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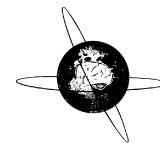
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Incongruent visual feedback during a postural task enhances cortical alpha and beta modulation in patients with Parkinson's disease



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HIGHLIGHTS

- Parkinson's disease (PD) patients rely more on visual information than healthy controls when controlling their balance.
- We determined cortical activity with event-related EEG during a weight-shifting task with (in)congruent visual feedback.
- Alpha/beta modulation in primary visual/motor areas discriminated between PD and controls.

ABSTRACT

Objective: In patients with Parkinson's disease (PD), augmented visual feedback (VF) can improve functional motor performance. Conversely, they appear to rely more on visual information than healthy subjects, which is unfavorable when this information is unreliable. Cortical beta activity is thought to be associated with the need for motor adaptation. We here compared event-related EEG parameters during a whole-body postural weight-shifting task between congruent and incongruent feedback conditions.

Methods: Twenty-four patients with PD and fifteen healthy, age- and gender-matched controls performed rhythmic swaying movements. VF was presented in real-time (congruent), delayed (incongruent), or was entirely absent. We estimated source activity in four regions-of-interest and determined motor-related spectral power and power modulation in alpha and beta frequency bands.

Results: For congruent VF no significant differences in cortical activity between the two groups were present. For incongruent VF, the PD group showed significantly higher beta modulation in primary motor cortex, and higher alpha modulation in primary visual cortex.

Conclusions: Event-related beta modulation in the motor network and alpha modulation in visual areas discriminated between groups, suggesting altered visuomotor processing in PD patients.

Significance: This study finds evidence for increased modulation of alpha/beta activity during perceptual-motor tasks in PD, possibly indicating an unwarranted higher confidence in VF.

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Abbreviations: COP, center-of-pressure; VF, Visual feedback.

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1. Introduction

Balance performance is not exclusively controlled at a subcortical level but requires non-trivial contributions from the cerebral cortex (Jacobs and Horak, 2007). Dual-task paradigms have

revealed that balance performance deteriorates when an additional cognitive load is added (Maki and McIlroy, 2007; Woollacott and Shumway-Cook, 2002). On the other hand, cognitive strategies can also facilitate motor performance, including those related to balance performance (Morris et al., 2009). Accordingly, cognitive strategies are included in the guidelines for physiotherapy in patients with PD (Bloem et al., 2010), for whom postural instability presents one of the major motor impairments (Rogers, 1996). Such strategies may range from memorizing explicit step-by-step instructions on how to best initiate and/or maintain a movement (Morris et al., 2009) to cueing, in which one tries to synchronize one's movements with a (rhythmic) external stimulus (Lim et al., 2005; van Wegen et al., 2014). Besides the use of cognitive strategies, motor function can also improve when movement-related feedback is provided (Huang et al., 2006). Augmented visual feedback (VF) helps both healthy subjects and patients with PD to better coordinate their movements with an external target (van den Heuvel et al., 2016). These and related technologies are hence increasingly adopted within therapeutic settings (Dockx et al., 2016).

The improvements in gait and gait-related activities in patients with PD due to cueing and VF raise the question which neural pathways and/or processes might be involved in facilitating these improvements (Jahanshahi et al., 1995). Over the past two decades it has become clear that motor symptoms in PD are associated with abnormally high levels of neural activity in the basal ganglia in a frequency range of 13–30 Hz, otherwise known as the beta band (Brown, 2007). Such oscillatory activity in the central nervous system arises from the synchronized firing patterns of local populations of neurons, and is typically studied in terms of (changes in) spectral power. Intriguingly, in patients with PD, exaggerated beta power (in basal ganglia) correlates with the degree of motor impairment (Brown, 2007; Jenkinson and Brown, 2011; Neumann et al., 2016) and it tends back to normal with dopamine replacement therapy (Hammond et al., 2007; Kühn et al., 2009; 2006; van Wijk et al., 2016). With respect to the positive effects of cueing on motor behavior, it is of particular interest that salient cues have been found to modulate “reactive” beta activity in the period prior to movement (Oswal et al., 2012). In the cortex, rhythmic stimulus presentation in a finger-tapping task was seen to produce an increase in post-movement beta-synchronization (te Woerd et al., 2015). It remains unclear, however, whether the role of beta power is functional or whether the activity is merely an epiphenomenon. That being said, beta power does provide an interesting window into the task-related changes in neural activity prior to, during, and following motor activity.

At present, there are no studies that have addressed the influence of VF on beta band activity. There are two reasons why such an influence is expected: first, VF and cueing both produce improvements at a behavioral level; second, it has been shown that, at the cortical level, movement error is negatively correlated to beta band activity (Tan et al., 2014). VF provides the subject with an explicit movement error and might therefore affect the beta band activity in similar ways. Importantly, in the current study, we focus on whole-body movement as cueing strategies have thus far been implemented in, and shown greatest benefits for, gross motor tasks. Specifically, we asked participants to perform a rhythmic swaying task with and without VF.

While VF may be a useful avenue for promoting motor behavior and learning, there is also evidence that subjects with PD overly rely on visual information (see for instance Azulay et al., 2002; Bronstein et al., 1990; De Nunzio et al., 2007). This makes them particularly vulnerable to incongruent visual information, in which the mapping between executed movement and the visual consequences of that movement is corrupted. In a previous study we found that patients with PD are less proficient in adapting to situ-

ations with incongruent VF than healthy controls (van den Heuvel et al., 2016). Recent research suggests that beta activity may indeed have a role in assessing the reliability of such sensory feedback. Tan et al. (2016) suggested that post-movement beta synchronization over the sensorimotor cortex negatively correlated with the uncertainty in feedforward estimations. In the present study, we therefore also contrasted motor-related activation in the cortex between conditions of incongruent and congruent VF comparing a group of patients with PD with a group of healthy controls. In line with the aforementioned findings we hypothesized beta activity to alter in the presence of congruent VF dependent on group (*hypothesis 1*). More importantly, we expected group-specific differences in cortical activity in the presence of incongruent VF (*hypothesis 2*).

2. Methods

2.1. Design

We performed a cross-sectional study of neurophysiological responses during a postural sway task in a group of patients with PD and a group of age- and gender-matched healthy controls. Data were derived from baseline assessments performed in a randomized clinical trial (RCT), registration number ISRCTN47046299 (van den Heuvel et al., 2013). The protocol was approved by the Medical Ethics Committee of VU University Medical Centre (VUmc) Amsterdam. All participants signed informed consent. A posturographic analysis as well as the results from the RCT have been reported elsewhere (van den Heuvel et al., 2014, 2016).

2.2. Participants

Subjects with PD were recruited from the Department of Rehabilitation Medicine of VUmc. Inclusion criteria were (i) a diagnosis of idiopathic PD according to the UK Brain Bank criteria (Gibb and Lees, 1988), mild to moderate stage (i.e. Hoehn & Yahr stages II and III), (ii) able to participate in the training programs associated with the RCT, and (iii) written and verbal informed consent. Exclusion criteria were: (i) presence of (other) neurological, orthopedic, or cardiopulmonary problems that could impair participation, (ii) Mini Mental State Examination score below 24 points, (iii) a recent change in dopaminergic medication, and (iv) cognitive, visual, and/or language problems impeding participation. Patients underwent the assessment in the ON-phase of levodopa medication, approximately 1.5 hours after intake of the last medication dosage. Control subjects were recruited from the social environment of the participating PD patients.

2.3. EEG-acquisition

All subjects wore a 64-electrode EEG headcap (TMSi, Enschede, The Netherlands), mounted in accordance with the 10–20 standard electrode placement. Electrode gel was applied between scalp and Ag/AgCl electrodes in order to minimize impedance below 10 k Ω , with an impedance of <20 k Ω considered acceptable. EEG signals were recorded against the common average using a 64-channel amplifier (Refa, TMSi, Enschede, The Netherlands) and sampled at 2048 Hz.

2.4. Performance measure and procedures

The postural assessment consisted of a lateral weight-shifting task in which participants stood upright and shifted their center of mass in a rhythmic fashion. The task was performed while standing on a force plate (Kistler 9281B, Ostfildern, Germany,

600 × 400 mm, sampled at 1 kHz) and facing a computer monitor (15"-LCD at eye-height about 80 cm away). Trials consisted of 100 s of voluntary rhythmic swaying in the frontal plane (i.e. side-ways) under different feedback conditions. Before and after each trial the subject stood quietly for 20 s. During a trial, a target circle moved from side to side at a frequency of 0.5 Hz. The task was to track the motion of this target by swaying the body sideways. The movement frequency of 0.5 Hz was selected as pilot measurements had shown this to be a frequency at which the task could be carried out comfortably throughout the duration of the experiment. Visual feedback consisted of the participant's center-of-pressure (COP) motion, which was indicated on the screen by a red circle. COP feedback was limited to motions along the medio-lateral (ML) axis and smoothed using an online low-pass filter (25 Hz cut-off). Feedback was presented either in real time, or delayed by 250 or 500 ms, further referred to as VF_{rt}, VF₂₅₀, and VF₅₀₀, respectively. In the control condition, only the target signal was visible (i.e. feedback was absent, VF_{no}) and participants were asked to match the motion of the target by swaying comfortably. After familiarization, every condition was repeated three times, with repetitions presented in randomized blocks.

2.5. Data analysis

Full details with respect to the posturographic data analysis can be found in van den Heuvel et al. (2016). In brief, along the ML axis the difference between the normalized COP and target time series served to define a tracking error (*Error*). Tracking stability was quantified as the circular variance (Var_c) of the relative Hilbert phase between COP and target motion (Mardia and Jupp, 2000). The normalized amplitude (A_{norm}) was determined as the COP's average peak excursion during each trial. For the sake of completeness, conventional posturographic outcomes related to quiet standing are provided in the supplementary materials.

2.6. Preprocessing

EEG data processing was performed in Matlab (The Mathworks, Natick, MA, version R2016b) using the fieldtrip toolbox (www.fieldtriptoolbox.org, Oostenveld et al., 2010). Data were first resampled to 1 kHz for compatibility with the co-registered force plate. Data were notch-filtered at $k \cdot 50$ Hz, ($k = 1 \dots 5$, bandwidth $\pm \frac{1}{2}$ Hz) to remove power line hum and subsequently band-pass filtered with a second-order bi-directional Butterworth band-pass filter (1.5–250 Hz) to reduce movement artifacts and high-frequency noise. Bad channels were detected on the basis of too large or too small means or standard deviations, and if necessary, interpolated via the surrounding channels using spherical splines.

For every trial, data were subjected to an independent component (IC) analysis (fastICA, Hyvärinen (1999)). ICs were considered artifacts if (i) median frequency <1 Hz (~movement artifact), (ii) median frequency >60 Hz (~EMG activity), (iii) if topography was dominated by the prefrontal channels (~EOG activity, i.e. eye movements). After omitting these ICs in the mixing matrix, the sensor EEG was reconstructed for further analysis.

2.7. Source reconstruction

We determined spatial filters in terms of linearly constrained minimum variance beamformers (Hillebrand and Barnes, 2003; Van Veen et al., 1997). An MRI template from the fieldtrip toolbox was used, segmented using a boundary element method. The lead field was computed using standard conductances of the different tissues (gray/white matter, skull, scalp). The MRI was parcellated using the automated anatomical labeling (AAL) atlas containing 90 regions-of-interest (ROIs). In line with our two hypotheses

listed below under *Statistical analysis*, and given the limited resolution of EEG, we restricted the analysis to bilateral primary motor cortex (M1), primary sensory cortex (S1), primary visual cortex (V1), and auditory areas (STS/STG). In the AAL atlas these regions correspond to the precentral gyrus, postcentral gyrus, the calcarine fissure, and superior temporal gyrus, respectively (Schmahmann et al., 1999; Tzourio-Mazoyer et al., 2002). Since no consistent activity was observed in other brain areas across participants these activities were not further analyzed and reported.

After broad-band filtering (1–80 Hz), spatial filters were computed for each ROI using EEG-covariance estimates in an event-related design. Events were defined as the moments of maximum right sway excursion and epochs were defined at ± 400 ms around events. In the case of quiet stance, events are constructed by randomly taking non-overlapping epochs at set intervals. After averaging the obtained beamformer weights within a ROI, EEG signals were projected to obtain source time series for every ROI and further assessed for their spectral contents. Since visual inspection did not suggest signs of lateralization we combined power values of homologous ROIs.

2.8. Spectral analysis

Spectrograms were estimated by means of a short-time Fourier transform using a 1-s sliding Hamming window (see Fig. 1A and B for illustration). To stabilize normality, spectrograms were log-transformed. The mean power of the quiet stance condition (baseline condition) was subtracted for normalization per subject. Next to the beta frequency band (15–30 Hz) we also considered alpha activity (8–14 Hz); the gamma frequency band (30–80 Hz) was analyzed as well but poor signal-to-noise ratio and large inter-subject variability hampered consistency in the results of this analysis. We note that we abstained from analyzing theta band activity (4–8 Hz) in view of the influence of residual movement artifacts. In every frequency band the spectrograms were averaged yielding the following alpha and beta power outcomes: (i) the mean power over time and (ii) the standard deviation over time, with the latter serving as measure of power modulation. Recall that we combined homologous ROIs.

2.9. Statistical analysis

All statistical assessments were realized using IBM SPSS Statistics 24. Outcomes were tested for departures from normality using the Shapiro-Wilk test and inspected for outliers. Differences in spectral power and power modulation were tested using multiple mixed-design ANOVAs, one for each frequency band and type of outcome (mean power, power modulation). To examine group differences in EEG activity with and without feedback, we used the between-subjects factor *group* and the within-subjects factor *feedback*, which only contained the conditions VF_{no} and VF_{rt} (hypothesis 1, *group* × *feedback*).

Since differences in motor performance may confound the analysis of the influence of incongruent VF, data were normalized with respect to VF_{no}. We examined group differences in EEG activity as a function of feedback congruency (hypothesis 2, *group* × *congruency*), using the between-subjects factor *group* and the within-subjects factor *congruency*, containing the conditions VF_{rt}, VF₂₅₀, and VF₅₀₀. Huynh-Feldt corrections are reported if Mauchly's test of sphericity was significant. For every ANOVA, group differences for outcomes with a significant interaction effect were analyzed by computing simple main effects, whereas group differences for outcomes without a significant interaction effect were analyzed using the main, between-subjects, effects reported by the ANOVA. A sequential Bonferroni-type procedure was applied to each ANOVA to control the false discovery rate, thus giving rise to cor-

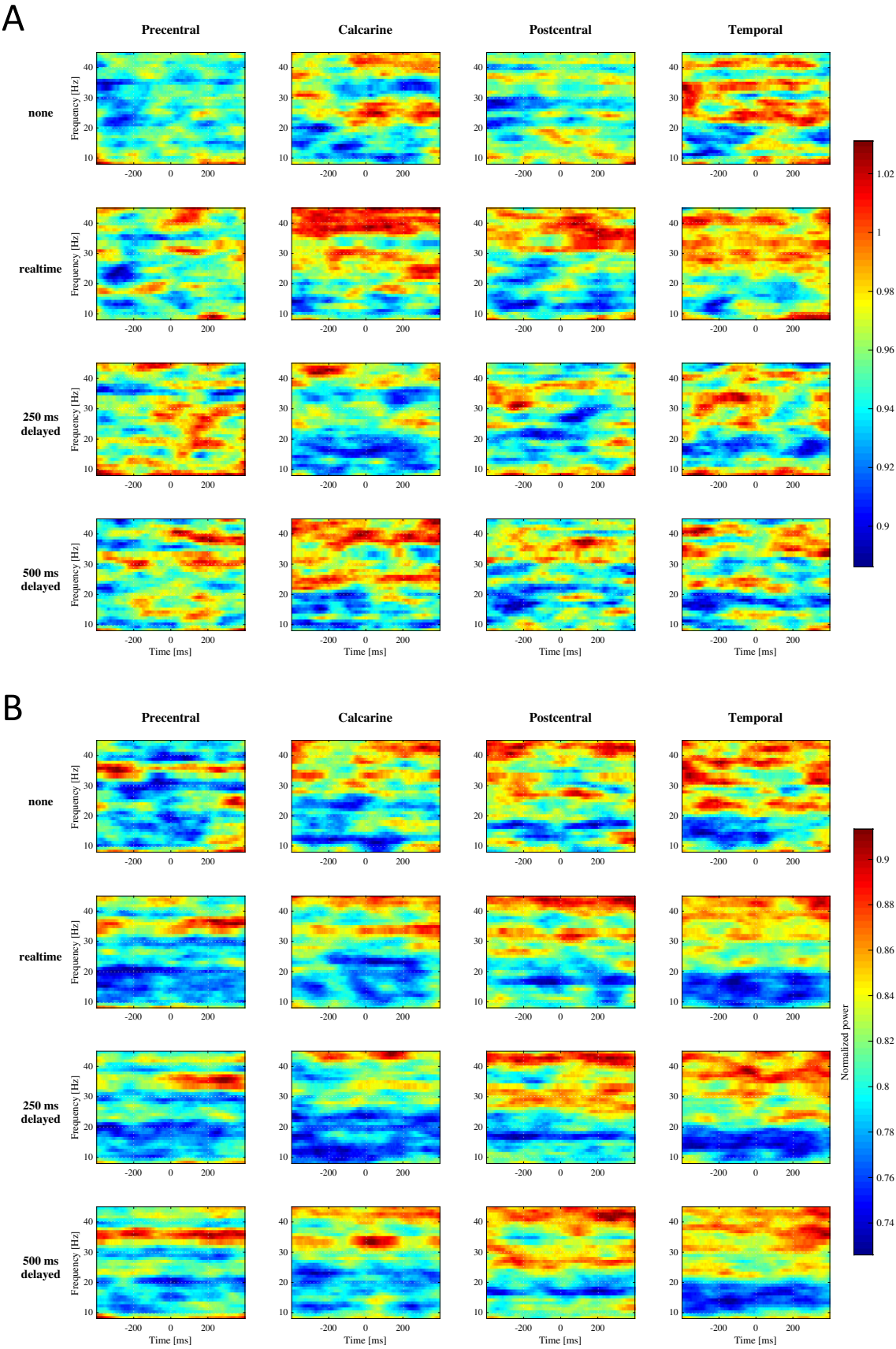


Fig. 1. Mean spectrograms for patients with PD (A) and healthy age-matched controls (B) for the four regions-of-interest (in columns) and the four feedback conditions (in rows). Spectral power is shown ± 400 ms around the event (i.e. the time of maximal right COP discursion to the right-hand side). We restricted our analysis to alpha (8–14 Hz) and beta bands (15–30 Hz).

rected significance criteria of various magnitude (Benjamini and Hochberg, 1995).

3. Results

3.1. Participants

Table S1 in the supplementary materials shows the participants' characteristics. Data of one healthy and one PD subject deviated from the mean by more than five times the standard deviation and were therefore excluded from the analyses. A total of 24 patients (8F/16 M, 67.6 ± 8.7 yrs) and 15 healthy age-matched controls (7F/8M, 66.9 ± 6.8 yrs) were entered in the final analyses.

3.2. Posturography

Hypothesis 1. Fig. 2 shows the effects of congruent (i.e. VF_{no} vs VF_{rt}). Patients with PD had significant higher *Error* ($F(1,37) = 8.887$, $p = 0.003$) and higher *Var* ($F(1,37) = 8.897$, $p = 0.001$), than healthy controls. The amplitude A_{norm} did not differ significantly between groups ($F(1,37) = 0.973$, $p = 0.417$). Significant group \times VF interaction effects for sway performance were absent.

Hypothesis 2. The interaction effects of group \times congruency were significant at the corrected significance level $\alpha = 0.0333$ for normalized *Error* and *Var* ($F(1.577,61.250) = 13.115$, $p < 0.001$, and $F(1.769,68.988) = 22.051$, $p < 0.001$, respectively), but not for normalized A_{norm} ($F(1.319,51.443) = 2.783$, $p = 0.142$). Both normalized *Error* and *Var* were significantly higher in healthy controls than in patients with PD: for *Error* in the conditions VF_{250} ($F(1,37) = 8.149$, $p = 0.003$) and VF_{500} ($F(1,37) = 31.940$, $p < 0.001$), and for *Var* in VF_{500} ($F(1,37) = 26.001$, $p < 0.001$); see Fig. 3. Recall that for this test the three outcomes were normalized to VF_{no} and that the non-normalized error was significantly higher in PD (also see Discussion). Normalized A_{norm} did not differ significantly between groups ($F(1,37) = 0.648$, $p = 0.289$).

3.3. EEG

Hypothesis 1. No significant interaction effects were present, and neither mean power nor power modulation displayed a significant main effect of group in any of the four ROIs; see Fig. S2 in the supplementary materials.

Hypothesis 2. None of the normalized outcome measures displayed a significant group \times congruency interaction effect (corrected significance level $\alpha = 0.00313$). Normalized alpha modulation in S1 showed a pronounced trend towards a significant interaction of group and delay ($F(2,74) = 5.280$, $p = 0.007$). Between-subject effects were tested against a corrected significance level of $\alpha = 0.00625$. Both normalized alpha modulation in V1 ($F(1,37) = 9.480$, $p = 0.004$) and normalized beta modulation in M1 ($F(1,37) = 9.293$, $p = 0.004$) were found to be significantly higher in PD than in healthy controls (Fig. 4B). For normalized mean power, none of the effects were significant in any of the ROIs (Fig. 4A).

4. Discussion

We investigated cortical synchronization and desynchronization accompanying the performance of a standing postural sway task in the presence of VF. Task-related spectral power and modulations thereof were examined under various feedback conditions. When congruent VF was provided, no significant differences in spectral power and power modulation between the patient group and healthy controls were found. However, as hypothesized, we observed a differential response in cortical activity under conditions of incongruent VF.

Our first hypothesis was based on the notion that changes in motor function in PD are associated with changes in cortical activation (van Wijk et al., 2012). In PD, the availability of external cues and/or task-related feedback can improve motor function (Lim et al., 2010; Nieuwboer et al., 2007; Rubinstein et al., 2002). Posturographic results did reveal an impaired task performance in patients with PD (Fig. 3), but this disparity was not reflected in any of the EEG measures, presumably because clear patterns of movement-related desynchronization and synchronization did not emerge. Typically, right before movement onset the amplitude of beta oscillations decrease and they remain suppressed until a post-movement rebound, that can exceed the baseline activity level (Pfurtscheller and Lopes da Silva, 1999; for a review see van Wijk et al., 2012). However, these findings mostly come from studies on movements of the upper extremity (i.e. hand or finger). Far fewer studies have investigated cortical activity during postural and gait-related tasks, (see e.g. Bruijn et al., 2015; Gwin et al., 2011). Nevertheless, taken at face value, the present results suggest that for this rhythmic swaying task with congruent VF beta activity did not differ for subjects with PD and healthy controls.

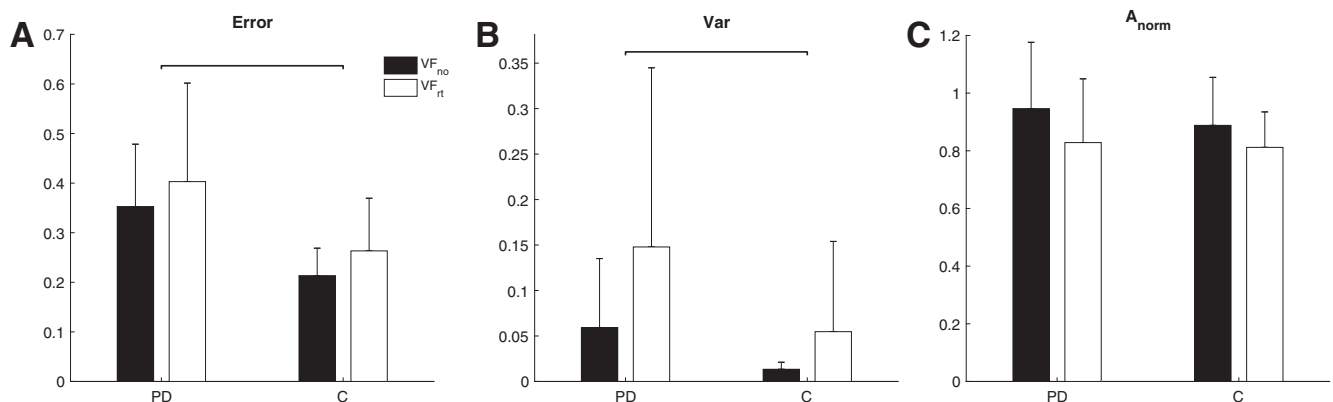


Fig. 2. Posturographic outcomes summarizing the effect of congruent VF (VF_{no} vs VF_{rt}). PD: patients with Parkinson's disease; C: healthy control subjects; *Error*: tracking error; *Var*: circular variance; A_{norm} : normalized amplitude. Error bars indicate the standard deviation. Note that for *Var*, untransformed data are shown to improve legibility; statistical analysis was performed on Fisher-transformed data.

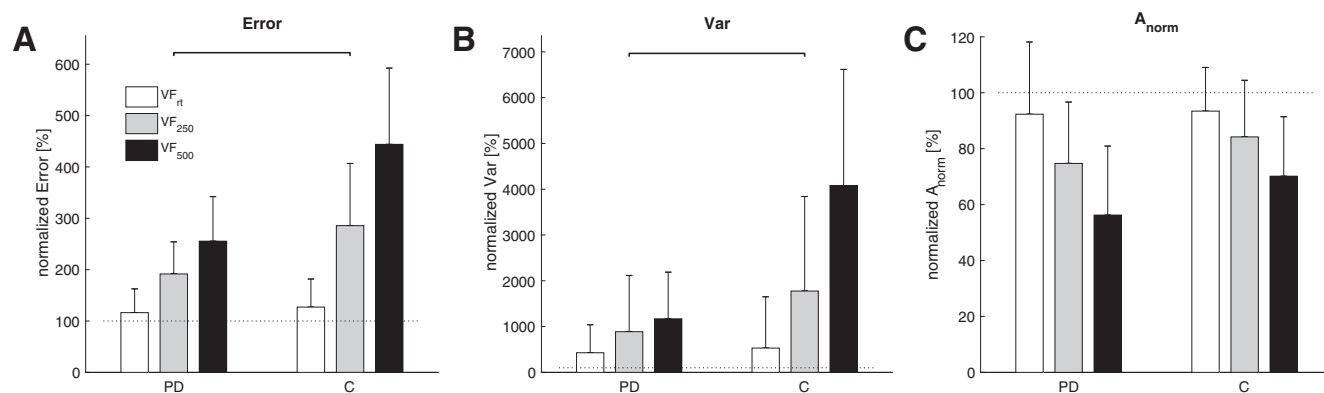


Fig. 3. Posturographic outcomes showing the effect of incongruent VF (VF_{rt} vs VF₂₅₀ and VF₅₀₀). Data have been normalized with respect to VF_{no} to control for differences in motor performance between the groups. PD: patients with Parkinson's disease; C: healthy control subjects; Error: tracking error; Var: circular variance; A_{norm}: normalized amplitude.

By extension, this may suggest that peripheral, PD-related effects like an increased rigidity were of greater significance for diminishing task performance.

Our second hypothesis was based on the assumption that patients with PD are more dependent on VF (Azulay et al., 2002; Bronstein et al., 1990; De Nunzio et al., 2007). If so, their task performance would suffer more from incongruent VF than that of healthy controls and show altered beta modulation in M1. Whereas congruent VF may enable subjects with PD to establish some form of voluntary control to overrule disturbed automatic reflexes, such a strategy would not work in conditions with incongruent VF. We therefore expected that both sway performance and cortical activity would reflect the increased task complexity. Our results revealed significantly greater event-related normalized beta modulation in the motor cortex for patients with PD. With incongruent VF, the PD group showed an increase in M1 beta activation relative to VF_{no} (Fig. 4B). On the other hand, healthy controls showed a decrease in the level of M1 activation relative to VF_{no}. It thus appears that in the presence of incongruent VF, the modulation of beta activity was suppressed in the healthy controls, but not in the patients with PD. This was expected, as beta synchronization has been found to be related to movement error (Tan et al., 2014) and here increased with incongruent VF (see Fig. 3). In conditions of unfamiliar or unreliable feedback, (pre-)existing motor programs become invalidated. Current sensory feedback needs to be integrated in order to update the internal model (Shadmehr et al., 2010). Post-movement beta synchronization has been shown to negatively correlate with the uncertainty in feedforward estimations derived from the internal model (Tan et al., 2016). Beta power modulation might thus reflect the relative usability of the VF and, thereby, the need for motor adaptation. The present results might therefore be interpreted as indicating that the relative uncertainty in the feedforward estimations in healthy controls is higher in conditions with VF than without VF. VF instilled relative lower confidence in the motor execution, thereby reflecting the need for adaptive behavior. The PD group, in contrast, may rely more on the existing internal model, and thus have a relatively lower need for updating the feedforward control. This fits with the behavioral observations: for healthy controls Var is higher for VF_{rt} than for VF_{no} and increases with VF₂₅₀ and VF₅₀₀; see Figs. 1 and 2, respectively, indicating much more variable tracking patterns that are reflective of active adaptive behavior. For PD patients, this effect on Var was not nearly that compelling, suggesting that they much less tried to adapt their motor behavior. It may reflect a difficulty to 'uncouple' the movement from the target motion. It may also reflect a general inability to generate a

proper response, as was explored by other studies on motor perseveration in PD (see e.g. Stoffers et al., 2001; Mohammadi et al., 2015). We must admit that these interpretations remain speculative as a single, conclusive view of the role of beta synchronization has not yet emerged (van Wijk et al., 2012).

The PD group showed greater normalized alpha modulation in V1; see Fig. 4B. Again, this suggests that with incongruent VF, the modulation of V1-activity was reduced in healthy controls, but not in the patients with PD. Modulation of synchronized alpha activity in this region (i.e. event-related desynchronization) has been ascribed to (anticipation of) processing of visual information and feature extraction (Pfurtscheller et al., 1994). It remains unclear whether the alpha and beta modulation are in some way related or whether they represent different phenomena.

4.1. Limitations

Next to the already acknowledged limitations in terms of spatial resolution, which precludes the reliable analysis of activity in smaller brain areas (e.g. supplementary motor area, cingulate motor area), and movement artifacts, we here remark on a few other design-related issues. The alignment of neural activity took place with respect to the maximum amplitude of the COP of successive swaying movements. It is debatable to what extent this parameter – and not, for example, the point of maximal COP velocity – is the best choice to which to align cortical activity. It should also be kept in mind that, in contrast to many other studies on event-related synchronization and desynchronization, the task studied here is a continuous task; after all, VF was provided continuously, giving the participant an ongoing indication of the error. If beta power is indeed a function of the extent to which a motor plan requires updating (Brittain and Brown, 2014; Tan et al., 2014), neural desynchronization/synchronization might have been taking place unsystematically, at various points in the sway circle, ultimately getting obscured through the averaging over events.

We would like to note that one of the premises of our study was that VF helps improve performance. Although at first glance it seemed that task performance did not appear to improve under conditions of VF_{rt}, this is not entirely true: detailed analysis revealed learning effects that took place over the course of the assessment (van den Heuvel et al., 2016). Given that performance was not (yet) at a steady state level for all subjects, this could very well have led to increased variability in the EEG activation patterns. Although it would certainly have been rather interesting to investigate learning effects in the EEG data as well, the number

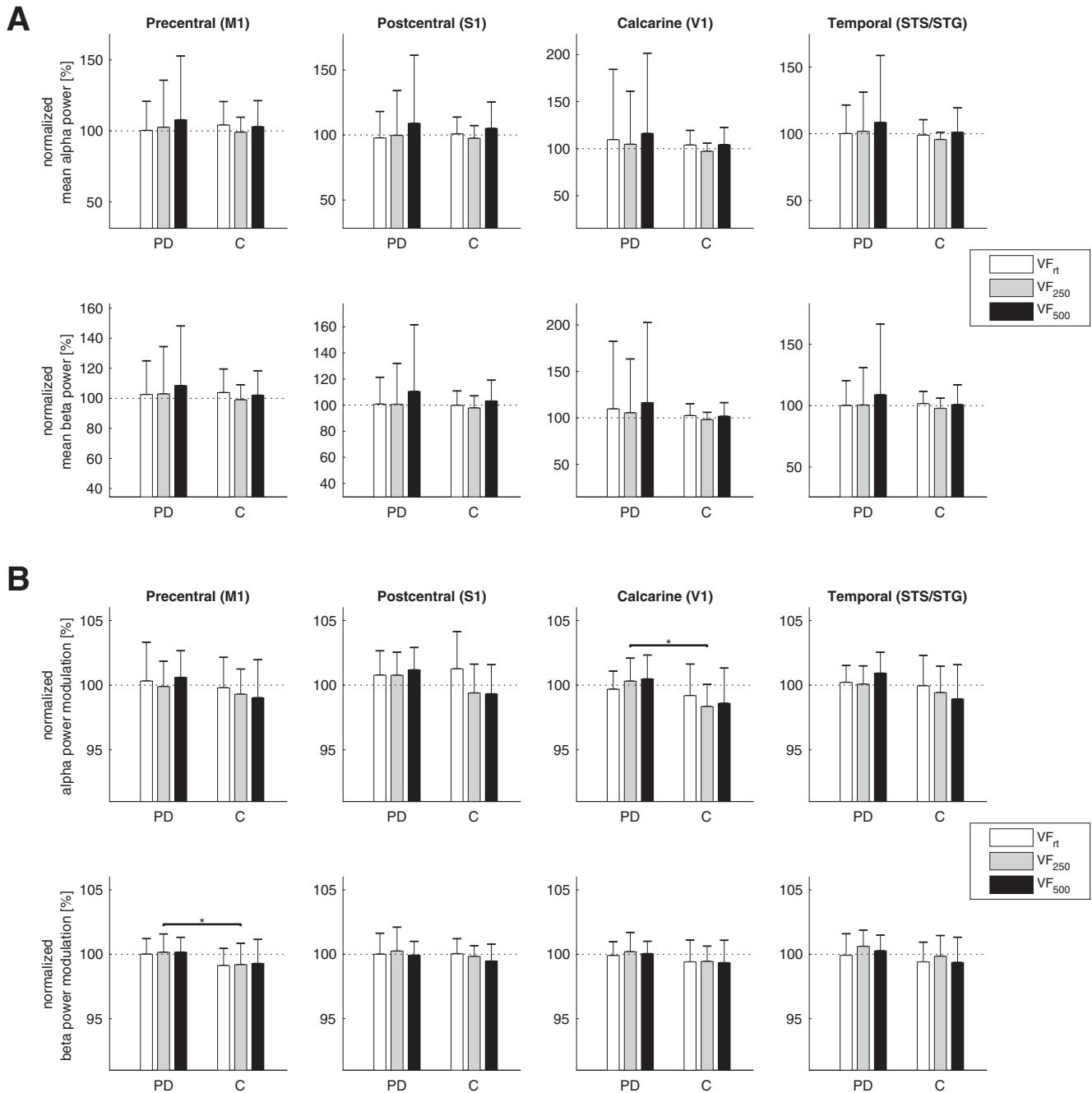


Fig. 4. Normalized mean power (A) and normalized power modulation (B) in the alpha and beta frequency bands for the PD group and the healthy, age-matched controls. Data were normalized with respect to VF_{no} , i.e. the outcome of either feedback condition was divided by that of VF_{no} and converted to percentages. The four regions-of-interest relate to primary motor cortex (M1), primary sensory cortex (S1), visual cortex (V1), and auditory areas (STS/STG). Activity was collapsed over left and right hemispheres. Asterisks indicate a significant effect of group. Error bars indicate the standard deviations. PD: patients with Parkinson's disease; C: healthy control subjects; Error: tracking error; Var: circular variance; A_{norm} : normalized amplitude.

of events needed for a reliable analysis of spectral power unfortunately did not allow for such an analysis.

Lastly, we point out that we did not formally assess visual acuity, vestibular function, proprioceptive function, and sensitivity of cutaneous mechanoreceptors in the foot, all of which can influence the maintenance of posture through their respective pathways.

5. Conclusion

The goal of the present study was to investigate the effects of VF on cortical activation during a postural sway task. When congruent

VF was provided, no significant differences in synchronized oscillatory activity were present between patients with PD and healthy controls. In contrast, when incongruent VF was provided, increased event-related alpha and beta modulation across the motor network were found in the PD group. This supports previous findings on altered movement-related modulations of alpha/beta activity in patients with PD, and is consistent with data showing greater reliance on congruent VF in PD patients. We can confirm the notion of beta modulation as a cortical controller of (rhythmic) motor performance (Brittain and Brown, 2014; Houweling et al., 2010; van Wijk et al., 2012).

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.clinph.2018.04.602>.

References

- Azulay JP, Mesure S, Amblard B, Pouget J. Increased visual dependence in Parkinson's disease. *Percept. Mot. Skills* 2002;95:1106–14. <https://doi.org/10.2466/pms.2002.95.3f.1106>.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B-Methodol.* 1995;57:289–300.
- Bloem BR, van Laar T, Keus SHJ, De Beer H, Poot E, Buskens E, Aarden W, Munneke M. Multidisciplinaire richtlijn ziekte van Parkinson. Alphen aan den Rijn: Van Zuiden Communications; 2010.
- Brittain JS, Brown P. Oscillations and the basal ganglia: Motor control and beyond. *NeuroImage* 2014;85:637–47. <https://doi.org/10.1016/j.neuroimage.2013.05.084>.
- Bronstein AM, Hood JD, Gresty MA, Panagi C. Visual control of balance in cerebellar and parkinsonian syndromes. *Brain* 1990;113:767–79. <https://doi.org/10.1093/brain/113.3.767>.
- Brown P. Abnormal oscillatory synchronisation in the motor system leads to impaired movement. *Curr. Opin. Neurobiol.* 2007;17:656–64. <https://doi.org/10.1016/j.conb.2007.12.001>.
- Brujin SM, van Dieën JH, Daffertshofer A. Beta activity in the premotor cortex is increased during stabilized as compared to normal walking. *Front. Hum. Neurosci.* 2015;9. <https://doi.org/10.3389/fnhum.2015.00593>.
- De Nunzio AM, Nardone A, Schieppati M. The control of equilibrium in Parkinson's disease patients: Delayed adaptation of balancing strategy to shifts in sensory set during a dynamic task. *Brain Res. Bull.* 2007;74:258–70. <https://doi.org/10.1016/j.brainresbull.2007.06.020>.
- Dockx K, Bekkers EM, van den Bergh V, Ginis P, Rochester L, Hausdorff JM, Mirelman A, Nieuwboer A. Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst. Rev.* 2016. <https://doi.org/10.1002/14651858.CD010760.pub2>.
- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 1988;51:745–52. <https://doi.org/10.1136/jnnp.51.6.745>.
- Gwin JT, Gramann K, Makeig S, Ferris DP. Electroocutaneous activity is coupled to gait cycle phase during treadmill walking. *NeuroImage* 2011;54:1289–96. <https://doi.org/10.1016/j.neuroimage.2010.08.066>.
- Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: Networks, models and treatments. *Trends Neurosci.* 2007;30:357–64. <https://doi.org/10.1016/j.tins.2007.05.004>.
- Hillebrand A, Barnes GR. The use of anatomical constraints with MEG beamformers. *NeuroImage* 2003;20:2302–13. <https://doi.org/10.1016/j.neuroimage.2003.07.031>.
- Houweling S, Beek PJ, Daffertshofer A. Spectral changes of interhemispheric crosstalk during movement instabilities. *Cereb. Cortex* 2010;20:2605–13. <https://doi.org/10.1093/cercor/bhq008>.
- Huang H, Wolf SL, He J. Recent developments in biofeedback for neuromotor rehabilitation. *J. NeuroEngineering Rehabil.* 2006;3:11. <https://doi.org/10.1186/1743-0003-3-11>.
- Hyvärinen A. Fast and robust fixed-point algorithms for independent component analysis. *IEEE Trans. Neural Netw.* 1999;10:626–34. <https://doi.org/10.1109/72.761722>.
- Jacobs JV, Horak FB. Cortical control of postural responses. *J. Neural Transm.* 2007;114:1339–48. <https://doi.org/10.1007/s00702-007-0657-0>.
- Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain* 1995;118:913–33. <https://doi.org/10.1093/brain/118.4.913>.
- Jenkinson N, Brown P. New insights into the relationship between dopamine, beta oscillations and motor function. *Trends Neurosci.* 2011;34:611–8. <https://doi.org/10.1016/j.tins.2011.09.003>.
- Kühn AA, Kupsch A, Schneider G-H, Brown P. Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur. J. Neurosci.* 2006;23:1956–60. <https://doi.org/10.1111/j.1460-9568.2006.04717.x>.
- Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, Schneider G-H, Brown P. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Exp. Neurol.* 2009;215:380–7. <https://doi.org/10.1016/j.expneurol.2008.11.008>.
- Lim LIIK, Van Wegen EEH, De Goede CJT, Deutekom M, Nieuwboer A, Willems A, Jones D, Rochester L, Kwakkel G. Effects of external rhythmic cueing on gait in patients with Parkinson's disease: a systematic review. *Clin. Rehabil.* 2005;19:695.
- Lim LIIK, van Wegen EEH, Jones D, Rochester L, Nieuwboer A, Willems A-M, Baker K, Hetherington V, Kwakkel G. Does cueing training improve physical activity in patients with Parkinson's disease? *Neurorehabil. Neural Repair* 2010;24:469–77. <https://doi.org/10.1177/1545968309356294>.
- Maki BE, McIlroy WE. Cognitive demands and cortical control of human balance-recovery reactions. *J. Neural Transm.* 2007;114:1279–96. <https://doi.org/10.1007/s00702-007-0764-y>.
- Mardia KV, Jupp PE. *Directional Statistics*. Chichester: Wiley; 2000.
- Mohammadi F, Brujin SM, Vervoort G, van Wegen EEH, Kwakkel G, Verschueren S, Nieuwboer A. Motor switching and motor adaptation deficits contribute to freezing of gait in Parkinson's disease. *Neurorehabil. Neural Repair* 2015;29:132–42. <https://doi.org/10.1177/1545968314545175>.
- Morris ME, Iansek R, Kirkwood B. A randomized controlled trial of movement strategies compared with exercise for people with Parkinson's disease. *Mov. Disord.* 2009;24:64–71. <https://doi.org/10.1002/mds.22295>.
- Neumann W-J, Degen K, Schneider G-H, Brücke C, Huebl J, Brown P, Kühn AA. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Mov. Disord.* 2016;31:1748–51. <https://doi.org/10.1002/mds.26759>.
- Nieuwboer A, Kwakkel G, Rochester L, Jones D, van Wegen EEH, Willems AM, Chavret F, Hetherington V, Baker K, Lim LIIK. Cueing training in the home improves gait-related mobility in Parkinson's disease: The RESCUE trial. *J. Neurol. Neurosurg. Psychiatry* 2007;78:134. <https://doi.org/10.1136/jnnp.200X.097923>.
- Oostenveld R, Fries P, Maris E, Schoffelen J-M. Fieldtrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput. Intell. Neurosci.* 2010;2011. <https://doi.org/10.1155/2011/156869>.
- Oswal A, Litvak V, Sauleau P, Brown P. Beta reactivity, prospective facilitation of executive processing, and its dependence on dopaminergic therapy in Parkinson's disease. *J. Neurosci.* 2012;32:9909–16. <https://doi.org/10.1523/JNEUROSCI.0275-12.2012>.
- Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin. Neurophysiol.* 1999;110:1842–57. [https://doi.org/10.1016/S1388-2457\(99\)00141-8](https://doi.org/10.1016/S1388-2457(99)00141-8).
- Pfurtscheller G, Neuper C, Mohl W. Event-related desynchronization (ERD) during visual processing. *Int. J. Psychophysiol.* 1994;16:147–53. [https://doi.org/10.1016/0167-8760\(89\)90041-X](https://doi.org/10.1016/0167-8760(89)90041-X).
- Rogers MW. Disorders of posture, balance, and gait in Parkinson's disease. *Clin. Geriatr. Med.* 1996;12:825–45.
- Rubinstein TC, Giladi N, Hausdorff JM. The power of cueing to circumvent dopamine deficits: A review of physical therapy treatment of gait disturbances in Parkinson's disease. *Mov. Disord.* 2002;17:1148–60. <https://doi.org/10.1002/mds.10259>.
- Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, Kabani N, Toga A, Evans A, Petrides M. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. *NeuroImage* 1999;10:233–60. <https://doi.org/10.1006/nimg.1999.0459>.
- Shadmehr R, Smith MA, Krakauer JW. Error correction, sensory prediction, and adaptation in motor control. *Annu. Rev. Neurosci.* 2010;33:89–108. <https://doi.org/10.1146/annurev-neuro-060909-153135>.
- Stoffers D, Berendse HW, Deijen JB, Wolters EC. Motor perseveration is an early sign of Parkinson's disease. *Neurology* 2001;57:2111–3. <https://doi.org/10.1212/WNL.57.11.2111>.
- Tan H, Jenkinson N, Brown P. Dynamic neural correlates of motor error monitoring and adaptation during trial-to-trial learning. *J. Neurosci.* 2014;34:5678–88. <https://doi.org/10.1523/JNEUROSCI.4739-13.2014>.
- Tan H, Wade C, Brown P. Post-movement beta activity in sensorimotor cortex indexes confidence in the estimations from internal models. *J. Neurosci.* 2016;36:1516–28. <https://doi.org/10.1523/JNEUROSCI.3204-15.2016>.
- te Woerd ES, Oostenveld R, Bloem BR, de Lange FP, Praamstra P. Effects of rhythmic stimulus presentation on oscillatory brain activity: The physiology of cueing in Parkinson's disease. *NeuroImage Clin.* 2015;9:300–9. <https://doi.org/10.1016/j.nicl.2015.08.018>.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002;15:273–89. <https://doi.org/10.1006/nimg.2001.0978>.
- van den Heuvel MRC, Daffertshofer A, Beek PJ, Kwakkel G, van Wegen EEH. The effects of visual feedback during a rhythmic weight-shifting task in patients with Parkinson's disease. *Gait Posture* 2016;48:140–5. <https://doi.org/10.1016/j.gaitpost.2016.03.020>.

- van den Heuvel MRC, Kwakkel G, Beek PJ, Berendse HW, Daffertshofer A, van Wegen EEH. Effects of augmented visual feedback during balance training in Parkinson's disease: A pilot randomized clinical trial. *Parkinsonism Relat. Disord.* 2014;20:1352–8. <https://doi.org/10.1016/j.parkreldis.2014.09.022>.
- van den Heuvel MRC, van Wegen EEH, de Goede CJT, Burgers-Bots IAL, Beek PJ, Daffertshofer A, Kwakkel G. The effects of augmented visual feedback during balance training in Parkinson's disease: Study design of a randomized clinical trial. *BMC Neurol.* 2013;13:137. <https://doi.org/10.1186/1471-2377-13-137>.
- Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Trans. Biomed. Eng.* 1997;44:867–80. <https://doi.org/10.1109/10.623056>.
- van Wegen EEH, Hirsch MA, Huiskamp M, Kwakkel G. Harnessing cueing training for neuroplasticity in Parkinson disease. *Top. Geriatr. Rehabil.* 2014;30:46–57. <https://doi.org/10.1097/TGR.0000000000000005>.
- van Wijk BCM, Beek PJ, Daffertshofer A. Neural synchrony within the motor system: What have we learned so far? *Front. Hum. Neurosci.* 2012;6. <https://doi.org/10.3389/fnhum.2012.00252>.
- van Wijk BCM, Beudel M, Jha A, Oswal A, Foltynie T, Hariz MI, Limousin P, Zrinzo L, Aziz TZ, Green AL, Brown P, Litvak V. Subthalamic nucleus phase–amplitude coupling correlates with motor impairment in Parkinson's disease. *Clin. Neurophysiol.* 2016;127:2010–9. <https://doi.org/10.1016/j.clinph.2016.01.015>.
- Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* 2002;16:1–14. [https://doi.org/10.1016/S0966-6362\(01\)00156-4](https://doi.org/10.1016/S0966-6362(01)00156-4).