Slow Brain Potential and Oscillatory EEG Manifestations of Impaired Temporal Preparation in Parkinson’s Disease

Peter Praamstra1,2 and Paul Pope1

1Behavioural Brain Sciences Centre, University of Birmingham; and 2Department of Neurology, Queen Elizabeth Hospital, Birmingham, United Kingdom

Submitted 1 March 2007; accepted in final form 29 August 2007

Praamstra P, Pope P. Slow brain potential and oscillatory EEG manifestations of impaired temporal preparation in Parkinson’s disease. J Neurophysiol 98: 2848–2857, 2007. First published August 29, 2007; doi:10.1152/jn.00224.2007. Performance in behavioral tasks is influenced by temporal expectations shaped by the temporal structure of the task. Such implicit temporal preparation is reflected in slow brain potentials and electroencephalographic oscillations and is attributed to interval timing mechanisms that probably depend on intact basal ganglia function. We investigated implicit timing in Parkinson’s disease using a choice reaction task with two temporally regular stimulus presentation regimes, both including occasional deviant interstimulus intervals. Control subjects, but not patients, demonstrated temporal preparation in the form of an adjustment in time course of slow brain potentials to the duration of the interstimulus interval. However, in both groups, timing perturbations were accompanied by a slow brain potential amplitude drop at the time of expected stimulus occurrence, demonstrating intact representation of time in patients. In patients, oscillatory activity in beta and alpha bands showed attenuated preparatory desynchronization and reduced postmovement event-related desynchronization, reflecting abnormal engagement and disengagement of sensorimotor and parietal areas. The results demonstrate profoundly deficient temporal preparation with preserved encoding of temporal information, a dissociation that may be explained by impaired dopamine-dependent motor learning. The results are discussed in the context of recent work on oscillatory activity in the basal ganglia.

INTRODUCTION

An important function believed to be supported by the basal ganglia is the processing of temporal information. Such a role is supported by animal models of striatal dysfunction and neuropharmacological experiments (Buhusi and Meck 2005) and by human functional neuroimaging (Jahanshahi et al. 2006; Rao et al. 2001). Consistent with a timing function of the basal ganglia, patients with Parkinson’s disease display an abnormal performance in motor and perceptual timing tasks (Harrington et al. 1998; O’Boyle et al. 1996; Pastor et al. 1992), although there are also reports of normal timing performance (Schnider et al. 1995; Spencer and Ivry 2005). The question whether the basal ganglia subserve a timing function is important in its own right, but is also of special relevance to the parkinsonian motor disorder. Altered motor function in Parkinson’s disease includes changes in movement preparation that may have deficient timing as an important component.

Interval timing is commonly investigated using tasks with explicit timing requirements such as tapping at a certain rate (e.g., O’Boyle et al. 1996) or the comparison of different temporal intervals (e.g., Pastor et al. 1992). Another approach is the manipulation of the timing of behaviorally relevant events such as the conditional probability of occurrence of reaction stimuli. This “implicit timing” approach addresses timing processes through the behavioral adjustment of subjects to the timing characteristics of the task. The approach has its roots in the observation that reaction time performance is influenced by temporal expectations that are shaped by the temporal structure of a task (Näätänen 1981 and has recently been applied in neurophysiological investigations in monkey (Gold and Mansell 2002; Janssen and Shadlen 2005; Riehle et al. 1997) and man (Praamstra et al. 2006; Schoffelen et al. 2005; Trillenberg et al. 2000).

Praamstra et al. (2006) used electroencephalographic (EEG) slow brain potentials and oscillatory EEG changes to investigate preparatory adjustments to the timing structure of a task. Following the first description of the contingent negative variation (CNV) by Walter et al. (1964), other EEG studies have confirmed this preparatory slow wave’s sensitivity to temporal parameters of a task. Building on previous work using explicit timing tasks (Macar and Vidal 2003; Pfeuty et al. 2005), we found that adjustments to task timing were manifested in the time course of the CNV and in the time course of the anticipatory decrease (event-related desynchronization, ERD) of EEG activity in the beta frequency band (cf. Alegre et al. 2003). In the present study, we used the same task and EEG measures to investigate temporal preparation in Parkinson’s disease. Previous work has already shown that preparatory slow brain potentials differ preceding predictably timed versus variably timed reaction signals (Cunnington et al. 1995), but effects have not been consistent across studies (Jahanshahi et al. 1995). The goal of our study was to investigate whether Parkinson patients show normal temporal preparation effects adjusted to task timing. In case of altered temporal preparation, we aimed to establish whether this reflects impaired temporal processing per se or a failure to utilize temporal information.

In addition to investigating temporal preparation in Parkinson’s disease, we evaluated task-related changes in oscillatory EEG activity from the perspective of pathological oscillatory activity in basal ganglia–cortical circuits. In the parkinsonian monkey, dopamine deficiency causes abnormal synchronization of neural activity in basal ganglia structures (for review, see Boraud et al. 2005). Presumably related phenomena have been found in the scalp-recorded EEG of Parkinson patients,
i.e., a reduced responsiveness in terms of movement-related (de)synchronization (e.g., Brown and Marsden 1999; Defebvre et al. 1996), and abnormal coherence between different recording sites (e.g., Silberstein et al. 2005). The available data are mainly recorded with relatively few electrodes and/or from tasks that predominantly used self-paced movements at very slow rates. Because the present study used high-density EEG and involved movements to reaction stimuli presented at relatively fast rates, it provided an opportunity to evaluate movement-related (de)synchronization in Parkinson’s disease with greater spatial resolution in hitherto unexplored task conditions.

In summary, we used slow brain potentials and analyses of oscillatory EEG changes to investigate whether, as a result of basal ganglia involvement in timing, Parkinson patients are impaired in adjusting their performance to the temporal information implicit in the timing of an experimental task. The results bear on the use of temporal information for movement preparation in Parkinson’s disease but also contribute new information regarding slow brain potential and spectral EEG changes as cortical manifestations of basal ganglia dysfunction.

METHODS

Participants

The Parkinson’s disease group consisted of 10 men with a mean age of 62 yrs (range: 56–68). The age-matched controls were 12 men with a mean age of 62 yrs (range: 54–71). All but one of the participants (1 patient) were right-handed as determined by self-report. Both groups had normal or corrected-to-normal vision. Participation was based on informed consent and the study was approved by the South Birmingham Research Ethics Committee. All patients were on dopaminergic medication and had moderate disease severity as assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) (Lang and Fahn 1989). The mean score on the motor subsection was 28 ± 9 (mean ± SD; range: 15–41; maximal range: 0–108). Disease duration ranged between 3 and 9 yr. All patients had bilateral motor symptoms with minor asymmetry. The investigation and the UPDRS rating were performed after overnight withdrawal from medication (>12 h).

Procedures and stimuli

The experiment consisted of a choice response task to arrow stimuli presented on a computer screen. The critical experimental manipulations concerned the interval between successive reaction stimuli or trials, i.e., the stimulus-onset-asynchrony (SOA). Likewise, neurophysiological analyses (see following text) specifically addressed the preparatory activity during these intervals. The experiment was divided in eight blocks of ~6 min each. Within each block, individual trials were presented in series of 11, 13, 15, 17, 19, or 21 trials. In each series, the SOA between successive reaction stimuli was either 1.5 or 2.0 s except for the last SOA, which was always 1.75 s, that is, 250 ms shorter (short deviant) or longer (long deviant) than the preceding SOAs (see Fig. 1). Trial sequences with long and short SOAs followed each other randomly with pauses of 8 s between them to give subjects time to blink. The total number of sequences presented was 96 equally divided in short and long SOA series. Responses to each stimulus were made with the index or middle finger depending on the direction of the arrow, which pointed to the left and right with equal probability. Subjects started the experiment with the left or right hand and switched response hand every two blocks. Within each group, half of the subjects started with the left, the other half with the right hand.

![FIG. 1. Schematic of the different stimulus presentation regimes. Reaction stimuli were presented at stimulus-onset-asynchrony (SOA) of 2.0 or 1.5 s in long and short SOA trial series. Trial series had a variable number of trials (11–21 trials) and always ended with a timing perturbation in the form of a deviant SOA of 1.75 s, i.e., shorter or longer than the preceding standard SOA. Analyses compared preparatory activity in the short and long SOAs and addressed the effect of entrainment to the standard SOA on the preparatory activity during the deviant SOA.](http://jn.physiology.org/)

The experiment was preceded by a short practice block that contained sequences with long and short SOAs. Participants were not made aware of the deviant final SOA. They were debriefed after the experiment and asked whether they had been aware of any temporal irregularity other than the different SOAs between series.

The experiment was run in a normally illuminated room. Stimuli were presented on a 17-in monitor at a resolution of 800 × 600. Participants were seated comfortably in an armchair with their eyes 100 cm from the monitor. Response keys were attached to the armrests of the chair and subjects rested their fingers on the keys. The stimuli were presented in white on a gray background for a duration of 200 ms. A fixation area was indicated by permanently displayed brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of 1 × 1° of visual angle; the arrows measured 0.75 × 0.75° of visual angle.

EEG recording, data processing, and analysis

EEG was recorded continuously with Ag/AgCl electrodes from 128 scalp electrodes relative to averaged left and right mastoid reference. The electrodes were placed according to the 10–5 electrode system (Oostenveld and Praamstra 2001) using a nylon electrode cap. Eye movements were monitored by bipolar horizontal and vertical electrooculographic (EOG) derivations. EEG and EOG signals were sampled at 512 Hz and amplified with a band-pass of 0–128 Hz by BioSemi ActiveTwo amplifiers. The continuous EEG recordings were off-line segmented in 3,500-ms epochs starting 500 ms before stimulus onset and spanning one intertrial interval. Subsequently, separate averages were constructed for short and long SOA conditions performed with the left and with the right hand. To capture the preparatory activity at a time when subjects were adjusted to the series’ fixed SOA, these averages excluded the first five trials of each series. Averages of the final deviant SOAs were constructed separately for short deviant and long deviant SOAs but collapsed across response hands given the small number of deviant trials. Eye movement and blink artifacts were corrected using a multiple source analysis approach (Berg and Scherg 1994).

Slow brain potential amplitudes were analyzed by pooling the values of neighboring electrodes within regions of interest, identified on the basis of the scalp topography of the CNV in control subjects, enhanced by a current source density derivation (Perrin et al. 1989). Thus the amplitude and the slope of the CNV were analyzed in regions of interest (ROIs) overlying left and right frontocentral areas (C1, C3, F3, FC3, FC1, F1, C2, C4, FC4, FC2, FC4). The ROIs were almost identical to the ROIs used in Praamstra et al. (2006), where the CNV was of considerably higher amplitude and localized to the lateral premotor cortex. The amplitude was quantified as the mean amplitude in the final 100 ms before the next reaction signal, i.e., 1,400–1,500 ms poststimulus in the short SOA condition and 1,900–2,000 ms in the long SOA condition. The slope was determined from the mean amplitude in the window 700–800 ms and the mean amplitude in the terminal 100 ms of the CNV.
In addition to analyses of slow brain potentials, we performed time-frequency analyses to extract task-related changes in spectral amplitude, i.e., ERD and event-related synchronization (ERS). These analyses were performed with BESA (Brain Electrical Source Analysis, MEGIS GmbH) and with FieldTrip, a toolbox developed at the F.C. Donders Centre for Cognitive Neuroimaging (http://www.ru.nl/fconders/fieldtrip) using Matlab (MathWorks, Natick, MA). After segmentation and artifact correction, each single trial was transformed in the time-frequency domain using complex demodulation set to a frequency resolution of 1 Hz and temporal resolution of 50 ms in the frequency range 5–50 Hz. Time-frequency representations per channel and subject were created by averaging spectral density amplitude over trials. Inspection of the individual subject and grand average time-frequency representations enabled the identification of time-frequency windows defining peaks and troughs of spectral amplitude. In terms of the frequency axis, the windows were selected in such a way that they were within the alpha or beta frequency range. In terms of the time axis, the windows had a narrow width in view of the rapid time course of changes in spectral amplitude, and were positioned symmetrically around the peak and trough latencies.

The three-dimensional (channel, frequency, time) data produced by the time-frequency analysis were evaluated with cluster-level randomization tests in FieldTrip, developed to handle the multiple comparison problem inherent in the statistical evaluation of high-density EEG and magnetoencephalographic (MEG) data. The cluster-level randomization method first identifies electrodes where the difference between two conditions exceeds a chosen significance level. These electrodes are candidates for inclusion in clusters determined by a cluster-finding algorithm. The method takes the cluster with the maximum test statistic, i.e., the cluster with the maximum difference between conditions, to calculate a critical value for statistical significance under the null distribution for this test statistic. The null distribution is computed by means of a permutation method that randomly reassigns replications to conditions (between-subjects design) or randomly permutes the order of paired observations (within-subjects design). This computation is performed by a Monte Carlo approximation involving a user-specified number of random draws. Because $P$ values for any given cluster are computed under the null distribution of the maximum cluster-level statistic, the method controls for type I errors. We used default parameters for the definition of a cluster (electrodes within 4 cm distance and a minimum of 2 neighbor channels). The number of random draws for reference distributions was always ≥500. For earlier application see Osipova et al. (2006).

In addition to analyses at the sensor level, the task-related changes in spectral amplitude in the beta band were also analyzed by means of a beamformer source reconstruction to localize the beta modulation. The beamformer technique scans the brain voxel wise, computing activity at each voxel by applying a spatial filter. The BESA beamformer that was used is a modified version of the linearly constrained minimum variance vector beamformer in the time-frequency domain as described in Gross et al. (2001). The beamformer operator is computed using the cross spectral density matrix (the time-frequency equivalent of the data covariance matrix) computed from the single-trial data. This allows one to image evoked as well as induced oscillatory activity in a user-defined time-frequency range relative to a triggered event.

Reaction time analyses were performed on the responses following standard long and short SOAs and the responses to trials following a deviant SOA, separately for short deviant and long deviant SOAs. For the analysis of responses following standard long and short SOAs, the first five responses in each trial series were discarded. In addition, outliers (≥3 SD from the mean) were excluded. The responses to the remaining trials were averaged to obtain mean values for short standards and long standards, respectively. The EEG slow brain potential and reaction time data were analyzed using ANOVA in SPSS.

**Results**

**Response times**

Participants were debriefed to assess whether they had been aware of the different duration of the final deviant SOAs. In neither of the groups did participants notice the timing perturbations. Breaches of temporal expectation were, nonetheless, reflected in reaction times. Across groups, responses were slower after deviant (484 ± 57 ms) than after standard (475 ± 56 ms) intervals [$F(1,20) = 9.03, P < 0.01$]. This effect was not significantly different between groups and was not influenced by whether the standard SOA preceding the final deviant SOA was long or short. Overall reaction times were not significantly different between groups [$F(1,20) = 2.73, P = 0.11$], although patients were numerically slower than control subjects (499 ± 56 vs. 460 ± 53 ms). For both groups, response times were slower with the left than with the right hand (491 ± 62 vs. 468 ± 54 ms), yielding a main effect of hand [$F(1,20) = 12.03, P < 0.01$]. There were no significant differences in error rate between patients and controls (2.1% vs. 1.1%) or between short and long SOA conditions (1.6% vs. 1.6%).

**Neurophysiology**

**Slow brain potentials. Effects of SOA.** If subjects demonstrate temporal preparation adjusted to the different stimulus presentation regimes, this should be reflected in the time course of the CNV. In particular, the long SOA condition should have a slower rising CNV than the short SOA condition, both culminating in a terminal CNV segment of the same amplitude. The CNV amplitude was quantified in two groups of electrodes over left and right frontocentral areas, where the CNV reached its maximum amplitude in the control group. As shown in Fig. 2, in control subjects, the amplitude of the CNV is comparable between short and long SOA conditions. This was expressed in the absence of an effect of SOA on the terminal CNV amplitude [$F(1,11) = 2.27, P = 1.60$]. The mean slope across the two groups of electrodes was $-2.9 ± 3.1 \mu$V/s for the short SOA conditions and $-1.8 ± 2.3 \mu$V/s for the long SOA conditions, which yielded a significant difference [$F(1,11) = 6.91, P < 0.05$].

In the Parkinson patient group, there was not just a reduced amplitude CNV but a complete absence of an anticipatory negative wave. The terminal CNV had the same amplitude in long and short SOAs and was significantly smaller than in control subjects [$F(1,20) = 11.80, P < 0.005$]. Comparing the short and long SOA CNV in the interval 1.4–1.5 s (i.e., during the terminal 100 ms of the short SOA CNV), the long SOA CNV was of smaller amplitude in control subjects [$F(1,11) = 6.23, P < 0.05$] but not in patients [$F(1,9) < 1$]. This yielded a significant group by SOA interaction [$F(1,20) = 4.50, P < 0.05$] and indicates temporal preparation adjusted to the SOA duration in control subjects but not in patients. Of note, the Parkinson patients had a higher amplitude early CNV (termed O-wave) than control subjects. The functional significance of the early O-wave of the CNV is unclear, and this result will not be further considered.

**Effects of timing perturbations.** We have previously found that temporal preparation is also manifested in an abrupt drop in CNV amplitude after the time of expected stimulus occur-
rence when the stimulus occurs later than anticipated. Hence we evaluated whether there was an abrupt change in slope of the CNV in the long deviant condition. This was performed by comparing the slope in the window from 1,400 to 1,600 ms to the slope in the subsequent window of 1,600–1,800 ms based on inspection of the grand average data in both groups (see Fig. 3). Slopes were determined by fitting a linear regression line to the data in each time window. The analysis was performed on the same group of electrodes as the previous CNV analyses. Results demonstrated a significant difference between the slope of the CNV in the early and the slope in the late time window across groups [$F(1,20) = 9.12$, $P < 0.01$] without an interaction with the factor group ($F < 1$). This finding indicates that although patients did not show signs of temporal preparation in the negative rise of the CNV, they did encode the regular interstimulus interval durations and registered the deviant final interval when it was longer than expected.

TIME-FREQUENCY ANALYSES. Analyses of task-related changes in spectral amplitude were guided by an initial inspection of the grand average time-frequency spectra, represented in terms of percentage change relative to the 500 ms preceding the reaction stimulus. The predominant spectral changes occurred in the beta band in a range of 14–28 Hz and in the alpha band in a range of 8–12 Hz. The spectral changes consisted of an initial reduction in activity (ERD), followed by a return to baseline and then an increase of activity (ERS). Further analyses addressed whether groups differed in terms of the magnitude of these spectral changes, their time course, and their distribution. Absolute spectral amplitudes in the relevant frequency ranges were not significantly different between the groups and are not further considered.

**Beta band ERD/ERS.** Time-frequency spectra for the long SOA condition are represented in Fig. 4A with the rectangular frames delineating time-frequency windows of beta ERD and beta ERS. The windows are centered on the times of maximal change, as identified visually in the grand averaged spectra, and differed slightly between the groups. The ERD analysis window for the control group was from 250 to 550 ms and the ERS window from 1,000 to 1,300 ms. The corresponding windows for the PD patients were from 300 to 600 ms and from 1,100 to 1,400 ms. To capture the beta modulation in its entirety, it was quantified from peak to peak, i.e., ERD relative to ERS, using the above-defined windows. The beta modulation was localized bilaterally over sensorimotor areas, as illustrated in Fig. 4B. To assess the distribution of this beta modulation within groups, we used a cluster randomization analysis which identified cluster(s) of electrodes where ERD and ERS significantly differed (see METHODS). With an $\alpha$-threshold of $P < 0.001$ for individual electrodes to be considered as candidates in a cluster, a single large cluster of electrodes covering the central sensorimotor areas was found in both groups, defining the region of maximal beta modulation. The beta modulation, in long and short SOA conditions, did not

**FIG. 2.** Contingent negative variation (CNV) waveforms in short and long SOA conditions, averaged across left and right hand response blocks. The waveforms represent the mean activity recorded from the electrodes marked in white, located approximately over the left (PM-L) and right (PM-R) premotor cortex. The gray bars indicate the time windows for quantification of the CNV. The dashed lines indicate the 1,500- and 2,000-ms SOA durations. The scalp topographies are averaged across short (1,400–1,500 ms) and long SOA conditions (1,900–2,000 ms) and represent current source density distributions to enhance spatial detail.

**FIG. 3.** Effect of timing perturbation on slow brain potentials in the long deviant condition. The CNV over left and right premotor areas peaks around 1,600 ms in control subjects and in patients, i.e., shortly after the expected time of stimulus arrival (1,500 ms), and drops in amplitude well before stimulus presentation at 1,750 ms (indicated by arrow head). The regression line, fitted to the downgoing slope of the CNV in the traces for the patient group, emphasizes the similarity between groups.
choosing a narrow time window around the time of stimulus modulation is continuous and without stable baseline before data inherent in the experimental design, i.e., that the beta band frequency representations. The graphs emphasize a feature of the patients. demonstrated beta modulation that differed between controls and individual electrodes to be considered as candidates in a significant ($P < 0.05$) clusters over sensorimotor areas. Simi-
larly localized clusters were identified in the short SOA condition. Moreover, equivalent results were obtained when the ERD phases were compared between patient and control group.

These analyses show that task-related modulation of beta activity is of the same magnitude in patients and controls and retains a focal distribution in patients. However, the modulation is abnormal in the patient group in the sense of being shifted in its entirety as measured relative to the beta level at stimulus onset. The net effect of this shift is that patients show an attenuated preparatory ERD and, instead, a more reactive stimulus-driven ERD.

Beta band ERD/ERS: beamformer analysis. The modulation of beta band amplitude was also analyzed with a beamformer approach that localized the cortical sources of the beta activity modulation. For this purpose, the time-frequency windows of ERD and ERS were tailored individually on the basis of each subjects’ time-frequency spectra. The width of the windows was fixed at 300 ms, as in the preceding text, but they were placed so as to best capture the individual ERD and ERS maxima, which occurred slightly later in patients than in control subjects ($F(1,20) = 5.11, P < 0.05$). The timing of the maxima was also influenced by SOA ($F(1,20) = 13.69, P < 0.01$). In terms of the frequency range included in the individually tailored time-frequency windows, there was no difference between groups ($F < 1$). The maximum and minimum frequencies were 28 and 14 Hz, respectively.

The beamformer analysis demonstrated bilateral sources in contralateral and ipsilateral sensorimotor areas as illustrated for two conditions in Fig. 6. The activation maxima had virtually identical locations between groups, with mean Talairach-Tournoux coordinates for left and right hemisphere sources $x = -28 \pm 3$, $y = -17 \pm 7$, $z = 56 \pm 5$ and $x = 29 \pm 4$, $y = -17 \pm 8$, $z = 53 \pm 6$ for control subjects and $x = -29 \pm 4$, $y = -19 \pm 6$, $z = 54 \pm 5$ and $x = 28 \pm 6$, $y = -19 \pm 7$, $z = 54 \pm 6$ for patients. The further analysis consisted of a ROI approach that evaluated the relative strength

differ between groups in either the depth of modulation or the scalp distribution. That is, with an $\alpha$-threshold of $P < 0.05$ for individual electrodes to be considered as candidates in a cluster, there was not a single group of electrodes that demonstrated beta modulation that differed between controls and patients.

To evaluate the beta band modulation in more detail, time plots of the modulation were constructed from the time-frequency representations. The graphs emphasize a feature of the data inherent in the experimental design, i.e., that the beta band modulation is continuous and without stable baseline before stimulus presentation. The data were therefore aligned by choosing a narrow time window around the time of stimulus presentation as baseline (−100 to 100 ms; see Fig. 5). Thus aligned, the time series of the beta band modulation reveal a deeper ERD phase in patients but a higher amplitude ERS phase in control subjects. The ERS phase was evaluated in the window 1,000–1,200 ms, separately for the long and short SOA conditions performed with right and left hands. Figure 5 shows scalp distributions of the ERS difference between control subjects and patients for the long SOA condition with significant ($P < 0.05$) clusters over sensorimotor areas. Similarly localized clusters were identified in the short SOA condition. Moreover, equivalent results were obtained when the ERD phases were compared between patient and control group.

These analyses show that task-related modulation of beta activity is of the same magnitude in patients and controls and retains a focal distribution in patients. However, the modulation is abnormal in the patient group in the sense of being shifted in its entirety as measured relative to the beta level at stimulus onset. The net effect of this shift is that patients show an attenuated preparatory ERD and, instead, a more reactive stimulus-driven ERD.
of left and right hemisphere sources between groups and conditions. Two ROIs were defined, each including the voxels within a 10-mm radius of the mean activation maxima in the contralateral and ipsilateral sensorimotor cortex. The analysis did not show an overall activation difference between the groups \((F < 1)\) nor significant interactions involving the factor group. There was a significant effect of hemisphere \([F(1,20) = 6.25, P < 0.05]\) with a stronger ERD/ERS in the left compared with the right hemisphere. This effect was due to relatively stronger involvement of this hemisphere in ipsilateral movements. Nonetheless, there was also a significant hemisphere by hand interaction \([F(1,20) = 21.95, P < 0.001]\) due to stronger ERD/ERS in the contralateral than in the ipsilateral hemisphere. The short SOA conditions had an attenuated beta modulation compared with the long SOA conditions, as expressed in a marginally significant effect of SOA \([F(1,20) = 2.99, P = 0.099]\).

Alpha band ERD/ERS. In the time-frequency representation, alpha band activity was clearly distinguishable from beta band activity (see Figs. 4 and 7A). Time-frequency representations for electrode Pz with windows delineating maximal ERD and ERS in the control group are shown in Fig. 7A. Relative to baseline \((-100–100\text{ ms})\), the ERD phase, quantified in a window 300–500 ms, involved posterior occipitoparietal scalp areas as well as central areas. This was the case in control subjects and patients alike (see Fig. 7B) without significant differences between the groups as established with cluster randomization tests. By contrast, there was a rapid reversal of ERD to ERS in control subjects, whereas ERD in patients only returned to baseline in a more gradual fashion, which is especially clear in the time plots of the alpha modulation (see Fig. 7C). Importantly, the resolution of ERD and reversal to ERS moved from posterior to anterior, as can be seen in Fig. 7B, where at 650–850 ms, there is occipitoparietal ERS with a residual island of ERD over the sensorimotor cortex contralateral to the response hand. At the same latency, there is still a much broader area of ERD in the patient group. A comparison between the groups in this latency window demonstrates a cluster of parietal electrodes with a significant amplitude difference between the groups. Similar results were obtained for the other conditions as represented in time plots of the alpha modulation in Fig. 7C. These traces further reveal that short SOAs do not attenuate the ERS phase in control subjects. In patients, the ERS phase is absent for both short and long SOA conditions.

The changes in alpha activity modulation in patients can be described as qualitatively similar to those in the beta band but with an elimination instead of reduction of the ERS phase. Hence in both frequency bands, Parkinson patients demonstrate a change from a biphasic ERD/ERS pattern of modulation in control subjects toward a monophasic ERD pattern of modulation. This pattern reflects a loss of anticipatory ERD, which is replaced by an increased stimulus-driven ERD after the reaction stimulus.

**D I S C U S S I O N**

This investigation used a motorically undemanding choice response task to investigate temporal preparation in an implicit fashion, that is, by means of the uninstructed adjustments in preparation to experimental manipulations of task timing. In terms of choice performance, both groups performed equally well. In terms of temporal preparation, patients demonstrated profound changes in slow preparatory brain potentials and in oscillatory synchrony. The slow brain potential and oscillatory EEG findings will be discussed in relation to temporal preparation and more broadly in relation to Parkinson’s disease and basal ganglia-thalamocortical function.
Contingent negative variation and implicit timing

In control subjects, the CNV demonstrated a time course determined by the duration of the interstimulus interval. More specifically, the CNV reached the same amplitude in trial series with short and long interstimulus intervals, achieved through an adjustment in slope. Although the amplitude of the CNV was $\sim 50\%$ smaller compared with the younger participants in Praamstra et al. (2006), the time course effects were identical. The adjustment of the CNV to the timing regime of the task means that subjects temporally prepared for the presentation of the reaction signal and optimized their response readiness. The Parkinson patients showed no preparatory slow wave activity over motor regions of the cortex, suggesting that there was no adjustment to the timing of the task.

The CNV recorded during the sequence final trials with deviant interstimulus interval provided a means to address whether the CNV characteristics in patients reflect a temporal processing deficit per se or a failure of the motor system to engage in temporal preparation. Unexpectedly, not only control subjects but also patients showed an abrupt drop in amplitude of the CNV at the time of expected stimulus arrival when the interstimulus interval was lengthened. This implies that even in the absence of CNV signs of temporal preparation, patients built up a representation of the interstimulus interval duration, enabling the neural detection of the deviant interval. The failure to engage in temporal preparation without being deficient in the encoding of temporal information has some resemblance to an earlier observation that Parkinson patients can be deficient in temporal preparation related to voluntary movement but have normal temporal preparation in relation to reflexive behaviors (Jurkowski et al. 2005).

In Praamstra et al. (2006), we identified the lateral premotor cortex as the main source of the CNV in the implicit timing paradigm, which accords with the presence of anticipatory neural activity, influenced by event predictability, in the macaque lateral premotor cortex (Lucchetti et al. 2005; Mauritz and Wise 1986). In human neuroimaging, the lateral premotor cortex is consistently activated in tasks with continuous timing requirements (Schubotz and Von Cramon 2001) and may be involved in both extraction and prediction of sequential/temporal information (Schubotz and Von Cramon 2003). The CNV of control subjects in the present study had a scalp distribution compatible with contributions from the lateral premotor cortex. Hence the absent CNV in Parkinson’s disease agrees with a temporal prediction function of the lateral premotor cortex but not with a central role in the extraction of temporal information, given that patients remained able to encode the interstimulus interval and were sensitive to deviant interval durations.

Cunnington et al. (1995) found that temporally predictable movement cues increased preparatory slow wave activity in healthy controls, whereas it eliminated such activity in Parkinson patients. Limited by recordings from just one electrode positioned over the midline, they inferred that absent midline activity implied a shift to the lateral premotor cortex. The present data correct this view, showing an absence of temporal preparation as such. The combined data now provide strong evidence that Parkinson patients do not spontaneously take advantage of temporal cues implicit in the timing structure of a task. However, when instructed to use the temporal information implicit in a regular stimulus presentation regime, patients are able to exploit that information (Cunnington et al. 1999), just as they are able to use advance spatial information (Praamstra et al. 1996; Stelmach et al. 1986).

Relevant in this context, the CNV is more affected in advanced parkinsonism than the readiness potential (RP) preceding self-paced movements (Ikeda et al. 1997). In addition, Parkinson patients tested before pallidotomy still show sizeable RPs that do not change after the intervention (Limousin et al. 1999). Similarly, deep brain stimulation of the internal globus pallidus or the subthalamic nucleus does not alter the RP (Brown et al. 1999), whereas stimulation of the subthalamic nucleus significantly improves the CNV (Gerschlagel et al. 1999). The greater vulnerability of the CNV compared with the RP is consistent with the present data and with the notion that Parkinson patients are impaired on temporal aspects of preparatory set in tasks where preparation is optional.

Event-related synchronization and desynchronization

We have previously found that not only the CNV but also oscillatory activity in the beta band is modulated by temporal expectancy, entrained by the timing regime of the task (Praamstra et al. 2006; see also Alegre et al. 2003). Here the predicted result was therefore a loss of temporal preparation effects in event-related desynchronization of Parkinson patients, accompanying the loss of such effects in the CNV. The results show beta band activity with the same depth of modulation in patients and controls, localized to sensorimotor areas. The beta modulation in patients was abnormal in showing a deeper ERD and lower-amplitude ERS peak than control subjects. Consequently, there was very little anticipatory ERD, as illustrated in Fig. 5. This effect was even more pronounced in the alpha band: because the ERS phase was absent in patients, alpha activity remained inert for a sustained period of time before stimulus presentation (see Fig. 7). Together, oscillatory activity in beta and alpha range showed a reduced (beta) or absent (alpha band) preparatory ERD phase, which resembles findings of a delayed and/or reduced suppression preceding self-paced movements (Devos and Defebvre 2006).

The reduced and delayed beta ERS effect in the Parkinson group accords with earlier reports that associate such a reduction with impaired recovery of the motor cortex following movement or with changes in the termination of movements in Parkinson’s disease (Labyt et al. 2005; Pfurtscheller et al. 1998). Postmovement rebound of beta or an increase when a planned movement must be suppressed (Kühn et al. 2004) provides evidence that beta desynchronization antagonizes movement and helps to re-establish postural set (Brown and Williams 2005). The pathological nature of reduced beta ERS is confirmed by the enhancing effect of dopaminergic treatment and of deep brain stimulation of the subthalamic nucleus (Devos et al. 2003). Like the reduced beta ERS, the absent alpha ERS in patients may be associated with deficient inhibition. Recall that alpha ERD showed a distribution over occipital, parietal, and sensorimotor areas. The subsequent deactivation of these areas in control subjects, accompanied by an increase of alpha activity, progressed from posterior to anterior (occipital to central), reproducing their physiological order of activation. An inhibitory role of synchronized alpha oscilla-
tions is supported in the motor domain (Hummel et al. 2002) and has recently been suggested in the context of visual spatial attention (Kelly et al. 2006; Worden 2000; see also Klimesch et al. 2007). In the present context, the notion that low alpha and beta amplitude facilitate, and increased alpha and beta inhibit, visual and motor processing entails that cortical areas engaged in the task are switched on and off in a controlled fashion in control subjects. In patients, by contrast, activation only starts after stimulus presentation and gradually returns to baseline instead of being actively terminated as in control subjects (cf. Chen et al. 2001). Hence the (timing of) activation of an area is predominantly determined by the external stimulation instead of being tuned to its processing contribution in the task in a predictive mode.

**Slow brain potentials and oscillatory activity**

How do the changes in oscillatory activity fit with existing views on the role of oscillations in basal ganglia-thalamocortical circuits, and how do they relate to slow brain potential activity? Initially thought to characterize the parkinsonian state (Bergman et al. 1998; Nini et al. 1995), synchronous oscillatory activity in basal ganglia structures is now recognized as part of their normal function (Boraud et al. 2005; Courtemanche et al. 2003; Sochurkova and Rektor 2003), although exaggerated synchronization in the 8- to 30-Hz range could still contribute to the bradykinesia of Parkinson’s disease (Brown and Williams 2005). In our scalp-recorded EEG data, alpha and beta rhythms were not of higher amplitude in patients than in control subjects in spite of the fact that patients were tested after overnight withdrawal from dopaminergic medication. The data suggest instead a difference in the dynamics of oscillatory activity. In essence, a biphasic ERD/ERS pattern of alpha and beta activity modulation in control subjects is replaced by a monophasic ERD pattern of modulation. That is, patients showed an attenuated or absent ERS phase and very little anticipatory ERD but still a brisk and high-amplitude ERD response after the reaction stimuli. This indicates that task-relevant neural populations were released from background oscillatory activity to engage in visual and motor processes—albeit in a stimulus-driven fashion—, whereas the recruitment back into ensemble oscillatory activity was clearly abnormal.

Although a suppression of oscillatory synchrony in the alpha-beta range is necessary to allow voluntary movement, the nature of this relation is still unclear. According to a recent hypothesis, widespread 10- to 25-Hz synchronous oscillations in cortico-striatal networks could act as a spatiotemporal filter or thresholding device that selectively enables focal striatal output with focal disengagement from background oscillations being helped by striatal network neurons such as tonically active neurons (TANs) (Courtemanche et al. 2003). This hypothesis is relevant to our data in the following way. TANs could be especially important for the selection of striatal output in the temporal domain because their responsiveness to movement-triggering stimuli is influenced by the temporal context (Sardo et al. 2000) and because there is evidence that they are specialized for learning of temporal relations among external cues and events (Ravel et al. 2001). However, based on the cooperative role of striatal cholinergic and dopaminergic systems in the basal ganglia’s response to environmental events, the behavioral expression of this sensitivity will be dependent on intact dopaminergic innervation of the striatum (Cragg 2006; Morris et al. 2004). That is, the development of anticipatory neural activity in striatum and cortex, as a learned response to temporal regularity, may be compromised if the TAN response is not accompanied by (appropriately timed) dopamine release in the striatum (Morris et al. 2004; Suri and Schultz 2001). Translated to our data, we hypothesize that the absence of cortical preparatory brain potentials may be due to a failure of striatal learning mechanisms to respond to the temporally patterned input of behaviorally relevant signals. The same mechanism would explain why patients continue to exhibit a strong stimulus-driven ERD response instead of developing an anticipatory ERD profile.

In conclusion, the present data show that patients with Parkinson’s disease do not spontaneously engage in temporal preparation in a context where temporal regularity strongly encourages such preparation. This was evident in slow brain potentials and in task-related modulations of oscillatory synchrony, which showed a stimulus-driven pattern with reduced anticipatory suppression of oscillatory activity. Importantly, abnormal temporal preparation was not due to compromised encoding of interval durations but due to a failure to exploit temporal information. The preserved encoding of interval information argues against abnormal interval timing in Parkinson’s disease and steers the interpretation of the present findings into the domain of implicit learning and habit formation and their dependence on the basal ganglia (Graybiel 1995; Knowlton et al. 1996).

**ACKNOWLEDGMENTS**

The authors thank C. Miall for comments on the manuscript, R. Oostenveld for advice on cluster randomization analysis in FieldTrip, and N. Roach and E. Seiss for technical and programming support.

**REFERENCES**


Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchroniza-


Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchroniza-


Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchroniza-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Buhusi CV, Meck WH. What makes us tick? Functional and neural mecha-


Janssen P, Shadlen MN.

Kelly SP, Lalor EC, Reilly RB, Foxe JJ.

Knowlton BJ, Mangels JA, Squire LR.


