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Highlights

- Identifies EEG markers for depressive symptoms in a large sample of PD patients
- Uses an affective priming paradigm to identify ERP responses in PD
- PD patients with higher depression scores show reduced ERP responses
- Pz, P300, N400, and LPP serve as markers for emotional dysfunction in PD

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Depression symptomatology correlates with event-related potentials in Parkinson's disease: an affective priming study

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Abstract

Background

Depression is a predominant non-motor symptom of Parkinson's disease (PD), which is often under recognised and undertreated. To improve identification of depression in PD it is imperative to examine objective brain-related markers. The present study addresses this gap by using electroencephalography (EEG) to evaluate the processing of emotionally valenced words in PD.

Methods

Fifty non-demented PD patients, unmedicated for depression or anxiety, completed an affective priming task while EEG was simultaneously recorded. Prime and target word pairs of negative or neutral valence were presented at a short 250ms stimulus onset asynchrony. Participants were asked to evaluate the valence of the target word by button press. Depression was measured using an established rating scale. Repeated measures analysis of covariance and correlational analyses were performed to examine whether event-related potentials (ERP) varied as a function of depression scores.

Results

Key ERP findings reveal reduced responses in parietal midline P300, N400 and Late Positive Potential (LPP) difference waves between congruent and incongruent neutral targets in patients with higher depression scores.

Limitations

Comparisons of ERPs were limited by insufficient classification of participants with and without clinical depression. A majority of PD patients who had high depression scores were excluded from the analysis as they were receiving antidepressant and/or anxiolytic medications which could interfere with ERP sensitivity.

Conclusions

The present study suggests that the Pz-P300, N400 and LPP are ERP markers relates to emotional dysfunction in PD. These findings thus advance current knowledge regarding the neurophysiological markers of a common neuropsychiatric deficit in PD.

Keywords: Parkinson's disease, Electroencephalography, Event related potentials, Affective priming task, Depression

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1. Introduction

Depression is a predominant non-motor symptom in Parkinson's disease (PD) that reduces patients' quality of life (Dissanayaka et al., 2011a). On average, 35% of PD patients experience depression (Reijnders et al., 2008). Depression is often under recognised and therefore, undertreated in PD. Untreated depressive symptoms in patients with PD contribute to greater functional disability, poorer activities of daily living, and greater caregiver distress (Dissanayaka et al., 2011a; Marsh, 2013; Mosley et al., 2017). Poor recognition of depression is predominantly due to overlapping symptoms between depression and PD, including autonomic dysfunction, sleep disturbances, and psychomotor retardation, and lack of knowledge in mechanisms underpinning emotional dysfunction in PD (Slaughter et al., 2001). The present study examines electrophysiological correlates of depressive symptoms in PD using an automatic affective priming paradigm previously published by our group (Dissanayaka et al., 2017).

Affective priming allows investigation into the cognitive processes related to emotion processing by examining how an affectively valenced first stimulus (prime) influences the judgement of a second stimulus (target) when two stimuli are presented consecutively. Using a short stimulus onset asynchrony (SOA) of <300ms, early processing of the stimuli can be examined (Fazio et al., 1986; Hermans et al., 2003) and can be used to identify deficits in automatic processes. Early processing deficits are evident in depressed individuals and are exhibited by having persistent automatic thoughts of negativity due to difficulty in disengaging attention from the negative stimulus (Eugene et al., 2010). In depressed patients, attentional resources are more rapidly recruited in response to negative than to positive or neutral events. This negative bias has been shown to occur throughout the early (e.g. attention allocation) and late stages (e.g. context updating) of information processing (Yuan et al., 2007), and may consequently influence the ability to process emotion. The affective priming paradigm with negative stimuli utilised in this study allows investigations into regulatory deficits in processing emotion. The present study uses an emotion judgement task to explore the

influence of prime word valence on subsequent processing of a target word and the relationship to depressive symptoms in PD.

Deficits in emotional behaviour and impaired recognition of visual emotional stimuli have been suggested in PD (Peron et al., 2012). A reduction in accuracy when identifying disgust words compared to happy or fearful words, and deficits in the recognition and judgement of the emotional valence of words have been shown in PD (Borg et al., 2012; Hillier et al., 2007). Similarly, delays in recognising negative compared to neutral words in an affective priming paradigm using lexical decision have also been demonstrated in PD (Castner et al., 2007). The present study extends the Castner et al. (2007) study by investigating electroencephalography (EEG) correlates of automatic affective priming using an affective judgement task as per a recently published study (Dissanayaka et al., 2017).

A limited number of studies have used picture stimuli and the measurement of event related potentials (ERP) to investigate emotion processing in PD (Dietz et al., 2013; Morita et al., 2005; Wieser et al., 2012; Yoshimura et al., 2005). Reduced Late Positive Potential (LPP) amplitude in the parietal region have been observed for negative valence stimuli (Dietz et al., 2013), and increased P300 amplitudes for negative stimuli compared to positive picture stimuli in an odd ball task (Morita et al., 2005) have been demonstrated in PD. While Dietz et al. (2013) observed that the LPP from the centro-parietal electrode clusters positively correlated with a measure of apathy in PD, this study did not show associations between the LPP and depression. This suggests that the picture paradigm used in Dietz et al. (2013) may not be sensitive to depression, and that robust paradigms to capture deficits in automatic affective processes are required to elicit primary processing abnormalities relating to depressive symptoms in PD.

Our previous study (Dissanayaka et al., 2017) measured ERPs during performance of an automatic affective priming task in non-demented PD patients without depression or anxiety and compared them to healthy adults. Larger amplitudes in P300 and LPP were observed for negative compared to neutral target words (for both congruent and incongruent prime-target pairs) in frontal and parietal areas in both PD and control groups, suggesting both P300 and LPP demonstrate negative biases and are intact in PD patients with no affective disturbances. Similarly, the N400 (an ERP component relevant to word processing) generated for target word stimuli was larger for negative compared to neutral primes when followed by neutral target words (Negative-Neutral prime target pair compared to Neutral-Neutral condition) in both groups, suggesting automatic processing of negative information are intact in PD patients with no affective disturbances. The present study examines how the P300 and LPP, well known ERP components associated with emotion processing (Cermolacce et al., 2014; Delle-Vigne et al., 2014; Hu et al., 2017; Li et al., 2018), as well as the N400 component related to word processing, are moderated by depressive symptoms in PD (Kutas and Federmeier, 2011).

Depression literature suggests mixed results for the relationship between depression and ERP components described above. A reduction in P300 has been demonstrated with depression using auditory oddball paradigms, suggesting deficits in evaluation, attentional allocation and short term memory encoding (Jaworska and Protzner, 2013). On the other hand, priming studies using picture (faces) paradigms have demonstrated larger P300, LPP and N400 amplitude for negative stimuli in depression (Bistricky et al., 2014; Cermolacce et al., 2014; Delle-Vigne et al., 2014; Hu et al., 2017; Li et al., 2018), suggesting difficulty in disengaging with negative information in depressed persons. Against this background, it is hypothesized that ERP components, P300, LPP and N400 will demonstrate amplitude modulations between negative and neutral target words, that the valence of the preceding prime word will also influence the ERPs generated for the target stimuli, and that depression scores modulate the ERP waveforms.

2. Methods

2.1 Participants

This study included a convenience sample of 54 PD patients who met inclusion and exclusion criteria. PD patients were recruited from neurology out-patient clinics and the Queensland Parkinson's Project (QPP) database (Dissanayaka et al., 2011b) and were diagnosed according to the United Kingdom Brain Bank criteria by neurologists (Hughes et al., 1992). The exclusion criteria were signs of dementia identified by treating neurologists based on clinical impression or scoring <24 in the brief Standardised Mini-Mental Examination (SMMSE) (Molloy et al., 1991) or scoring <64 in the Parkinson's Disease Cognitive Rating Scale (PDCRS) (Pagonabarraga et al., 2008) conducted during a research interview, having a history of functional neurosurgery or other comorbid neurological diseases, or other complex psychological conditions such as psychosis, and having dyskinetic involuntary head movements or severe right hand tremor that interfered with EEG recordings. We also excluded persons taking antidepressants, anxiolytics or other CNS medications (other than treatment used for PD), as ERPs can be altered between treatment responders and non-responders (Wade and Iosifescu, 2016).

Those who met eligibility for the present study completed the EEG experiment. In brief, a total of 100 PD patients completed screening interviews, while 16 were excluded due to probable dementia (scoring <64 in the PDCRS (N=12)), or withdrawing from the study. Of the 84 PD patients who remained, 19 were excluded due to taking antidepressants or anxiolytics as these medications can influence the ERP signal, and 11 were excluded due to insufficient EEG data (EEG error or poor segment count of <25% per condition).

Out of the remaining 54 PD patients, all but 3 PD patients were optimally treated with medication for PD. For medicated patients, data was collected at "on" state where PD medication was at an

optimal response stage. All patients were right-handed according to the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) and had normal or corrected to normal visual acuity. Ethics approvals by the Royal Brisbane and Women's Hospital and University of Queensland human research ethics committees were obtained, and all participants provided written informed consent.

2.2 Assessments

The 17 item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) for depression and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) for anxiety were used. Severity of PD was assessed using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the Hoehn & Yahr Staging (HY) (Leentjens et al., 2008). Cognitive status was evaluated using the PDCRS (Pagonabarraga et al., 2008). The interview and the EEG experiment were conducted within 2 weeks.

2.3 The automatic affective priming paradigm

The study used an affective priming paradigm based on Dissanayaka et al. (2017). In brief, stimuli consisted of negative (valence rating <3) and neutral (valence rating 4-6) words selected from the affective norms for English words (ANEW) database (Bradley and Lang, 1999). Words were chosen to make pairs consisting of a prime word and a target word. Prime-target word pairs were classified into four different conditions (negative-negative, neutral-neutral, neutral-negative and negative-neutral) and further categorised as congruent (negative-negative, neutral-neutral) or incongruent (neutral-negative, negative-neutral). Each prime-target condition consisted of 40 trials contributing to a total of 160 trials. Target words across the four prime-target conditions were matched according to their lexical decision reaction time ($F=0.79$, $p=0.50$) (Balota et al., 2007), frequency of use ($F=0.06$, $p=0.98$) (Coltheart, 1981), imageability ($F=1.44$, $p=0.23$), and word length ($F=0.24$, $p=0.87$). The imageability and word length data were obtained using N-watch (Davis, 2005). Relatedness of prime and target words was determined with the Edinburgh

Associative Thesaurus (Kiss et al., 1973) and University of South Florida Free Associative Norms (Nelson et al., 2004) to ensure all stimuli pairs were unrelated.

The paradigm was presented on a 17" computer screen using the E-PRIME 2.0 software package (Schneider et al., 2002). Each trial involved the presentation of a fixation cross followed consecutively by the prime word and target word with a 250ms SOA to identify the influence of the prime on ERPs elicited from the target stimuli. Having a short SOA of <300ms is expected to provide automatic influence of the prime on target processing of emotional information (Dissanayaka et al., 2017). Patients were asked to make an evaluative judgement of the emotional connotation of each target word by pressing the corresponding button on the response pad (Serial model 200) as fast as possible. While participants completed the task, EEG was simultaneously recorded. Prior to commencing the experiment, participants completed a short practice task consisting of 8 prime-target pairs. The experiment consisted of 4 blocks of 40 trials, each lasting approximately 2 minutes.

2.4 EEG data acquisition and analysis

EEG data acquisition and analysis were performed consistent with Dissanayaka et al. (2017). In brief, a high density EGI Hydrocel Geodesic Sensor Net system with 128 channels was used to obtain ERPs generated when responding to target word stimuli in the affective priming task. ERP data was analysed according to standard guidelines (Picton et al., 2000), and the Net Station software package was used for acquisition and analysis (Electrical Geodesics, 2006). Data were filtered at a lowpass of 30Hz and a highpass of 0.1Hz. Epochs were defined as 100ms before and 1000ms after target stimulus onset. Trials with correct responses and reaction times between 200ms and 2000ms were included for analysis. Electro-ocular artefacts were monitored by electrodes positioned at the outer canthi of the eye and at infra and supra orbital locations (Hill et al., 2005).

Detected ocular artefacts along with any remaining artefacts were discarded from the analysis. After trials with eye movements, eye blinks and bad channels were discarded more than 60% of the trials remained, NegNeg (M=27.45, SD=7.00), NegNeu (M=30.67, SD=5.36), NeuNeg (M=26.92, SD=7.86), NeuNeu (M=31.16, SD=6.16). Re-referencing of the electrodes to the polar average reference was performed (Mazerolle et al., 2007) and the epoched data was baseline corrected to a 100ms pre-stimulus interval (Franklin et al., 2007). Based on results from the previous study by Dissanayaka et al. (2017), three time windows were analysed: 300-400ms (P300), 400-550ms (N400) and 600-800ms (LPP). Midline Fz, Cz, and Pz electrodes and electrode clusters were included for analyses as per previous studies (Dissanayaka et al., 2017; Simola et al., 2009).

2.5 Statistical analysis

The dependent variable of mean amplitude was derived for the ERP components of interest (P300, N400, and LPP). Each prime-target condition (negative-negative, neutral-neutral, neutral-negative, negative-neutral) was averaged for each individual participant and a grand average of all participants was obtained. Repeated-measures analysis of covariance (ANCOVA) was used to investigate the factors of target valence (negative and neutral target words) and affective congruency (incongruent and congruent prime-target conditions) and to identify any interactions with the following covariates: levodopa equivalent daily dosage (LEDD) (Tomlinson et al., 2010), age, and depression (HAM-D). Difference waves were constructed for significant results and correlations between the HAM-D and difference wave was examined. Results were adjusted for anxiety (HAM-A) and cognitive impairment (PDCRS) scores. Scores obtained from the PDCRS were re-calculated as impairment so that higher scores indicated more cognitive impairment. For this, each participant's total PDCRS score was subtracted from the total score obtained from the PDCRS (i.e. $PDCRS_i = 134 - \text{individual PDCRS score}$).

Q-Q plots were constructed to determine outliers. Outliers with extreme values outside the normal distribution curve were excluded from the analysis. Square root transformations were performed for HAM-D, and LEDD scores. Multiple comparisons for each electrode, per time window were adjusted using the Bonferroni adjustment.

3. Results

3.1 Participant characteristics

Of the 54 PD participants who completed the study, 4 were excluded due to having extreme mean amplitudes outside of the normal distribution curve. Out of the remaining 50 patients, the mean age was 67.43 (SD=8.22) years and 66% were males (Table 1). All patients were non-demented and were at a mild-moderate stage of PD. While 6 PD patients scored above threshold for depression (>13) in the HAM-D, the overall mean score for HAM-D (Mean=5.62, SD=6.54) was low and did not meet cut-off for depression (Dissanayaka et al., 2007; Torbey et al., 2015).

Table 1: Characteristics of 50 study participants.

Characteristic	Score range (Minimum- Maximum), cut-off	Frequency or Mean (standard deviation)
Gender (Males/females)		33/17
Age		67.43(8.22)
Standardised Mini Mental State Examination (SMMSE)	24-30, Dementia<24 ^a	28.34 (1.71)
PD Cognitive Rating Scale (PDCRS)	64-132, Dementia<64 ^b	96.76 (14.05)
PD Cognitive Rating Scale impairment (PDCRSi)		37.24 (14.05)
Hamilton Depression Rating Scale (HAM-D)	0-32, Depression>12 ^c	5.62 (6.54)

Hamilton Anxiety Rating Scale (HAM-A)	0-35, Anxiety>13 ^d	5.82 (7.63)
Cambridge Contextual Reading Test (CCRT)		38.24 (5.58)
Unified Parkinson's Disease Rating Scale (MDS-UPDRS)		41.96 (13.14)
Hoehn & Yahr (HY)		2.11 (0.47)
Levodopa Equivalent Daily Dosage (LEDD)		587.89 (415.87)

^aManning and Ducharme (2010), ^bPagonabarraga et al. (2008), ^cDissanayaka et al. (2007), ^dHamilton (1959)

3.2 Behavioural measures

3.2.1 Accuracy

Response accuracy data underwent arcsine transformations to normalise the distribution. Analysis was performed using the transformed data; however raw percentages are reported for ease of interpretation. A significant main effect of *Congruency* ($F_{1,48}=5.83$, $p=0.02$) was observed, reflecting lower accuracy for incongruent (Mean=79.5%, SD=9.9%) compared to congruent (Mean=80.9%, SD=9.7%) prime-target pairs. A main effect of *Target valence* ($F_{1,48}=18.09$, $p<0.001$) was also observed, in which accuracy was lower for negative (Mean=74.6%, SD=16.8%) compared to neutral (Mean=85.8%, SD=7.7%) target valence trials. There were no significant interactions with HAM-D, LEDD and age.

3.2.2 Reaction time

Reaction time data was subjected to square root transformations to normalise the distribution. Analysis was performed using the transformed data; however real time results are reported for ease of interpretation. A significant main effect of *Congruency* ($F_{1,49}=17.68$, $p<0.001$) was observed, reflecting longer reaction times for incongruent (Mean=939ms, SD=204ms) compared to congruent (Mean=919ms, SD=207ms) prime-target pairs. A significant main effect of *Target valence*

($F_{1,49}=6.92$, $p=0.01$) was also observed, in which reaction times were longer for negative (Mean=946ms, SD=208ms) compared to neutral (Mean=912ms, SD=214ms) target valence trials. There were no significant interactions with HAM-D, LEDD and age.

3.3 ERP findings

There were no significant ERP main effects or interactions for frontal and central midline (Fz and Cz) channels, and left and right hemisphere electrode clusters examined. Latency differences were not observed for all ERP components studied. Significant results were observed for ERP components P300, LPP and N400 amplitudes for the parietal midline (Pz) channel and are presented in Table 2 and Figure 1. All three ERP components demonstrated significant interactions between Target Valence X Word Pair Congruency X HAM-D scores (Table 2). Post hoc analyses demonstrated that these interactions were for prime-target pairs with neutral target words (Neutral Target Valence X HAM-D scores), but not negative target words (Negative Target Valence X HAM-D scores) (Table 2).

Table 2: Repeated measures analysis (ANCOVA) of ERP components following Bonferroni adjustment. Interactions were observed between target word valence, word-pair congruency, and HAM-D scores (square root adjusted).

Condition ($F_{1,48}$, p)	P300	LPP	N400
Target word valence X word-pair congruency X HAM-D	13.64 (0.001)	6.38 (0.015)	6.31 (0.015)
Neutral target word valence X HAM-D	11.29 (0.002)	13.95 (<0.001)	8.85 (0.005)
Negative target word valence X HAM-D	1.81 (0.19)	0.28 (0.60)	0.13 (0.72)

Figure 1: (A) Grand average waveform for neutral target word pairs of low and high scoring participants in the Hamilton Depression Rating Scale (HAM-D) at the parietal midline (Pz) channel. High and Low scores in the HAM-D was determined by median split. Neg-Neu_LOW: Negative-Neutral prime-target pair for patients scoring low HAM-D scores. Neu-Neu_LOW: Neutral-Neutral prime-target pair for patients scoring low HAM-D scores. Neg-Neu_HIGH: Negative-Neutral

prime-target pair for patients scoring high HAM-D scores. Neu-Neu_HIGH: Neutral-Neutral prime-target pair for patients scoring high HAM-D scores. (B) A topographic representation of all three ERP amplitudes (uV) across 128 channels for neutral target word pairs in low and high HAM-D categories.

3.3.1 Correlations of ERP components with depression rating scales

Difference waves were constructed to further examine the significant interactions described above for neutral targets and to examine how the prime facilitated target ERP waveforms. Although this facilitation was expected for negative target words, we did not observe interactions with negative targets (see above and Table 2). Interactions observed were for neutral target words and therefore, difference waves were constructed for neutral targets only. A significant correlations between HAM-D scores with P300/LPP modulation, defined as a difference in amplitude when viewing word pairs with neutral targets (NeuNeu-NegNeu; see Figure 1), confirmed these interactions (P300: $r_s = -0.37$, $p = 0.009$ (Figure 2A); LPP: $r_s = -0.35$, $p = 0.016$ (Figure 2B)). These results were adjusted for HAM-A and PDCRSi. We also observed a significant correlation between HAM-D scores with N400 modulation, defined as a difference in amplitude when viewing word pairs with neutral targets (NegNeu-NeuNeu), confirming this interaction ($r_s = -0.35$, $p = 0.016$). This result was adjusted for HAM-A and PDCRSi scores.

Figure 2: Scatterplot demonstrating the correlation between Hamilton Depression Rating Scale (HAM-D) scores and the difference in (A) P300 amplitude and (B) LPP amplitude when viewing congruent and incongruent prime-target pairs with neutral targets (NeuNeu – NegNeu).

To further examine these correlations, participants were dichotomised according to high and low HAM-D scores by median split. Median split was used since the mean HAM-D score was less than the threshold score for depression in PD, and having only 6 patients meeting criteria for depression provided insufficient power to evaluate group differences between depressed and non-depressed. Patients ($N=25$) who scored less than 5 in the HAM-D were grouped into the “Low HAM-D” group, and the other 25 patients who scored 5 or more were grouped into the “High HAM-D” group. Repeated-measures ANOVA were then performed, which showed a significant interaction between *Group* and *Congruency* for the P300 ($F_{1,48}=11.25$, $p=0.002$) and LPP ($F_{1,48}=11.81$, $p=0.001$). Specifically, the low HAM-D group compared to the high HAM-D group showed a significant increase in P300 and LPP modulation (Figure 3). This indicates that PD subjects scoring higher on the HAM-D are more likely to show minimal changes in amplitudes of P300 and LPP when viewing word pairs with neutral targets.

Figure 3: Difference waves for the amplitude between congruent and incongruent prime-target word pairs with neutral targets (NeuNeu – NegNeu) for low and high scoring participants in the Hamilton Depression Rating Scale (HAM-D). Low and high scoring in the HAM-D groups were determined by median split. The solid line indicates PD patients with low HAM-D scores. Dashed line indicates PD patients with high HAM-D scores. Windows presented are an indication of the time frames where the waveforms were elicited for analysis.

Further examination also revealed that when participants were split into groups, the high HAM-D group showed a significant increase in N400 modulation when compared to the Low HAM-D group (Figure 3).

4. Discussion

The findings of the present study confirm that PD patients with higher depression scores have altered ERP waveforms compared to PD patients with low depression scores. We report a reduced parietal midline (Pz) in P300 and LPP difference waves between congruent and incongruent neutral targets in patients with higher compared to lower ratings of depression scores and reduced Pz-N400 difference waves between incongruent and congruent neutral targets in patients with higher compared to lower ratings of depression scores.

Our behavioural results showed that the accuracy to respond to target stimuli was lower for incongruent compared to congruent prime-target pairs, and negative compared to neutral target valence trials, suggesting difficulty in processing negative and incongruent targets. We observed longer reaction times for incongruent compared to congruent prime-target pairs, and therefore automatic priming effects were observed for both negative and neutral target valences. Longer reaction times were also demonstrated for negative compared to neutral target valence. These congruency effects are consistent with automatic priming studies in PD patients (Castner et al., 2007), and in healthy adults (Herring et al., 2011; Zhang et al., 2006; Zhang et al., 2012). Interestingly, the delayed reaction time to negative target trials compared to neutral target trials coincides with previous findings in PD patients on DBS stimulation (Castner et al., 2007), and healthy adults (Castner et al., 2007; Dahl, 2001; Rossell and Nobre, 2004). Depression scores did not influence accuracy and reaction time in the present study. This is in line with previous automatic affective word priming studies in general that demonstrated no influence of depression scores on participant's reaction times (Dannlowski et al., 2006; Koschack et al., 2003).

The P300 modulation at the parietal midline channel was significantly associated with depression ratings. Specifically, PD patients with higher compared to lower depression scores had reduced neural activity discriminating between negative and neutral primes when attention was directed to a

subsequent neutral target. Our results suggest that automatic processing of negative information is impaired in PD patients with higher ratings of depression symptoms. PD patients with high depression scores may automatically view neutral stimuli similar to negative stimuli. Therefore, consistent with uncontrollable negative thoughts in depression, such individuals may perceive neutral targets as negative, resulting in an aberrant Pz-P300 wave. Although the scope of the present study was limited to ERPs, it can be speculated that the P300 sensitivity observed may be indicative of impairments in the locus coeruleus, amygdala, and mesolimbic dopaminergic neural systems in PD patients with emotional deficits (Carretie et al., 2009; Liddell et al., 2005; Nieuwenhuis et al., 2005). Our results warrant future investigations using fMRI to identify underpinning neural substrates and impaired neural networks relating to automatic affective processes in PD.

Similarly, the LPP modulation at the parietal midline (Pz) observed in the present study was sensitive to negative and neutral primes when making evaluative judgements for neutral target words, and was associated with higher depression ratings. The group with high depression scores demonstrated a significantly reduced amplitude difference between negative and neutral primes for neutral targets compared to the group with low depression scores, suggesting sustained processing deficits indexed via the LPP (Citron, 2012). Dietz et al. (2013) also demonstrated a reduction in the LPP for negative compared to neutral picture stimuli in PD patients, and mapped this LPP sensitivity to apathy, but not depression or anxiety. Depression and apathy often coexist in PD, although it is argued that these two neuropsychological conditions may have a shared and/or distinct pathophysiology (Oguru et al., 2010). The present study did not measure apathy, which was a limitation. Although the LPP signal varies according to the stimulus modality (Liu et al., 2012), investigating the influence of apathy on the LPP generated using our automatic affective priming paradigm with visual words warrants future study.

The use of word stimuli also allowed us to investigate ERP components relating to emotional word processing via analysis of the N400 (Kutas and Federmeier, 2011). Previous studies suggest that the N400 amplitude denotes the difficulty of retrieving stored information associated with a word, with an increased N400 amplitude being observed with increased demands on retrieval or integration (Duncan et al., 2009). The present study demonstrated that the parietal midline N400 is sensitive to depression scores when elicited using our automatic affective priming paradigm with words. A reduced amplitude difference between incongruent (negative-neutral) and congruent neutral targets was evident for patients with high depression scores compared to those with low depression scores. The previous study by Dissanayaka et al. (2017) used the same automatic affective priming paradigm and demonstrated that the parietal N400 congruency effects for neutral targets did not differ between non-depressed PD patients, and healthy controls (Dissanayaka et al., 2017; Simola et al., 2009).

The present results are of importance with respect to understanding neural activity relating to depressive symptoms in PD. This study suggests that PD patients with high depression scores may have difficulty in emotional evaluation, particularly for neutral information when primed by negative compared to neutral word stimuli. Therefore, we observed a reduction in the P300, LPP, and N400 amplitude difference between incongruent and congruent neutral targets and correlations with depression scores. Although recent priming studies using picture paradigms have demonstrated alterations in the P300, LPP and N400 ERP waveforms with respect to depression (in non-PD samples), the direction of the alterations were contrary to our findings. Previous literature (Cermolacce et al., 2014; Delle-Vigne et al., 2014; Hu et al., 2017; Li et al., 2018) suggests that depressed individuals show larger ERP amplitudes for negative compared to neutral targets and therefore, we expected a larger difference wave for evaluative judgements on target words when comparing negative with neutral prime or target words. Our results may suggest PD-specific emotional deficits, specifically PD-specific deficits in initiating emotional judgements in PD

patients with high depression score. Further studies using source localisation and functional connectivity network approaches will assist identification underlying mechanisms of depression specific to PD, which may subsequently have the potential to advance knowledge in biological contributions to an increased vulnerability to depression persons with PD (Dissanayaka et al., 2011a).

5. Limitations

There are a few limitations worthy of note. Our sampling was a convenience pool of patients recruited from neurology clinics. The majority of patients with high depression (6 out of 50 patients; Mean HAM-D score=12.95, SD=7.91) were currently receiving pharmacological treatment, and therefore were excluded to avoid ERP sensitivity to antidepressant and anxiolytic medication. Compared to this excluded group, our study sample had lower average depression scores, of which the majority (88% of patients) scored below the threshold for clinical depression. Therefore, our sample size was insufficient to group participants with and without clinical depression when comparing ERPs. Furthermore, to reduce complexity of the paradigm and considering the involvement of older persons with PD, who may present with some cognitive deficits, it was not feasible to include positive stimuli. Moreover, literature suggest larger ERP sensitivity (e.g. P300) for negative compared to positive stimuli in depressed persons (Bistricky et al., 2014). Therefore, it was important to identifying ERP components relating to negative biases and depression in the present study.

6. Conclusions

The present paradigm identified potential ERP markers for early detection of depressive symptoms in PD. We used a visual word automatic affective priming paradigm and identified that the parietal midline P300, N400 and LPP were sensitive to ratings of depressive symptoms in PD. To our understanding this is the largest study to date in PD examining ERPs related to emotional processing. We did not use a healthy adult control group because comparisons between PD (without depression or anxiety) and healthy adults have already been made in previous research (Dissanayaka et al., 2017). Our results suggest that certain ERP markers are sensitive to emotion processing in PD and further investigations are required to identify the relationship between these ERP markers and clinical depression, and to isolate the specificity of the markers compared to depression in healthy older adults and in other disease populations.

Contributors:

Nadeeka Dissanayaka: Conception, data collection, organisation, writing of the first draft, review and critique

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All authors have approved the final article.

Conflict of interest

Authors disclose no conflict of interest.

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