Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson’s disease
An electrophysiological study of the contingent negative variation

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Summary
Parkinson’s disease involves impaired activation of frontal cortical areas, including the supplementary motor area and prefrontal cortex, resulting from impaired thalamocortical output of the basal ganglia. Electrophysiologically, such impaired cortical activation may be seen as a reduced amplitude of the contingent negative variation (CNV), a slow negative potential shift reflecting cognitive processes associated with the preparation and/or anticipation of a response. Surgical interventions aimed at increasing basal ganglia–thalamic outflow to the cortex, such as electrical stimulation of the subthalamic nucleus with chronically implanted electrodes, have been shown to be effective in improving the clinical symptoms of Parkinson’s disease. This study examined changes in cortical activity, as reflected in the CNV, associated with bilateral subthalamic nucleus stimulation in Parkinson’s disease. The CNV was recorded from 10 patients with Parkinson’s disease when on and off bilateral subthalamic nucleus stimulation, and was compared with the CNV of 10 healthy control subjects. Without subthalamic nucleus stimulation, Parkinson’s disease patients showed reduced CNV amplitudes over the frontal and frontocentral regions compared with control subjects. With bilateral subthalamic nucleus stimulation, however, CNV amplitudes over the frontal and frontocentral regions were significantly increased. Results therefore suggest that impaired cortical functioning in Parkinson’s disease, particularly within the frontal and premotor areas, is improved by subthalamic nucleus stimulation.

Keywords: Parkinson’s disease; subthalamic nucleus stimulation; contingent negative variation

Abbreviations: CNV = contingent negative variation; GPi = globus pallidus internus; SNr = substantia nigra pars reticulata; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
Parkinson’s disease has been generally considered purely a movement disorder in which cognitive functions remain largely unimpaired. It is now clear, however, that it involves deficits in cognitive executive function, including deficits in planning, working memory and the allocation of attention, as well as visuospatial deficits (Brown et al., 1997; Dubois and Pillon, 1997). Such cognitive deficits are probably linked to impaired frontal cortex function. Parkinson’s disease involves a loss of dopaminergic neurons of the substantia nigra pars compacta, severely impairing dopaminergic input to the putamen of the basal ganglia. According to the model of basal ganglia–thalamocortical circuitry proposed by Wichmann and DeLong, this leads to excessive inhibitory outflow of the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) to the thalamus, and hence reduced outflow to the cortex (Wichmann and DeLong, 1996).

Five parallel, segregated circuits have been identified passing through the basal ganglia and thalamus, originating and terminating in discrete cortical areas (Alexander et al., 1990). In particular, a motor circuit links the supplementary motor area of the cortex, the putamen and the ventrolateral portion of GPi, while a ‘dorsolateral prefrontal’ circuit links the dorsolateral prefrontal cortex (Brodmann areas 9 and 10), the dorsolateral head of the caudate and the lateral dorsomedial portion of GPi. The supplementary motor area and dorsolateral prefrontal cortex are therefore both linked...
with basal ganglia function via discrete basal ganglia–thalamocortical circuits.

In Parkinson’s disease, activity of both the supplementary motor area and the dorsolateral prefrontal cortex is found to be significantly impaired during movement (Playford et al., 1992; Jahanshahi et al., 1995). Outflow of the right GPi has also been found to be impaired in Parkinson’s disease patients during cognitive tasks known to involve the prefrontal cortex (Owen et al., 1998). Impaired activation of the supplementary motor area is improved following treatment with levodopa (Rascol et al., 1994) and apomorphine (Jenkins et al., 1992; Rascol et al., 1992), both of which act to increase striatal dopamine levels and improve basal ganglia outflow. Posteroventral pallidotomy (Samuel et al., 1997) and high-frequency electrical stimulation of the subthalamic nucleus (Limousin et al., 1997), both aimed at reducing the excessive inhibitory outflow from the globus pallidus and thereby increasing basal ganglia–thalamic outflow to the cortex, also result in improved activation of the supplementary motor area and the dorsolateral prefrontal cortex during movement [although stimulation of GPi showed no effect on cortical activation during movement (Limousin et al., 1997)]. These studies highlight the important link between basal ganglia function and frontal cortex function, particularly within the supplementary and dorsolateral prefrontal areas.

Deficits in frontal cortex function in Parkinson’s disease patients have also been studied electrophysiologically by examining event-related potentials such as the Bereitschaftspotential and contingent negative variation (CNV). The Bereitschaftspotential (Kornhuber and Deecke, 1965) is a slow negative shift in the EEG that begins 1–2 s prior to voluntary movement, and is thought to reflect processes associated with the preparation for voluntary movement, involving the supplementary motor area and the primary motor cortex. The amplitude of the early Bereitschaftspotential is greatly reduced in patients with Parkinson’s disease (Deecke and Kornhuber, 1978; Dick et al., 1989; Cunnington et al., 1995, 1997), but is improved following treatment with levodopa (Dick et al., 1987), and therefore probably reflects impairment of the ‘motor’ loop of the basal ganglia–thalamocortical circuitry as defined by Wichmann and DeLong (Wichmann and DeLong, 1996).

The CNV is also a slow negative shift in EEG that occurs between a warning stimulus and an imperative stimulus (Walter et al., 1964), and is thought to reflect cognitive processes associated with planning and/or anticipation of the response to the imperative stimulus. The CNV is distributed widely over the scalp, with the maximum amplitude usually recorded at frontal and central electrodes. It is clear that activity of the frontal cortex contributes to the CNV. Oishi and Mochizuki showed recently that the amplitude of the CNV was significantly correlated with blood flow only within the frontal cortex (Oishi and Mochizuki, 1998). Hamano and colleagues, using subdural electrode recordings, localized the early component of the CNV to the prefrontal cortex and supplementary motor area, but with additional contributions from the primary sensorimotor, temporal and occipital areas during the later phase (Hamano et al., 1997). There is also debate over the extent to which the late component of the CNV and the Bereitschaftspotential reflect different processes, particularly for movement tasks with differing anticipatory and/or strategic components (Cunnington et al., 1999). Nonetheless, it is clear that activity of the prefrontal cortex contributes to the amplitude of the CNV.

The amplitude of the CNV is significantly reduced in Parkinson’s disease patients compared with controls (Wright et al., 1993; Praamstra et al., 1996; Pulvermüller et al., 1996; Ikeda et al., 1997; Wascher et al., 1997), although the topography and extent of CNV impairment vary considerably depending upon the task employed. Ikeda and colleagues found that the level of CNV reduction in Parkinson’s disease patients, particularly over the frontal areas, is directly related to the severity of disease (Ikeda et al., 1997), and the amplitude of the CNV has been shown to increase following treatment with levodopa (Amabile et al., 1986; Oishi et al., 1995). This suggests that the CNV amplitude is closely linked with basal ganglia functioning. Ikeda and colleagues suggest that the cortical–basal ganglia–thalamocortical circuit plays a major role in the generation of the CNV (Ikeda et al., 1997), based on evidence from animal studies of ‘behaviourally contingent activity’, equivalent to the CNV, found in neurons within areas of the putamen, globus pallidus and thalamus that project to the supplementary motor and prefrontal cortical areas (Kimura, 1986, 1990; Jinnai et al., 1993).

The aim of this study was to investigate further the relationship between basal ganglia and cortical functioning in Parkinson’s disease by examining the nature of deficits in the CNV for patients when on compared with off high-frequency stimulation of the subthalamic nucleus. Surgical procedures such as lesioning or stimulation of the subthalamic nucleus or GPi are now used commonly in the treatment of Parkinson’s disease. Theoretically, these procedures aim to reduce the excessive inhibitory outflow of the GPi/SNr, and thereby to increase the basal ganglia–thalamic outflow to the cortex. Continuous high-frequency stimulation appears to inhibit the target region, producing an effect similar to a lesion (Benazzouz et al., 1995, 1996), but has the advantage that the effect is reversible and may be modified by altering the stimulation parameters. Surgical intervention at the level of the subthalamic nucleus could theoretically be more effective than intervention at the level of the pallidum, since it could affect the activity of the SNr as well as of the GPi. Indeed, it has been shown that, compared with stimulation of the GPi, subthalamic nucleus stimulation leads to greater improvement of cortical activity during movement (Limousin et al., 1997) as well as greater clinical improvement in motor symptoms (Krack et al., 1998).

In this study, Parkinson’s disease patients with stimulators implanted bilaterally within the subthalamic nuclei of both hemispheres were examined when both on and off stimulation, and were compared with age-matched control subjects. The
Table 1 Clinical details and subthalamic nucleus stimulation parameters for Parkinson's disease subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>PD duration (years)</th>
<th>Medication</th>
<th>L-Dopa dose (mg/day)</th>
<th>UPDRS III Off stimulation</th>
<th>UPDRS III On stimulation</th>
<th>Side of stimulation</th>
<th>Voltage (V)</th>
<th>Frequency (Hz)</th>
<th>Pulse width (µs)</th>
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<tr>
<td>68</td>
<td>F</td>
<td>10</td>
<td>L-Dopa/benserazide pergolide</td>
<td>200</td>
<td>40.5</td>
<td>30.5</td>
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<td>2.4</td>
<td>130</td>
<td>60</td>
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<tr>
<td>62</td>
<td>M</td>
<td>20</td>
<td>L-Dopa/carbidopa amantadine</td>
<td>300</td>
<td>36.5</td>
<td>25.5</td>
<td>Left</td>
<td>3.4</td>
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<td>90</td>
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<tr>
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<td>16</td>
<td>L-Dopa/benserazide pergolide</td>
<td>100</td>
<td>39</td>
<td>25.5</td>
<td>Left</td>
<td>2.1</td>
<td>130</td>
<td>60</td>
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<td>58</td>
<td>M</td>
<td>21</td>
<td>Selegiline</td>
<td>–</td>
<td>51</td>
<td>23.5</td>
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<td>1.8</td>
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<td>34.5</td>
<td>Left</td>
<td>1.1</td>
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<tr>
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<td>31.5</td>
<td>22</td>
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<tr>
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<tr>
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<tr>
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<td>M</td>
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<td>–</td>
<td>43</td>
<td>19</td>
<td>Left</td>
<td>3.3</td>
<td>185</td>
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PD = Parkinson’s disease; UPDRS III = Unified Parkinson’s Disease Rating Scale section III (Motor).

CNV was examined as an index of basal ganglia–thalamocortical functioning, in order to examine the effectiveness of subthalamic nucleus stimulation in improving cortical functioning in Parkinson’s disease.

Methods

Subjects

Ten patients with Parkinson’s disease (six male, four female), aged between 38 and 68 years (mean = 55.9 years), and 10 healthy control subjects (six male, four female; mean age = 45.1 years) participated in the study. All Parkinson’s disease patients had chronic bilateral electrodes (Medtronic Inc., Minneapolis, Minn., USA) implanted in the subthalamic nucleus of both hemispheres. Electrodes had been placed by stereotaxic guidance, with the target identified by both MRI and ventriculography (Alesch et al., 1995). Stimulation parameters (Table 1) had been set individually for optimal clinical benefit.

All patients remained on their normal anti-Parkinsonian medication throughout the study (Table 1). Clinical assessment was performed immediately prior to on- and off-stimulation sessions using the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS). Stimulation was clearly effective for every patient (Table 1); hence, a significant improvement in clinical state was found when patients were on stimulation (mean motor UPDRS = 25.9) compared with off stimulation (mean motor UPDRS = 45.5) [t(9) = 5.98, P < 0.001].

All subjects gave their informed consent prior to participation in accordance with the Declaration of Helsinki, and all experimental work was carried out with the approval of the Ethics Committee of the General Hospital of Vienna.

Procedure

Subjects performed a bilateral Go/NoGo choice reaction time task in which a pair of tones was presented via headphones. A low-frequency (1000 Hz, duration = 20 ms) warning stimulus was first presented, and was followed exactly 2 s later by an imperative stimulus consisting either of a high-frequency (2000 Hz, 20 ms) or a medium-frequency tone (1500 Hz, 20 ms), representing NoGo and Go signals, respectively. Subjects rested the index finger of both hands on buttons mounted on the arm-rests of the EEG chair and were instructed to press both left and right buttons simultaneously upon presentation of the medium-frequency stimulus, but to withhold responses to the high-frequency tone (NoGo stimulus). Go and NoGo stimuli were given with equal probability of occurrence (i.e. equal numbers over the entire study), but the order of presentation varied randomly between trials. The warning stimulus for the subsequent trial was given 5 s after the imperative stimulus for the preceding trial.

Two recording sessions were completed, each consisting of 200 trials and lasting ~25 min, with an interval of ~20 min between sessions. The two sessions were equivalent for control subjects in order to examine effects due to practice or fatigue across sessions, while Parkinson’s disease subjects were tested with stimulation on during the first session and stimulation off during the second session. All patients had their stimulators switched off immediately after completing
the first session, and clinical assessment of patients with stimulators off was carried out immediately before beginning the second session.

Event-related potentials were recorded from electrodes at Fp1, Fp2, F7, F3, Fz, F4, F8, FC1, FC2, FC5, FC6, T7, C3, CZ, C4, T8, P7, P3, Pz, P4 and P8, with linked mastoid electrodes as a reference. Horizontal EOG (electrooculogram) (lateral orbital rim of the left compared with right sides) and vertical EOG (upper compared with lower orbital rim of the right eye) were also recorded.

Non-polarizable Ag/AgCl electrodes were connected to the scalp via salt bridges (silicon rubber filled with electrode gel) in order to reduce skin potentials and to stabilize electrode potentials (Bauer et al., 1989). Electrode sites were prepared with a conductive abrasive solution to reduce electrode impedance at 5 Hz to <5 kΩ. A computer-based multichannel DC amplifier with digital filtering (Lindinger et al., 1991) was used. Data were digitized at 250 Hz using a bandpass ranging from DC to 100 Hz. During off-line processing, eye-blink artefacts were detected in EEG channels and corrected in EEG channels using a linear regression method (Jervis et al., 1988). Data for every channel were then inspected manually for further artefacts. Trials in which the majority of channels were affected by artefact were totally excluded, otherwise data were excluded only in channels affected by artefact.

Data from the extreme frontal electrodes (Fp1 and Fp2) often showed artefact and drift, probably due to their close proximity to eye and facial musculature. As a result, a large proportion of trials from these channels were excluded during manual inspection and, due to the low number of remaining trials, these channels were subsequently excluded from further analysis. For all other channels, a mean of 98 ± 36 trials were included in the average.

Event-related potentials were averaged time-locked to stimulus presentation and corrected to a baseline consisting of the average amplitude over the period of 1 s before the warning stimulus. Go and NoGo trials were averaged together since the CNV should be equivalent for all trials prior to the imperative stimulus, as subjects are not aware whether the trial is Go or NoGo until the imperative stimulus is given.

Mean amplitudes of the event-related potentials were calculated for each of the four 500 ms intervals between the warning and imperative stimuli (0–500, 500–1000, 1000–1500 and 1500–2000 ms after the warning stimulus). These mean amplitudes were then examined using analysis of variance with the repeated factors of electrode position (19 sites), time interval (four periods) and session/stimulation (first/on compared with second/off), and the between-subjects factor of group (Parkinson’s disease compared with control subjects).

In order to examine possible change, CNV amplitudes throughout the course of the study, which may give rise to order effects in the results of Parkinson’s disease subjects for comparisons of on- and off-stimulation conditions, separate potentials were averaged from approximately the first third and the last third of trials for both conditions. Mean amplitudes of these potentials were examined using analysis of variance with the repeated factors of electrode position (19 sites), time interval (four periods), session (on compared with off) and stage (early compared with late).

Results

Average waveforms of the CNV across the different electrode positions are shown for control subjects in Fig. 1 and for Parkinson’s disease subjects in Fig. 2. A negative potential shift, beginning within 200 ms after the warning stimulus and increasing slowly until the time of the imperative stimulus, was present for both Parkinson’s disease and control subjects. This negative shift was particularly pronounced over the frontal and central electrode sites for control subjects and Parkinson’s disease patients when on stimulation, but appeared greatly reduced in patients off stimulation.

Overall analysis of variance showed a significant four-way interaction between electrode position, time interval, session/stimulation and subject group [F(54,972) = 1.617, P < 0.01]; therefore, results for Parkinson’s disease and control subjects were analysed separately. Control subjects showed a significant effect of electrode position [F(18,162) = 6.591, P < 0.01] and time interval [F(3,27) = 5.169, P < 0.01], and a significant interaction between these factors [F(54,486) = 2.827, P < 0.01]. This indicates, as is apparent in Fig. 1, that the CNV amplitude for control subjects changed significantly over time but showed a different pattern over time at different electrode positions. Control subjects, however, showed no significant difference in CNV amplitude between the two recording sessions [F(1,9) = 0.001, P > 0.95] and showed no significant interactions involving the factor session [P > 0.05].

Reaction time data showed a trend towards longer reaction times for Parkinson’s disease patients when off stimulation (mean ± standard deviation = 933 ± 339 ms); reaction time improved when on stimulation (793 ± 230 ms), but was still longer than that for control subjects (session 1: 690 ± 245 ms; session 2: 702 ± 284 ms). However, analysis of variance showed no significant main effect of subject group [F(1,17) = 2.25, P > 0.05] or session [F(1,17) = 1.71, P > 0.05] and no significant interaction [F(1,17) = 1.16, P > 0.05]. It seems that, since speed of responding was not emphasized in this task and is not necessary for measurement of the CNV, intertrial variability in reaction times was high for all subjects.

Control subjects compared with Parkinson’s disease subjects off stimulation

Since there was no significant difference in CNVs for control subjects over the two recording sessions, data for the two sessions were combined and compared with Parkinson’s disease patients off stimulation, using three-way analysis of
STN stimulation in Parkinson’s disease

Fig. 1 Mean CNV traces for control subjects over all electrode positions for the first (thick line) and second (thin line) recording sessions. Potentials are shown from 200 ms before the warning stimulus until 600 ms after the imperative stimulus (total duration 2.8 s).

variance (factors: electrode position, time interval and subject group). As reported above for control subjects, there were significant main effects of electrode position \( [F(18,324) = 7.344, P < 0.01] \) and time interval \( [F(3,54) = 9.770, P < 0.01] \) and a significant interaction between these factors \( [F(54,927) = 3.247, P < 0.01] \), indicating that the temporal pattern of the CNV amplitude varied across electrode positions. There was no significant three-way interaction \( [F(54,972) = 2.811, P > 0.05] \) and no significant interaction between time interval and subject group \( [F(3,54) = 1.650, P > 0.05] \), indicating that the pattern of change in CNV amplitude over time was not significantly different for control subjects compared with Parkinson’s disease patients off stimulation.

The overall difference in CNV amplitudes for control subjects compared with Parkinson’s disease patients off stimulation did not quite reach significance \( [F(1,18) = 4.064, P = 0.059] \); however, there was a significant interaction between subject group and electrode position \( [F(18,324) = 2.509, P < 0.01] \), indicating that the difference in CNV amplitude for the two subject groups varied significantly across electrode positions. This difference in CNV topography was examined in more detail, using independent \( t \) tests to compare CNV amplitudes for Parkinson’s disease and control subjects in frontal (positions F7, F3, Fz, F4, F7), frontocentral (FC5, FC1, FC2, FC6), central (T7, C3, Cz, C4, T8) and parietal (P7, P3, Pz, P4, P8) regions. These four electrode groupings were selected, as opposed to examining each electrode position independently, to maintain high experimental power and to examine the frontoparietal distribution rather than the lateralization of the response. The CNV amplitude was found to be significantly greater for Parkinson’s disease subjects off stimulation at frontal \( [t(18) = 2.388, P < 0.05] \) and frontocentral positions \( [t(18) = 2.315, P < 0.05] \), but showed no significant difference between subject groups at central \( [t(18) = 1.681, P > 0.05] \) and parietal sites \( [t(18) = 1.059, P > 0.05] \) (Fig. 3).

Parkinson’s disease subjects off stimulation compared with on stimulation

The effect of subthalamic nucleus stimulation in Parkinson’s disease patients was examined by three-way analysis of variance (factors: electrode position, time interval and stimulation). Again, there were significant main effects of electrode position \( [F(18,162) = 4.257, P < 0.01] \) and time interval \( [F(3,27) = 13.592, P < 0.01] \) and a significant interaction between these factors \( [F(54,486) = 2.614, P < 0.01] \). There was no significant three-way interaction \( [F(54,486) = 2.180, P > 0.05] \) and no significant interaction
Fig. 2 Mean CNV traces for Parkinson’s disease subjects with subthalamic nucleus stimulation on (thick line) compared with off (thin line) stimulation. Potentials are shown from 200 ms before the warning stimulus until 600 ms after the imperative stimulus (total duration 2.8 s).

The overall amplitude of the CNV with stimulation on compared with stimulation off approached significance \(F(1,9) = 4.933, P = 0.053\) and there was a significant interaction between stimulation condition and electrode position \(F(18,162) = 1.823, P < 0.05\), indicating that the effect of stimulation on the CNV amplitude varied significantly across electrode positions. This topographical difference was examined as described above, comparing the difference in CNV amplitude on stimulation and off stimulation at the frontal, frontocentral, central and parietal recording sites using dependent \(t\) tests. The CNV amplitude was significantly greater on stimulation compared with off stimulation at the frontal \([t(9) = 2.651, P < 0.05]\) and frontocentral sites \([t(9) = 2.294, P < 0.05]\), but was not significantly different at the central \([t(9) = 1.749, P > 0.05]\) and parietal sites \([t(9) = 1.321, P > 0.05]\).

Consequently, overall CNV amplitudes showed no significant difference between Parkinson’s disease patients on stimulation compared with control subjects \([F(1,18) = 0.431, P > 0.05]\), nor were there any significant interactions involving the subject group and time interval or electrode position for patients on stimulation compared with control subjects (Fig. 3).

Potentials averaged from early stages and late stages of both the on and the off condition were also examined. As with the overall analysis, there were significant main effects of electrode position \(F(18,162) = 3.53, P < 0.01\) and time.

Fig. 3 Mean and standard error of the CNV amplitude for control subjects (filled columns), Parkinson’s disease patients with subthalamic nucleus stimulation on (open columns) and patients with stimulation off (stippled columns). The mean CNV amplitudes were calculated over the 2 s interval between the warning and imperative stimuli, with individual electrode positions combined according to frontal, frontocentral, central and parietal regions.

between time interval and stimulation condition \(F(3,27) = 2.325, P > 0.05\), indicating that the temporal pattern of the CNV did not differ significantly between the on- and off-stimulation conditions.
interval $[F(3,27) = 4.79, P < 0.01]$, as well as a significant interaction between these factors $[F(54,486) = 1.92, P < 0.01]$. However, there was no significant main effect of stage (early compared with late) $[F(1.9) = 2.36, P > 0.05]$ and no significant interactions involving the stage $[P > 0.05]$, indicating that the pattern of CNV amplitudes across time intervals, electrode positions and on compared with off conditions did not vary significantly between early and late stages of each condition.

Discussion

Results of this study clearly show an impaired CNV amplitude in Parkinson’s disease patients compared with control subjects, particularly over the frontal and frontocentral areas, which improved significantly during high-frequency bilateral subthalamic nucleus stimulation.

CNV responses generally showed a slowly increasing negative shift, beginning ~100–200 ms after warning stimulus presentation, with apparently larger amplitudes over frontal and central recording sites compared with parietal sites. Compared with control subjects, Parkinson’s disease subjects, when not receiving subthalamic nucleus stimulation, showed significantly reduced CNV amplitudes over the frontal and frontocentral regions, probably reflecting impaired frontal cortex activation. This is in accord with previous functional imaging studies showing impaired supplementary motor and prefrontal cortex activation in patients with Parkinson’s disease (Playford et al., 1992; Jahanshahi et al., 1995).

Such impaired frontal cortex function probably stems from impaired basal ganglia outflow (Owen et al., 1998), which normally provides important input to frontal regions via motor and dorsolateral prefrontal basal ganglia–thalamocortical circuits (Alexander et al., 1990).

Bilateral stimulation of the subthalamic nuclei of both hemispheres, which greatly improved motor functions, as measured by the UPDRS, increased CNV amplitude significantly over the frontal and frontocentral regions. This is also in accord with previous functional imaging studies showing increased activation of the supplementary motor area, cingulate cortex and dorsolateral prefrontal cortex during effective stimulation of the subthalamic nucleus (Limousin et al., 1997).

It is unlikely that changes in CNV amplitude across sessions were due only to the order in which conditions were tested (on then off). Control subjects showed no significant difference in CNV amplitude across sessions, and Parkinson’s disease patients showed no significant change in CNV amplitude between the early and late stages of each session. This discounts any significant effects of fatigue or motivation loss on results throughout the period of the study. Parkinson’s disease patients also showed no significant difference in task performance, in terms of reaction time, across the two sessions. Similarly, a recent study by Brown and colleagues showed that movement performance (simple and choice reaction times, a pegboard task and finger-tapping speed) for Parkinson’s disease patients with bilateral stimulation of the subthalamic nucleus or GPi did not change significantly over a lengthy testing session when examined with stimulators off, then on, then off again (Brown et al., 1999). This indicates that such patients have no particular problems with easy fatigue or motivation loss that would be expected to influence results in our study.

Electrical stimulation of the subthalamic nucleus produces an effective lesion (Benazzouz et al., 1995, 1996), theoretically decreasing the excessive outflow of the subthalamic nucleus to the GPi/SNr and thereby decreasing the excessive inhibitory outflow of the GPi/SNr to the thalamus, according to the model of Wichmann and DeLong (Wichmann and DeLong, 1996). As a result, the normally impaired basal ganglia–thalamic outflow to the cortex is increased. Limousin and colleagues have found that electrical stimulation of the subthalamic nucleus (rather than GPi) is most effective in increasing activation of the frontal cortex, particularly the dorsolateral prefrontal cortex (Limousin et al., 1997), probably because subthalamic nucleus stimulation can also influence SNr outflow and the dorsolateral prefrontal cortex is a major target of the thalamic projection area of SNr (Ilinsky et al., 1985; Barbas et al., 1991).

Our results have shown similarly that subthalamic nucleus stimulation increases cortical activity, particularly over the frontal and frontocentral areas, probably reflecting improved frontal cortex function in Parkinson’s disease patients; however, these results also extend those reported previously. The PET study of Limousin and colleagues showed improved cortical activation only when the activity was averaged over a prolonged period of movement performance (a 90 s acquisition period was used) (Limousin et al., 1997). The present study has shown that deficits in frontal cortex activation in Parkinson’s disease and improvements with subthalamic nucleus stimulation occur during the preparatory phase prior to the initiation of a response. Our results, therefore, suggest that subthalamic nucleus stimulation in Parkinson’s disease improves the cortical activity that underlies cognitive processes associated with the preparation and organization of forthcoming responses.

Two recent studies have shown that the early component of the Bereitschaftspotential, which is usually found to be reduced in amplitude in Parkinson’s disease (Dick et al., 1989; Cunnington et al., 1995, 1997), does not change significantly with stimulation of the subthalamic nucleus or GPi (Brown et al., 1999) or following posteroventral pallidotomy (although the late-component amplitude was improved) (Limousin et al., 1999). This finding is somewhat unexpected given that stimulation of the subthalamic nucleus and of the GPi, as well as posteroventral pallidotomy, have all been shown to increase the normally impaired activation of the supplementary motor area in Parkinson’s disease (Samuel et al., 1997; Limousin et al., 1997), and the supplementary motor area is thought to play a major role in the preparation for movement and, hence, in the generation of the early component of the Bereitschaftspotential.
Nonetheless, studies by Brown and Limousin, using various performance measures of upper limb akinesia, show little effect of subthalamic nucleus or GPi stimulation or posteroventral pallidotomy on the early processes of movement preparation, but rather show improvement mainly in movement execution (Brown et al., 1999; Limousin et al., 1999). Conversely, although, as would be expected from studies of regional cerebral blood flow (Limousin et al., 1997; Samuel et al., 1997), we have now shown in this study an increase in CNV amplitude, reflecting improved frontal cortex function during early stages of response preparation, after subthalamic nucleus stimulation in Parkinson’s disease. The discrepancy between the effects of deep brain stimulation on premotor activity (reflected in the Bereitschaftspotential) and pre-response frontal activity (reflected in the CNV), particularly in relation to the changes in cortical activation found in studies of regional cerebral blood flow, certainly warrants further investigation.

Overall, this study has shown that cortical activity associated with the preparation for a response, as reflected in the CNV, is significantly impaired in patients with Parkinson’s disease. Bilateral subthalamic nucleus stimulation, however, significantly improves this impaired cortical activation, particularly over the frontal and frontocentral regions. Improvement of clinical symptoms with subthalamic nucleus stimulation in Parkinson’s disease has been well documented (Limousin et al., 1995, 1998). It is also now becoming clear that such stimulation, aimed at increasing the normally impaired thalamocortical output of the basal ganglia, also improves cortical functioning, particularly within the frontal and premotor areas.

References


