Disinhibition of the Sleep State-Dependent P1 Potential in Parkinson's Disease–Improvement after Pallidotomy

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We previously reported that the P1 or P50 midlatency evoked potential underwent decreased habituation or disinhibition in patients with Parkinson's Disease. This sleep state-dependent response appears to be generated by cholinergic elements of the reticular activating system. We attempted to determine if the decreased habituation or disinhibition of the P1 potential would be altered by bilateral pallidotomy. Twenty-three patients who met inclusion criteria for surgery underwent pre- and post-operative evaluation using a Modified United Parkinson's Disease Rating Scale (UPDRS) and P1 potential recordings. Decreased habituation of the P1 potential was determined using a paired stimulus paradigm in which click stimuli were presented at 250, 500 and 1000 msec interstimulus intervals (ISI). Pre-operatively, patients showed disinhibition of the P1 potential at the 250 msec ISI (60 ± 37% vs. 21 ± 20%) and 500 msec ISI (78 ± 47% vs. 43 ± 31%) compared to age-matched control subjects. Post-operatively, the same patients showed a significant improvement in habituation of the P1 potential at the same ISIs (250 msec 37 ± 21%; 500 msec 43 ± 32%). UPDRS scores for these patients pre-operatively were 59 ± 18 and 24 ± 11 post-operatively, resulting in a significant reduction in symptom severity. We conclude that bilateral pallidotomy resulted in a significant improvement in symptom ratings and reduced the disinhibition of the P1 midlatency evoked response.

CURRENT CLAIM: Bilateral pallidotomy in Parkinson Disease patients produced a significant improvement in symptom ratings and reduced the disinhibition of the P1 midlatency auditory evoked response.

The P1 or P50 midlatency auditory evoked response is a vertex-recorded, volume-conducted potential induced at a 50 msec latency following a brief click stimulus (Picton and Hillyard, 1974). The P1 potential has three main characteristics: 1) it is sleep state-dependent, that is, it is present during waking and rapid eye movement (REM) sleep but not during slow-wave sleep (i.e., during desynchronized electroencephalographic [EEG] states); 2) it undergoes rapid habituation following repeated stimulation, unlike primary auditory evoked responses; and 3) it is reduced or blocked by non-soporific doses of the cholinergic antagonist, scopolamine (Buchwald et al., 1991; Erwin and Buchwald, 1986a, 1986b). In addition, the equivalent of the P1 potential, wave A in the cat, is reduced or absent after lesions of the cholinergic pedunculopontine nucleus (PPN) (Harrison et al., 1990). The rodent equivalent of the P1 potential, the P13 response, can be reduced or blocked by localized injections of gabaergic agents into the PPN (Miyazato et al., 1996). These findings suggest that the P1 potential is generated, at least in part, by PPN outputs, which form the cholinergic arm of the reticular activating system (RAS) (Erwin and Buchwald, 1987; Reese et al., 1995). PPN neurons appear to be involved in generating pontoeniculoocipital (PGO) waves, inducing cortical EEG desynchronization and mediating the REM sleep state (Steriade and McCarley, 1990). PPN neurons are active during waking and REM sleep and inactive during slow-wave sleep (see Steriade and McCarley, 1990), that is, during the same sleep-wake states in which the P1 potential can be elicited (Erwin and Buchwald, 1986b). The PPN also appears to be involved in sensory gating, specifically, in the habituation of the startle response (Koch et al., 1993; Miyazato et al., 1997). In addition, the PPN is an integral part of basal ganglia circuitry, sending excitatory projections to the substantia nigra (Kelland et al., 1993; Scarnati et al., 1984) and receiving inhibitory input from it (Granata and Kitai, 1991; Noda and Oka, 1984).

Parkinson's Disease (PD) is characterized by a variety of symptoms which include resting tremor, rigidity, postural and gait abnormalities, bradykinesia, and freezing episodes. Moreover, a majority of untreated PD patients show sleep disturbances including "light fragmented sleep" (Lees et al., 1988; Nausieda et al., 1984), reductions in slow-wave sleep (Myslobodsky et al., 1982) and frequent nocturnal arousals (Askenasy and Yahr, 1985; Kales et al., 1971; Mouret, 1975). Following treatment with levodopa, REM sleep appears to be suppressed (Gillen et al., 1973; Kales et al., 1971). In addition, a number of other symptoms are present in this disorder, including such basic dysfunctions as abnormal reflexes as well as higher level impairments in frontal lobe function and cognition. While many of the symptoms become manifest after a idiopathic degenerative process has reduced the function of dopaminergic substantia nigra neurons below a certain threshold, it is evident that there are a number of additional degenerative or functional changes in such areas as the locus coeruleus, raphe nuclei, basal forebrain, frontal cortex, etc. (Jellinger, 1991). On the one hand, these patients show...
decreased habituation of the blink and other reflexes (Kimura, 1973; Penders and Delwaide, 1971; Rothwell et al., 1983), while also exhibiting anxiety disorder (including panic attacks) and depression (Cummings, 1992; Menza et al., 1993; Stein et al., 1990). Moreover, cognitive impairments related to attentional deficits are present (Jagust et al., 1992; Robbins et al., 1994) which, in general, correlate with decreased frontal lobe glucose utilization (Eidelberg et al., 1994; Jagust et al., 1992; Peppard et al., 1992). Interestingly, a recent study described the presence of decreased blood flow in the frontal lobes during REM sleep (Maquet et al., 1996), the one sleep-wake state during which the PPN, as the cholinergic arm of the RAS, is active while the catecholaminergic arm of the RAS is inactive.

Recently, we reported the presence of decreased habituation of the P1 midlatency auditory evoked potential in patients with PD (Teo et al., 1996, 1997a). This finding suggests the presence of dysregulation of the PPN in PD, which may account for some of the symptoms of the disorder. A therapeutic strategy for PD which has been used with increasing frequency is posteroverentral pallidotomy, either unilaterally or bilaterally (Baron et al., 1996; Iacono et al., 1994). Recent reports are at odds on a number of issues, including surgical technique, degree of complications and abatement of symptoms post-surgically. We studied a population of PD patients pre- and post-surgically using a Modified United Parkinson's Disease Rating Scale (UPDRS) and P1 potential recordings. We attempted to determine if the degree of clinical improvement as reflected by UPDRS scores was coincident with an improvement or normalization of P1 potential disinhibition. Such information may be helpful in assessing the potential use of this non-invasive electrophysiological measure to assess clinical outcome. Preliminary findings have been reported in abstract form (Teo et al., 1997b).

METHODS

Subjects

All patients were referred by neurologists and screened by the neurosurgeon (CT). Inclusion criteria were liberal. Candidates for surgery required a history compatible with idiopathic PD, responsiveness to levodopa, or at least a history of such, a Hoehn and Yahr (1967) severity score of 3 or greater while in the "on" condition, and clinical symptoms in addition to tremor and rigidity. The only absolute contraindications for surgery were dementia (more than mild) and Parkinson's Plus syndromes. Surgical exclusion criteria included other severe medical illnesses, bleeding diatheses and a head too large for the stereotactic frame. There were 23 PD patients studied, 18 males and 5 females, all Caucasian, with a mean age of 61 ± 9 (S.D.) years of age. The mean age at onset of the disease for these patients was 51 ± 9 years of age, with a mean duration of disease of 10 ± 5 years. Control subjects (n = 14) were 60 ± 12 years of age, including 8 males and 6 females, all Caucasian, without a history of neurological or psychiatric illness. All subjects signed consent forms approved by the Human Research Committee.

Clinical evaluation and surgery

UPDRS, Hoehn and Yahr staging, and Mini Mental Test scores were obtained while in the "on" state. Video documentation was obtained on the morning before surgery when patients were in the "on" state after taking their usual medications. Post-operative (2 months, 6 months and 12 months) testing included all of the above as well as formal visual field testing. It should be noted that UPDRS scores were tabulated by an independent observer (not the patient's physician or surgeon).

Patients were admitted on the day of surgery and allowed to take their morning medication. A Cosman-Roberts-Wells magnetic resonance imaging (MRI)-compatible frame was applied to the skull using local anesthesia. MRI using both T2 weighted and proton density scans was performed to estimate the approximate location of the internal pallidal segment (Gpi). This was determined to be 2 mm anterior to the midcommissural point, 18-22 mm lateral to the midline and 4-6 mm deep to the AC-PC plane. Coordinates were also obtained for the foramen of Monro. The head was fixed to the Mayfield headholder. Utilizing monitored anesthetic care, a baseline pure lateral skull X-Ray was taken to ensure minimal parallax when the ventriculogram was performed. A burr hole was then made 5 cm from the midline and just anterior to the coronal suture. Using the coordinates obtained from the MRI, a catheter was then passed into the third ventricle via the foramen of Monro. Omnipaque 300 (3 cc) was injected while an X-Ray was taken, providing a third ventriculogram. Once the X-Ray confirmed the position of the floor of the third ventricle, the catheter was removed and a 1.1 mm diameter probe with a 3 mm exposed tip was guided in the Gpi. Confirmation of the most posteroverentral portion of the Gpi was obtained by macrostimulation of the internal capsule (tongue twitching at 2-3 v using a frequency of 2 Hz) and the optic tract (phosphenes at 2-2.5 v using a frequency of 75 Hz). Furthermore, anatomical verification of the Gpi could be obtained by verifying that the tip of the probe was at the level of the floor of the third ventricle, and at the superoposterior part of the mammillary body as seen in profile in the ventriculogram. A test lesion of 50° for 30 sec was made before definitive lesion-making. Five lesions of 75° for 30 sec separated by 1 mm spaces as the probe was retracted were made to give a final lesion size of approximately 3 mm in diameter. The exact procedure was then repeated on the other side of the head. Clinical evaluation of movement, strength and visual fields was performed throughout the operation.

Recordings

Detailed description of our recording and analysis procedures has been published previously (Teo et al., 1997a). All subjects were seated on a recliner in a well-lit, sound attenuating, shielded room with an observation window. Gold-plated surface electrodes were used with a water-soluble conducting paste, and electrode resistance was maintained at < 5 Kohm. The P1 potential was recorded at the vertex (Cz) referenced to a frontal electrode (Fz). Eye movements (EOG) were detected using diagonally placed canthal electrodes, while jaw movements (EMG) were detected using a lead over
the masseter muscle referred to the chin. A subclavicular ground was used instead of mastoid or earlobe leads since the subjects wore headphones during the recording. Theta waves, indicative of drowsiness, were recorded using an occipital electrode (Oz) referenced to the Cz electrode. Each channel was led to a Grass Instruments 5P11 amplifier with high resistance input stage. The gain and bandpass were as follows: P1 potential x100 K and 3 Hz-1 KHz; Alpha x100 K and 1 Hz-300 Hz; EOG x20 K and 3 Hz-1 KHz; and EMG x10 K and 30 Hz-1 KHz, with a 60 Hz notch filter on each amplifier. Fast Fourier Transform analysis showed that the P1 potential was not degraded by the notch filter.

Prior to the recording, headphones were placed on each subject and the hearing threshold for each ear determined using a Grass Instruments Audiostimulator STM10. The test stimulus was a rarefied click of 0.1 msec duration set at 50 dB above threshold, usually 95-103 dB, as required. Testing consisted of three sessions presented in random order, each 5-7 min in duration, consisting of paired click stimuli at interstimulus intervals (ISIs) of 250, 500 and 1,000 msec. For each ISI, pairs of clicks were delivered once every 5 sec (previous studies have shown that stimulation at faster frequencies can lead to a decrement in the P1 potential amplitude [Erwin and Buchwald, 1986a, 1986b, 1987]) until 64 pairs of evoked potentials were acquired, averaged and stored by the computer. EEG signals which contained interference from EOG or EMG leads were excluded from the average. Amplified signals were displayed on an oscilloscope for visual monitoring, digitized using a GW Instruments I/O module, averaged using Superscope software (GW Instruments) and stored on computer (Macintosh Quadra 650) disk and on magnetic tape using a Neurodata VHS tape recorder.

The subjects were studied between 10 a.m. and 3 p.m., with each recording session lasting approximately 45 min, including placement of electrodes. To detect the presence of theta waves, the Fast Fourier Transform of the Oz electrode was computed and displayed on line for each trial. Data from trials with a peak in the theta range and no subsequent (higher frequency) peaks were assumed to signify drowsiness and excluded from the average. If more than 8 trials out of 64 required exclusion, the subject was removed from the study. The subjects were instructed to keep their eyes open and to count the number of stimuli presented as a means of maintaining vigilance. The counts of stimuli reported allowed comparison with those delivered, thereby enabling further assessment of the subject’s alertness. Since the amplitude of the P1 potential is sleep state-dependent (Erwin and Buchwald, 1986a, 1986b, 1987), it was important to monitor vigilance with counts and by visual inspection through the observation window. Only subjects who reported > 95% accuracy in stimulus counts and who showed no signs of drowsiness were included in this study (PD n = 23, controls n = 14). Two PD subjects were deleted from the study

<table>
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<tr>
<th>Table 1</th>
<th>Characteristics of PD Patients (n=23)</th>
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Mean 61 | 51 | 10 | 926 | 59 | 24 | 26 | 30 | 60 | 37 | 37 |
S.D. 9 | 9 | 5 | 613 | 18 | 11 | 12 | 12 | 37 | 21 | 21 |
for failing to meet these criteria. Recordings of PD subjects were carried out pre-operatively within one month of surgery and post-operatively only at 2 months after surgery.

**Data analysis**

The P1 potential was identified as the largest positive amplitude wave occurring between 40 and 70 msec after the stimulus. In our recordings, the peak of the potential usually occurred between 45 and 60 msec latency. The P1 potential follows the brainstem auditory evoked responses (BAER) at <10 msec latency and the primary cortical evoked response (Pa) at 25-40 msec latency. It should be noted that the P1 potential is reproducible within individuals, producing virtual overlap in waveforms recorded repeatedly over one year’s time, even in pathological conditions (Green et al., 1995). Peak latency and maximum amplitude were measured for each subject. The latency of the P1 potential induced by the first click stimulus of a pair was measured for each subject at each of the three ISIs tested, and a mean latency for each subject was then calculated using these three measures. The mean of the mean latencies for each group was determined. Amplitude measures were performed using the peak-to-peak method previously described (Erwin and Buchwald, 1986a, 1986b, 1987). Briefly, the amplitude from the preceding negativity (Nb), or from the preceding baseline if Nb was absent, to the peak of the P1 potential was measured. The amplitude of the P1 potential induced by the first click stimulus of a pair was measured for each subject at each of the three ISIs tested. A mean amplitude for each subject was then calculated using these three measures, and a mean of the mean amplitudes for each group was also determined. The degree of habituation was determined by calculating the amplitude of the P1 potential induced by the second stimulus of a pair as a percent of the amplitude of the P1 potential induced by the first stimulus of a pair. This takes advantage of the fact that the two stimuli are temporally close such that changes in vigilance would affect both stimuli and their ratio would remain constant. Once the percent habituation was determined for the second stimulus of each ISI (i.e., 250, 500 and 1,000 msec) for each individual, a mean percent habituation and its standard deviation were calculated for each group. All measures (latency, amplitude and habituation) were compared across groups of subjects using a one-way ANOVA followed by post hoc comparisons using a Newman-Keuls test when comparing pre- and post-operative patients and controls. Two sample correlated Student t-tests were used to compare pre- vs. post-operative results within the PD group, and independent t-tests used to compare PD results vs. controls. Statistical significance was assumed to be present at the $p < 0.05$ level.

**RESULTS**

**Subjects**

Statistical comparison showed there to be no difference in age between the PD patient group and the control group ($df = 22.13, t = 0.2, p = 0.8$, ns). Within the PD patient group, results
showed that the mean Modified UPDRS score before surgery was 59 ± 18, compared to 24 ± 11 post-operatively at 2 months. The score for two patients could not be obtained due to non-compliance. For the remainder of the group (n = 21), this represented a significant decrease in symptomatology (ANOVA p < 0.0001, Newman-Keuls post hoc p < 0.01) and > 50% improvement in UPDRS rating. All PD patients reported subjective improvement and objective improvement according to UPDRS scores ranging from 26-85%. Follow-up UPDRS ratings were carried out at 6 and 12 months post-operatively. The average UPDRS scores at 6 months post-operatively were 26 ± 12, while that at 12 months post-operatively was 30 ± 12. This represented a significant and enduring improvement in symptomatology (pre-operative UPDRS vs. each post-operative UPDRS, ANOVA p < 0.0001, Newman-Keuls post hoc vs. 6 months p < 0.01; vs. 12 months p < 0.01). Three PD patients have yet to reach 12 months post-operatively. It should be noted, however, that every patient rated pre-operatively (n = 21) had a lower UPDRS score at 2 months post-operatively, but 2/21 had increasing scores at 6 months and 5/18 had increasing scores at 12 months post-operatively. This suggests that, in some patients, the beneficial effects of surgery may wane somewhat at long post-operative intervals although the average UPDRS score remains significantly lower than pre-operatively.

It should be mentioned that over 150 pallidotomies have been performed at this institution since 1994. The current prospective study on a limited population is representative of the population at large. While the outcome of this small group which underwent electrophysiological testing was quite good, there are a number of complications associated with this surgical method. For this small group, complications included deficits in memory (4 patients), worsening of speech (3 patients), and visual field deficits (1 patient). All patients who experienced problems with memory had mild dementia pre-operatively (Mini Mental scores of 22-28) and moderate to severe dementia post-operatively (Mini Mental scores of 15-23). The patients with post-operative speech problems complained of an inability to project their voices. One patient had worsening of drooling and dysphagia. One patient had a small scotoma that only became clinically overt when reading small print. For the population at large, additional complications including death, stroke, visual disturbance, transient confusion, excessive somnolence and eyelid dyspraxia have been observed.

**Recordings**

Measures of the latency to the peak of the P1 potential were 48 ± 3 msec for the control group, and 48 ± 4 msec for the PD group pre-operatively and 47 ± 3 msec post-operatively. There were no statistical differences across or within groups in terms of latency (i.e., surgery did not affect latency).

Measures of peak amplitude for the control group averaged 2.1 ± 0.8 µV, while that of the PD patient group was 2.4 ± 1.6 µV pre-operatively and 2.5 ± 1.2 µV post-operatively. There were no statistical differences across groups in terms of amplitude, although the amplitude in the PD group tended to be numerically greater than the control group, in keeping with previous observations (Teo et al., 1997a). There was no difference in the mean amplitude pre- vs. post-operatively (i.e., surgery did not affect amplitude).

Measures of disinhibition of the P1 potential were carried out for each of the three ISIs. Figure 1 shows averages for an individual and grand averages of the P1 responses to pairs of stimuli delivered at the 250 msec ISI for pre-operative PD, post-operative PD and control groups. The P1 potential elicited by each of the two stimuli administered 250 msec apart showed that the P1 potential following the second stimulus was a greater percentage of the first in pre-operative PD patients compared to controls. Following surgery, the P1 potential elicited by the second stimulus was reduced to the level of the control subjects. Figure 2 summarizes the disinhibition of the P1 potential induced by the second click of a pair as a percent of the P1 potential induced by the first click stimulus for all ISIs tested. The mean percent disinhibition at the 250 msec ISI pre-operatively was 60 ± 37% compared to 21 ± 20% in controls (i.e., significantly disinhibited in the pre-operative PD group, p < 0.0003). After surgery, the P1 disinhibition was reduced to 37 ± 21% in the PD group (i.e., significantly re-inhibited in the post-operative PD group compared to pre-operative, p < 0.007; but still different from controls, p < 0.04). That is, there was a trend towards normalization of disinhibition of the P1 potential after surgery, but not all the way to control levels.

At the 500 msec ISI, the mean percent disinhibition pre-operatively was 78 ± 47% compared to 43 ± 31% in controls (i.e., significantly disinhibited in the pre-operative PD group, p < 0.01). After surgery, the P1 disinhibition was reduced to 43 ± 32% in the PD group (i.e., significantly re-inhibited in the post-operative PD group compared to pre-operative, p < 0.004; and no longer different from controls, ns). At the 1,000 msec ISI, there were no significant differences between controls (74 ± 41%), pre-operative PD (84 ± 36%) or post-operative PD (86 ± 34%).

Table 1 summarizes the data for pre- and post-operative (2 months) PD patients and for controls in terms of age, sex, stage, age of onset, duration of disease, Modified UPDRS score (pre-operatively and at 2, 6 and 12 months post-operatively) and percent habituation of the P1 potential at the 250 msec ISI pre-operatively and post-operatively. Also included is a summary of the drugs being taken by this group of patients. All but one patient was being treated pre-operatively with levodopa therapy, the average daily l-dopa equivalent dose being 926 ± 613 mg for the group. After 2 months post-operatively, at the time of the follow-up P1 potential recording, some adjustments were made to l-dopa dosages, leading to an average daily l-dopa equivalent dose of 851 ± 553 mg, which was not statistically different from the pre-operative dose (all but the same patient who was not being treated pre-operatively were treated post-operatively). Nine of the 23 PD patients underwent this small change in l-dopa dosage. The average UPDRS score pre-operatively for this subgroup of 9 patients was 63 ± 17, and 24 ± 15 post-operatively, indicating a similar post-operative improvement compared to the rest of the patient group. P1 potential latency,
amplitude and disinhibition were not different from the rest of the patient group. Four patients were receiving anticholinergic agents pre-operatively, with this drug being discontinued in one patient post-operatively. The pre-operative UPDRS score for this group of 4 patients was 62 ± 9, and 30 ± 5 post-operatively, again indicating a similar effect of pallidotomy on symptom severity compared to the rest of the patient group. P1 potential latency, amplitude and disinhibition were not different for this small group of patients compared to the rest of the PD group. Similar results were evident when comparing those patients receiving antidepressants (n = 9, pre-op UPDRS 58 ± 25, post-op UPDRS 29 ± 16) or monoamine oxidase inhibitor (n = 9, pre-op UPDRS 56 ± 13, post-op UPDRS 26 ± 14). These results are similar to those previously reported (Teo et al., 1997a).

In terms of staging for severity of disease, 5 patients were classified as stage 3; 12 were stage 4; and 6 were stage 5. There were no statistical differences between the age (stage 3, 61 ± 8; stage 4, 63 ± 8; stage 5, 58 ± 13 yrs), or between the duration of disease (stage 3, 10 ± 4; stage 4, 10 ± 6; stage 5, 11 ± 3 yrs) of patients at different stages. When P1 potential disinhibition was compared between stage 3 patients pre-operatively and post-operatively and the control subjects, no statistically significant differences were evident at any of the ISIs tested (250 msec ISI, pre-op 39 ± 22% vs. post-op 18 ± 13% vs. controls 21 ± 20%; 500 msec ISI, pre-op 59 ± 37% vs. post-op 30 ± 27% vs. controls 43 ± 31%; 1,000 msec ISI, pre-op 112 ± 36% vs. post-op 91 ± 39% vs. controls 76 ± 41%). That is, while there was a numerical decrease in the disinhibition of the P1 potential after surgery, when patients were divided into a stage 3 group, there were no statistical differences in P1 potential disinhibition. Stage 4 patients did show statistically significant differences at the 250 msec ISI, but not at the longer ISIs although percent disinhibition was numerically reduced by surgery (250 msec ISI, pre-op 58 ± 33% vs. post-op 42 ± 24% (ns vs. pre-op) vs. controls 21 ± 20% (p < 0.006 vs. pre-op, p < 0.03 vs. post-op); 500 msec ISI, pre-op 80 ± 58% vs. post-op 41 ± 29% vs. controls 43 ± 21%; 1,000 msec ISI, pre-op 58 ± 33% vs. post-op 42 ± 24% vs. controls 76 ± 41%). Stage 5 patients also showed statistical differences similar to those of stage 4 patients (250 msec ISI, pre-op 80 ± 48% vs. post-op 42 ± 13% (ns vs. pre-op) vs. controls 21 ± 20% (p < 0.03 vs. pre-op, p < 0.02 vs. post-op); 500 msec ISI, pre-op 88 ± 21% vs. post-op 58 ± 41% vs. controls 43 ± 31%; 1,000 msec ISI, pre-op 90 ± 54% vs. post-op 88 ± 42% vs. controls 76 ± 41%).

**DISCUSSION**

We previously reported that disinhibition or decreased habituation of the P1 potential was present in patients with PD (Teo et al., 1997a). The present study confirmed this finding, but also demonstrated that bilateral pallidotomy for the relief of symptoms of the disease led towards normalization of disinhibition of the P1 potential. These effects were coincident with improved symptom scores as reflected by reduced UPDRS ratings. One potential neurological substrate involved in the disinhibition of the P1 potential appears to be the PPN, which, therefore, is proposed to be overactive in PD, and down-regulated by pallidotomy. These findings confirm the possibility that there is dysregulation of elements of the RAS in PD, suggesting that alternative therapeutic strategies directed at this system may be of benefit. In addition, the trend towards normalization of habituation of the P1 potential induced by pallidotomy points to novel considerations on the interactions between the basal ganglia and the control of sleep-wake states and arousal by the RAS.

We first reported the presence of a disinhibition (or decreased habituation) of the P1 potential in PD (Teo et al., 1996, 1997a). This finding suggested the presence in PD of a deficit in sensory gating of auditory input by elements of the RAS. That is, inhibition or habituation of responses following repeated stimulation normally provides a mechanism for gating sensory inputs, presumably to avoid intrusive effects. When the system is disinhibited, these sensory inputs can become intrusive, producing a deficit in sensory gating, such as that observed in anxiety disorder (Gillette et al., 1995). Since the P1 potential may be generated, at least in part, by the PPN (Buchwald et al., 1991; Reese et al., 1995), this result implies...
that the cholinergic arm of the RAS is disinhibited or overactive in PD. The disturbance in information processing through this system may account for some of the symptoms of the disease, especially those related to altered reflex function and anxiety, and regulation of arousal.

Two other important observations from that study (Teo et al., 1997a) should be noted. One, analyses of covariance failed to detect any effects of medication (levodopa, anticholinergics and other agents) on P1 potential disinhibition. As far as the present results are concerned, it should be stressed that it is unlikely that medications could have produced the P1 potential changes induced by pallidotomy since levodopa therapy was continued post-operatively at close to the pre-operative levels. Two, disinhibition of the P1 potential was more marked in later stages of the disease (i.e., stage 5 and stage 4 disinhibition was greater than at stage 3, which was not different from control), suggesting that this phenomenon is present especially in later stages of PD. The results of the present study confirmed our earlier findings, showing a more marked disinhibition of the P1 potential at later, compared to earlier, stages of PD.

We were the first to report the effects of pallidotomy on the disinhibition of the P1 potential. The observation in a small group of patients was first included in a poster presentation but had not been mentioned in the published abstract (Teo et al., 1996), then, more recently, findings in a larger group of subjects was described in abstract form (Teo et al., 1997b). The main finding of the present study is the trend towards normalization of disinhibition of the P1 potential in PD following pallidotomy. This suggests that the surgical lesion somehow corrected the sensory gating deficit induced by disinhibition. The results indicate that neither amplitude nor latency of the P1 potential was affected by the surgery, suggesting a specific effect on disinhibition. Moreover, this effect was accompanied by an improvement in symptomatology as reflected in UPDRS scores. Consideration of the scores in Table 1 allows observations on the within- and between-subject variability of UPDRS scores over time. The most common pattern (23/23) involved a decrease in score at 2 months, and most (21/23) underwent little or no change at 6 months. In only two cases did the UPDRS scores increase at 6 months. At 12 months, some subjects (9/23) showed a modest increase in scores, but most of these (8/9) still showed scores well below the pre-operative levels. In only one case did the initial decrease in UPDRS score rise to a score greater than at pre-operative levels (i.e., a worsening of symptomatology).

Subjects
Statistical analyses showed that patients did not differ from controls in age. When the patients were divided according to severity of disease, there was no preferential age at which the different degrees of severity were manifested, since the mean age was similar across groups. Moreover, there was no statistical difference between duration of disease for any of the three stages, although stage 5 patients had a numerically increased duration, as would be expected.

Recordings
The mean peak latency of the P1 potential was similar between controls and patient groups, even when segregated according to severity. While the reported range of latencies for the P1 potential is rather wide (40-70 msec) (Erwin and Buchwald, 1986a, 1986b, 1987; Picton and Hillyard, 1974), our results showed a narrow range of latencies for all subjects (43-61 msec). This may be due to the slow frequency of stimulation employed (0.2 Hz), which would tend to allow full expression of the amplitude of the potential, whereas more rapid stimulation can lead to a decrease in amplitude along with a flattening of the peak, making latency measures more difficult (Erwin and Buchwald, 1986a, 1986b, 1987). The peak amplitude measures in this study are consistent with other studies which used long intertrial intervals (Erwin and Buchwald, 1986a, 1986b, 1987). More rapid stimulation (0.5 Hz or faster) tends to decrease P1 potential amplitude, accounting for reports suggesting a mean amplitude for the P1 potential of < 1 µv. Our results in normal controls show a mean peak amplitude of about 2 µv in older controls (65 ± 10 yrs) as well as in younger (25 ± 6 yrs, 45 ± 7 yrs) control groups (Rasco et al., personal communication).

The use of the paired stimulus paradigm to assess disinhibition or habituation is of great value in determining function. It is the relationship between responses elicited within a very short period of time that is of importance. Therefore, changes in state of alertness within a trial are unlikely, and the ratio of the first response to the second is likely to remain constant. The precautions taken in this study to control for alertness included measurement of theta frequency using an occipital lead along with on-line display of the Fast Fourier Transform of that channel. The presence of theta waves in the absence of higher frequency activity would indicate drowsiness, and those trials were not averaged when present. The use of stimulus counts also prevented, and allowed assessment of, drowsiness. Given the trend towards slightly higher amplitude P1 potentials in PD patients, it is probable that alertness was effectively maintained in patients in this study. The decrease in habituation was greater at the shorter ISI, that is, the percent habituation at the 250 and 500 msec ISIs differed from controls but the 1,000 msec ISI was similar to that of controls. Pallidotomy tended to reduce the disinhibition of the P1 potential significantly at the shorter ISIs (250 and 500 msec), but not at the 1,000 msec ISI. For the patient group as a whole, there was no difference between the post-operative and control percent habituation, indicating a trend towards normalization of the disinhibition of the P1 potential after surgery. Table 1, however, shows that not all patients underwent a decrease in habituation. While most subjects (20/25) underwent a decrease, some (5/25) underwent an increase, although only some of these (2/5) showed an increase of more than 20%. Therefore, while there was a significant population effect, there was some variability between subjects.

However, when the patient group was divided according to degree of severity, the statistical significance of the effect of surgery disappeared. That is, while the mean percent habituation was decreased post-operatively in every stage, the numerical difference was not significant. In fact, the post-operative percent habituation was different from controls at the shortest ISI tested (250 msec), suggesting that the trend...
towards normalization was not complete. We attribute these differences to the smaller sample sizes produced by breaking the PD group into stage 3, 4 and 5 subgroups. Perhaps a larger sample of patients at each stage would yield statistically significant differences, or it may indicate that pallidotomy may affect the P1 potential to a greater degree at later stages of the disease. The present results are not conclusive in this regard.

Possible Mechanisms

The possible mechanisms involved in the disinhibition of the P1 potential in PD, and the trend towards normalization of this disinhibition following pallidotomy, are not entirely understood. A great deal of research needs to be carried out to further understand these processes. The disinhibition of the P1 potential reported herein suggests the possibility that the PPN, as one of the neurological substrates of the P1 potential (Buchwald et al., 1991; Reese et al., 1995), is disinhibited or overactive in PD. If this interpretation is correct, such a condition would involve release of neurons which induce cortical desynchronization, control REM sleep, and generate PGO waves (Steriade and McCarley, 1990), possibly leading to disinhibition of blink and other reflexes, contributing to a sensory gating deficit and producing anxiety (i.e., many of the symptoms present in PD). This also can explain some of the sleep deficits observed in PD, specifically the reduction of slow-wave sleep (Myslobodsky et al., 1982) and frequent nocturnal arousals (Askenasy and Yahr, 1985; Kales et al., 1971; Mouret, 1975), since increased PPN output can account for increased arousal and REM sleep drive. Significantly, one of the benefits of levodopa therapy in PD appears to be a reduction of REM sleep (i.e., of output of the PPN) (Gillin et al., 1973; Kales et al., 1971).

Since the RAS modulates arousal and attention, dysregulation of this system could contribute to the attentional and, perhaps even cognitive, deficits evident in PD (Jagust et al., 1992; Robbins et al., 1994). A recent study demonstrated that frontal lobe blood flow is decreased during REM sleep (Maquet et al., 1996), a sleep-wake state in which the cholinergic arm of the RAS (i.e., the PPN) is preferentially active. Therefore, the disinhibition of the PPN in PD could account for some of the decrease in frontal lobe function observed in PD (Eidelberg et al., 1994; Jagust et al., 1992; Peppard et al., 1992). Much additional research is needed to properly understand this effect.

Simultaneous bilateral pallidotomy appears to reduce some of the adverse symptoms of PD. This has been demonstrated both subjectively and objectively. Furthermore, normalization of the P1 potential after surgery supports a mechanism related to the PPN. Although our surgical results are favorable, review of this population supports the suggestion that pallidotomy is not without risk. Although complications in this surgery have been downplayed (Iacono et al., 1994), our results are more in agreement with recent results showing that pallidotomy may cause speech and memory deficits (Baron et al., 1996). Similarly, the mild decline in post-operative improvement seen in this series of patients, and in others (Baron et al., 1996), over a 12-month period may be of concern. Longer follow-ups are required before statements can be made about the maintenance of surgical benefits. The P1 potential may be a useful tool in assessing surgical success and/or its maintenance, although larger populations need to be studied. Moreover, it may be possible that the P1 potential could be used as an additional exclusion criterion if the pre-operative P1 potential is not disinhibited (i.e., if percent disinhibition does not fall into the range seen in PD).

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REFERENCES


