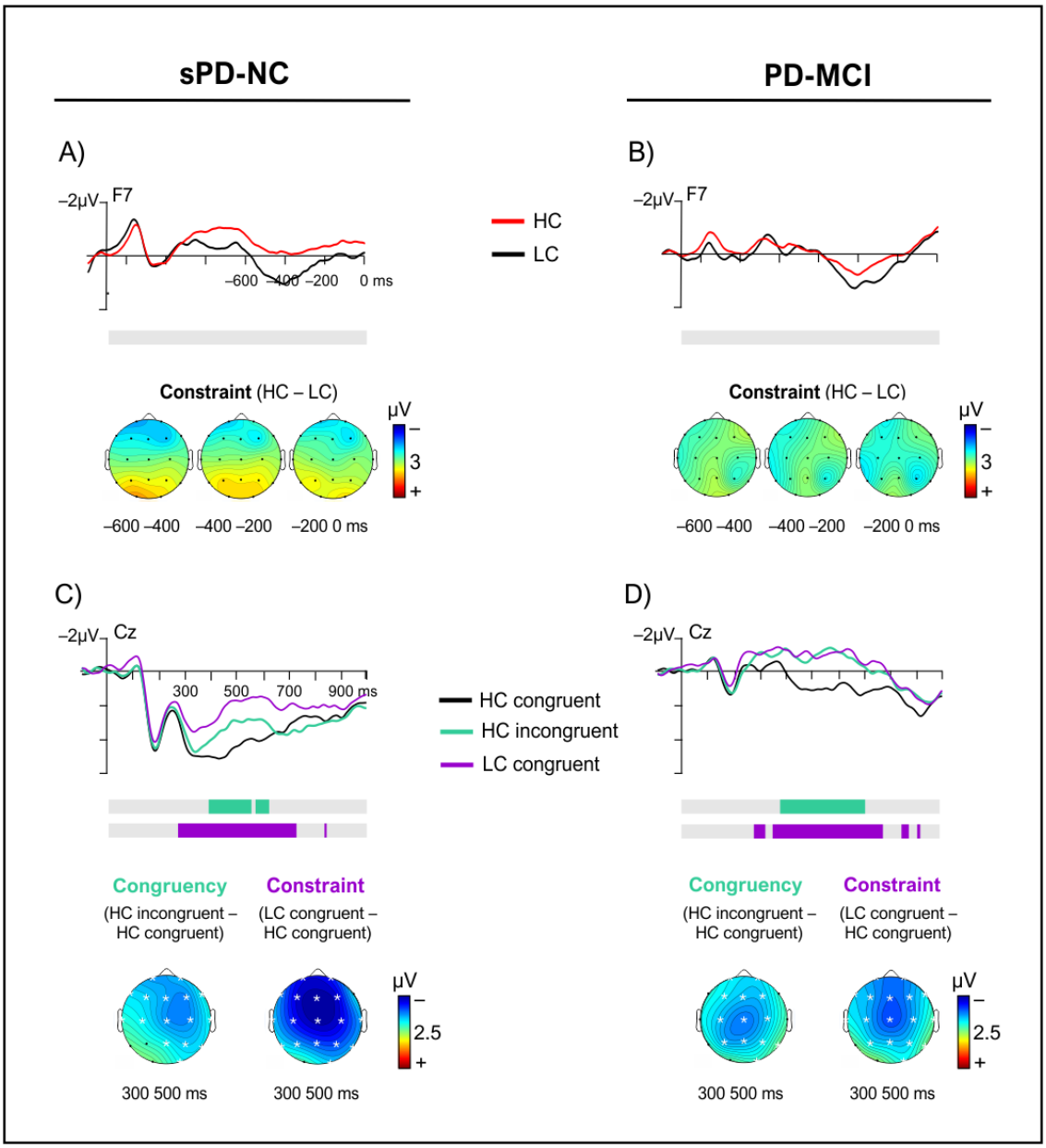

Figure 3. ERP results for the subgroup of PD patients wit normal cognition (PD-NC) and the group of PD-MCI patients. **A and B)** Grand-averaged ERPs at the F7 electrode during the pre-word interval for (A) sPD-NC and (B) PD-MCI patients. ERPs are time-locked to the presentation of the penultimate word (100 pre-stimulus baseline). The horizontal bar highlights (grey) the time interval in which significant differences were obtained. Below the ERPs, topographical maps indicating the electrodes (white asterisks) that showed a significant effect of constraint (HC minus LC) in the 600 ms prior to the critical word (in steps of 200 ms). **C and D)** Grand-averaged ERPs at Cz electrode after the presentation of the sentence-final word (100 pre-stimulus baseline) for (C) sPD-NC and (D) PD-MCI patients. The horizontal bars

highlight the time interval of the N400 effect of Congruency (green) and Constraint (purple). Topographical maps with electrodes (white asterisks) that showed effects in the time interval in which N400 effects were expected to be maximal (300 to 500 ms post-word onset).

After the presentation of the final word (**Fig. 3C** and **Fig. 3D**) there was an observable larger negativity for unexpected (HC incongruent and LC congruent) relative to expected words (HC congruent) in both groups, in line with classical N400 context effects. These observable differences were confirmed by significant clusters as specified next.

There were significant effects of constraint (HC congruent versus LC congruent) both for the group of PD patients without MCI ($p < .001$) (**Fig. 3C**) and the group of PD patients with MCI ($p < .001$) (**Fig. 3D**). That is, as expected, words in less predictive contexts elicited a larger N400 than words in strongly predictive contexts, a difference that encompassed the interval between about 300 to 700 ms post word onset. The scalp distribution of the effect covered a wide set of electrodes over frontal and central regions of the scalp, with a slight frontward amplitude maximum. No differences between groups were found.

As for the effect of congruency in predictive contexts (HC congruent versus HC incongruent), again as expected, significant clusters reflected that incongruent words had more negative amplitudes than congruent words in patients without MCI ($p = .005$) (**Fig. 3C**), and also in PD patients with MCI ($p = .001$) (**Fig. 3D**). Relevantly, in this case, there were significant differences between the groups (**Fig. 4**). The difference waveforms (HC incongruent minus HC congruent) of each group were contrasted in a between-group cluster-based permutation test including all electrodes and time-points (from 0 to 1000 ms). The test yielded a significant cluster ($p = .008$) that revealed a longer-lasting effect of congruency for the group of patients with MCI, which can be visualized in **Figure 4A**. More specifically, the cluster spanned approximately from 630 to 760 ms after word onset at centro-parietal sites (significant electrodes: C3, Cz, C4, P3, Pz, P4, T5, T4, T6, O2) (see the scalp distribution of *t*-values in **Fig. 4B**). This result suggests a prolonged N400 congruity effect in the group of PD patients with MCI relative to the group of PD patients without MCI.

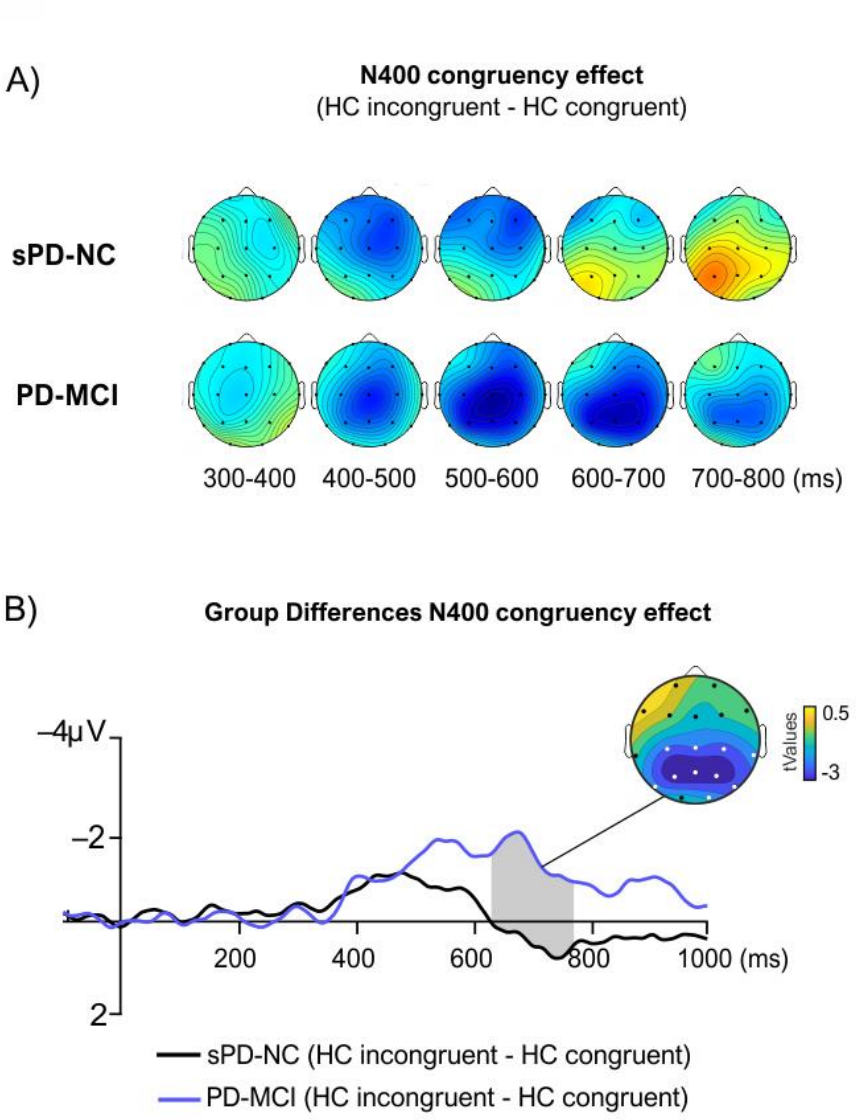

Figure 4. A) Topographical maps showing the temporal evolution and scalp distribution of the congruency contrast (HC incongruent minus HC congruent) during final word processing, showing a prolonged N400 congruency effect in the group of individuals with PD and MCI. **B**) Grand-averaged ERPs of the difference waveforms (HC incongruent and HC congruent) of both groups, averaged over the set of electrodes that were part of the significant cluster of differences between the groups (highlighted in white in the topographical map). The grey-colored area shows the timepoints included in the cluster. The topographical map shows the scalp distribution of the averaged t-values within the cluster (cluster t-value ± 2.02 for an alpha level of .05).

3.2. Correlations between ERP effects and verbal fluency scores

After establishing the ERP effects, we examined the association between ERP measures and verbal fluency scores in all PD patients (N = 78) (for further specification of this analysis, see **Section 2.7.3.**) by means of non-parametric Spearman correlations between direct scores in verbal fluency tests, and four ERP measures, namely, 1) PNP (LC minus HC), 2) N400 constraint effect (LC congruent minus HC congruent), 3) N400 congruency effect (HC congruent minus HC incongruent), and 4) prolonged N400 congruency effect (HC congruent minus HC incongruent). Note that, in these analyses, the direction of the condition subtraction is reversed, such that positive values represent differences in the expected direction of the effect (e.g., in the case of the PNP, positive values indicate larger amplitudes for HC than LC). All correlations were corrected using Holm-Bonferroni correction (indicated as *p*HB in the text).

Table 3. Results of correlational analyses between ERP measures and verbal fluency scores in PD patients.

Test	ERP effect	r	*p*-value (corrected)
Verbal fluency	PNP	.326	**.010***
	N400 constraint	.157	.336
	N400 congruency	–0.073	.525
	Prolonged N400 congruency	–.358	**.005***

PNP (LC minus LC); N400 constraint (LC congruent minus HC congruent); N400 congruency (HC congruent minus HC incongruent); Prolonged N400 congruency (HC congruent minus HC incongruent)

Holm-Bonferroni correction was applied to adjust *p*-values. Statistically significant correlations are highlighted with asterisks.

The results of the correlational analyses are presented in **Table 3**. After correcting for multiple comparisons, two of the ERP measures showed a significant correlation with verbal fluency scores: the PNP and the prolonged N400 congruency effect (**Fig. 5**). In particular, the PNP showed a

significant positive correlation with verbal fluency (r(77) = .326, pHB = .010). Note that we excluded one participant who had outlying scores in the PNP (z-score = –3.91) although the correlation was unaffected by its inclusion (r(78) = .326, pHB = .01), which is normal when using nonparametric Spearman correlations that are very robust to the presence of outliers. This indicates that a larger PNP (more negative amplitudes prior to words in predictive than in unpredictive contexts) is associated with better verbal fluency performance in patients with PD. In turn, the prolongation of the N400 congruency effect (more negative amplitudes for incongruent than congruent words 600-800 ms post-word) correlates with worse scores in verbal fluency (r(78) = –.358, pHB = .005). No other correlations were statistically significant.

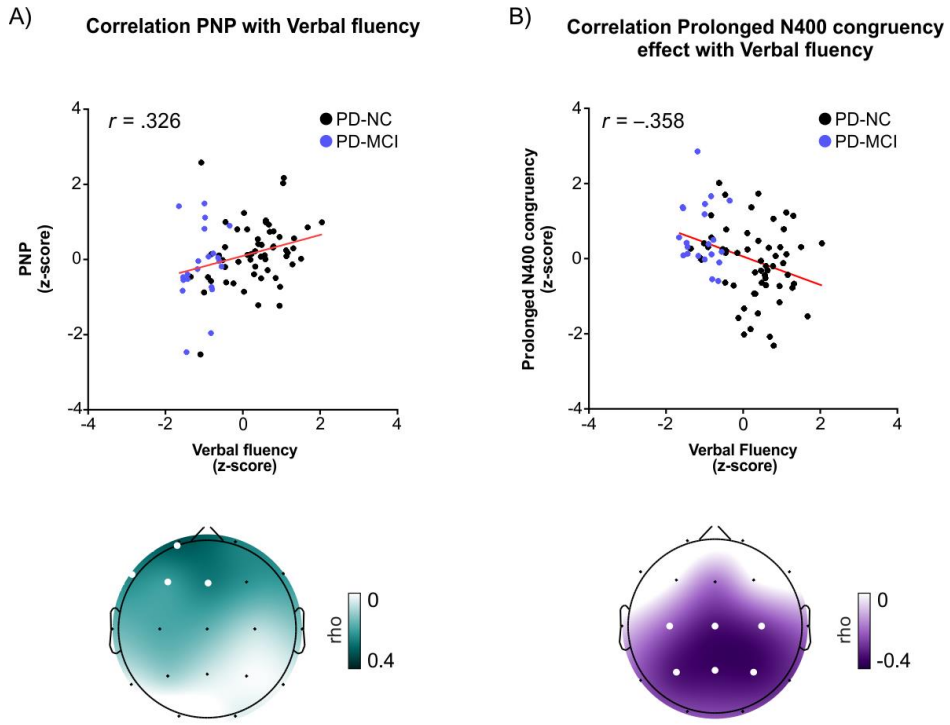

Figure 5. Scatterplots and scalp maps of significant correlations between ERP measures and verbal fluency scores in all PD patients (PD with and without MCI) (N = 78). A) Scatterplot of the positive correlation (r = .326, pHB = .010) between verbal fluency scores and the PNP (more negative amplitudes prior to words in HC than in LC contexts) and **B**) of the negative correlation (r = –.358, pHB = .005) between verbal fluency scores and the prolongation of the N400 congruency effect (more negative amplitudes for incongruent than congruent words 600-800 ms post-word). All values were normalized. Below the scatter diagrams, the r-values (Spearman rho) for all 19 electrodes are plotted on an idealized head. Darker shading indicates larger r-values in the direction of the correlation. Electrodes included in the

ROI used to perform the reported correlations with verbal fluency (shown in the scatter diagrams) are highlighted (in white). R-values between electrodes were estimated by spherical spline interpolation.

4. Discussion

Motivated by previous evidence of altered predictive language processing in populations with low cognitive resources (Federmeier et al., 2002; 2005; 2010), the present study assessed language prediction in PD with normal cognition and PD with MCI. To this end, ERP modulations were examined before and after encountering words that could or could not be predicted from context, thus capturing both the anticipatory and processing stage of prediction. Specifically, we focused on PNPs as signatures of semantic anticipation, and post-word N400 context effects as indices of predictive pre-activation. Relative to controls, PD patients with normal cognitive status exhibited the expected ERP signatures, pointing to preserved predictive language processing. In turn, PD patients with MCI showed absent PNPs and a significant prolongation of N400 congruency effects in predictive contexts, suggesting altered mechanisms tied to language prediction. Interestingly, correlational analyses revealed that worse verbal fluency performance was associated with the presence of the ERP pattern observed in the group of PD patients with MCI.

4.1.Neural correlates of predictive sentence processing are preserved in PD

Consistent with prediction, PD patients with normal cognition exhibited the canonical reduction of N400 amplitude for expected (HC congruent) compared to unexpected words (LC congruent and HC incongruent) (Kutas & Hillyard, 1984). This effect is taken to reflect facilitated lexical and semantic activation of expected words as a result of their pre-activation (Federmeier & Kutas, 1999; Lau, Phillips & Poeppel, 2008). In line with this interpretation, in predictive contexts (HC), PD patients with normal cognition exhibited a frontally distributed negative PNP that developed progressively prior to the presentation of the final word (León-Cabrera et al., 2017; 2019; for similar results, see Grisoni, Miller & Pullvermüller, 2017; Li, Zhang, Xia & Swaab, 2017). Studies in healthy population suggest that such PNPs capture anticipation of semantic aspects of the upcoming word (for a recent review, see Pullvermüller & Grisoni, 2020). More specifically, it may reflect retrieval or maintenance of pre-activated lexical and/or semantic representations (Li et al., 2017; León-Cabrera et al., 2019). Altogether, PD patients with normal cognition seem to make proper use of sentence contexts to predict upcoming linguistic information during comprehension.

More broadly, the present findings are in line with previous studies showing intact N400 effects in sentence processing in PD patients with normal cognition (Friederici et al., 2003; Angwin et al., 2017b), and, in turn, contrasts with behavioral and electrophysiological evidence pointing to altered lexical and semantic processing in these patients (Angwin et al., 2004a; 2004b; 2006; 2017a; 2009; Arnott et al., 2001; 2010; Copland et al., 2009; Kutas et al., 2013). Of note, most studies showing abnormal lexical and semantic processing employed tasks that consisted of single-word contexts, instead of sentence contexts. Importantly, sentence processing involves the construction of a high-level meaning representation (Graesser, Singer & Trabasso, 1994), which serves to constrain in a top-down manner towards the appropriate lexical and semantic representation, perhaps compensating for activation problems within semantic networks in these individuals. Nonetheless, note that all patients in the current study were on dopaminergic medication. PD patients on dopaminergic medication perform better in semantic priming tasks than PD patients off medication (with normal cognition) (Angwin et al., 2004a; Angwin et al., 2009), suggesting that dopamine (DA) mediates semantic activation, arguably through calibration of the spread and focus of activation within semantic networks (Kischka et al., 1996). DA has also been linked with anticipatory processes in PD. Specifically, PD patients with normal cognition off medication show reduced amplitudes of the *stimulus-preceding negativity*, suggesting that the DA system is implicated in the anticipation of motivationally salient and rewarding stimuli (Mattox Valle-Inclán & Hackley, 2006). Future studies testing patients off medication would help untangle to what extent dopaminergic compensation contributed to the preservation of otherwise altered mechanisms.

4.2.PD-MCI impacts late semantic processing in predictive contexts

To further investigate the impact of cognitive impairment, we also examined neural responses in a smaller sample of PD-MCI patients. Compared to a matched subgroup of PD patients with normal cognition, PD patients with MCI exhibited expected N400 amplitude modulations within the normal onset latency (i.e., about 300-400 ms post-word onset). However, most remarkably, PD patients with MCI showed a significantly prolonged N400 congruency effect in predictive contexts, extending up to 700 ms after word onset. Critically, this was not observed in the N400 constraint contrast (LC congruent versus HC congruent), which suggests that the prolongation stemmed from the ERP response to incongruent words, rather than to congruent words (i.e. from

HC incongruent, instead of HC congruent). With that in mind, it is important to note that N400 context effects do not solely capture prediction effects, but also integration demands (van Berkum, Hagoort & Brown, 1999). Interestingly, a recent study showed that prediction effects dominate the earlier portion of the N400 context effect (starting as early as 200 post-word onset), whereas integration effects began later and continued until about 650 ms after word onset (Nieuwland et al., 2020; see also, Brothers, Swaab & Traxler, 2015; Lau, Namyst, Fogel & Delgado, 2016). As such, prolonged N400 congruency effects may reflect abnormally sustained efforts to integrate the incongruent word with the previous context (Nieuwland et al., 2020). Curiously, a previous study found that patients with bilateral basal ganglia lesions exhibited similarly prolonged N400 effects in sentence processing (up to 700 ms post-word) (Kotz , Frisch, Von Cramon & Friederici, 2003). In PD, the worsening of the condition from PD with normal cognition to PD with MCI may lead to altered late integrational semantic processing as well.

More recently, N400 effects have postulated to reflect the 'prediction error' (albeit with nuances in their definition, see Willems, Frank, Nijhof, Hagoort & Van den Bosch, 2016; Rabovsky, Hansen & McClelland, 2018; Kuperberg, Brothers & Wlotko, 2020). In predictive processing frameworks (Clark, 2013), predictions are sent top-down from higher to lower level regions to 'explain away' the incoming sensory input and, then, the 'prediction error' – the portion of information that remains unexplained – is sent back and used as a learning signal to update internal models and improve future predictions. Thus, prolonged N400 congruency effects may indicate difficulties in this 'learning' phase, leading to less efficient internal model updating.

Furthermore, also in line with less efficient predictive language processing in PD patients with MCI, there were no effects in the anticipatory stage in this group, pointing to absent semantic anticipation. Note, however, that there were no effects in the matched subgroup of PD patients with normal cognition either. In fact, there were no differences between the two groups. Therefore, the absence or extreme reduction of the PNP in these groups might be associated with factors other than MCI, such as the older age of the patients in these samples (compared to the whole sample of PD with normal cognition), or insufficient statistical power to detect differences, as sample size was smaller in this case.

4.3. Worse verbal fluency performance is associated with altered signatures of predictive language processing in PD

Interestingly, correlational analyses revealed that lower verbal fluency scores were associated with reduced PNP and prolonged N400 congruency effects. Similarly, previous evidence has shown that verbal fluency scores are a good predictor of the status of predictive language processing in healthy older population (Federmeier et al., 2002). Worse performance in verbal fluency is generally associated with executive dysfunction, such as difficulties in rule switching or inhibition. Executive dysfunction is common with the progression of fronto-striatal deterioration in PD with and without MCI (Kudlicka et al., 2011; Monchi et al., 2004; Aarsland et al., 2010) and has been proposed to indirectly hinder language processing in PD (Grossman et al., 2002; 2003). However, verbal fluency performance depends not only on frontal lobe function, but also on lexical and semantic retrieval processes dependent on temporo-parietal structures (Unsworth, Spillers & Brewer, 2011). In fact, recent findings point to a greater weight of language-related processes than executive function in verbal fluency (Whiteside et al., 2016). Recent meta-analyses and lesion-based studies have also shown that verbal fluency is supported by standard language networks and underlying white-matter connectivity (Griffis, Nenert, Allendorfer & Szaflarski, 2017; Costafreda et al., 2006; Baldo, Schwartz, Wilkins & Dronkers, 2006). Therefore, the ERP pattern associated with lower verbal fluency – suggestive of less efficient predictive processing mechanisms, as previously discussed – may reflect not only executive dysfunction, but also disruption in semantic networks, in line with recent findings of difficulties in temporal-dependent functions in PD with and without MCI (Horta-Barba et al., 2020; Martínez-Horta & Kulisevsky, 2019; Lang et al., 2019).

4.4.Concluding remarks and future directions

Overall, the results suggest preserved predictive language processing in PD patients with normal cognitive status. In turn, in PD patients with MCI, further cognitive limitations hinder mechanisms associated with semantic prediction in normal circumstances. While these limitations may not prevent the pre-activation of relevant representations, they might negatively affect sentence processing due to poorer semantic anticipation and less efficient semantic processing when contexts are predictive. Furthermore, both executive dysfunction and damage within semantic networks may underlie these difficulties, as suggested by their association with low verbal fluency scores. Along with recent research (Horta-Barba et al., 2020; Martínez-Horta & Kulisevsky, 2019; Lang et al., 2019), these findings emphasize the value of examining cognitive changes in PD

patients with and without MCI in domains beyond executive functions, like the language domain. Interestingly, altered N400 effects are associated with a higher risk of transiting to dementia in individuals with amnesic MCI (Olichney et al., 2008). Therefore, future longitudinal studies in PD could evaluate changes in N400 congruency effects as potential markers of the transition to PD with MCI and PD with dementia (for interested readers, see Supplementary Materials for a hierarchical regression analysis further attesting that the N400 congruency effect is a good predictor of global cognitive decline in PD). Finally, as previously highlighted, future studies testing patients off medication could assess the exact role of DA in predictive sentence comprehension. Yet, the value of evaluating PD patients on stable doses of dopaminergic medication must be emphasized, as it is representative of their habitual cognitive status and thus has the potential to uncover limitations that may impact the everyday functioning of individuals with PD.

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Declaration of competing interests

The authors declare no disclosure of financial interests and potential conflict of interest.

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