Dopaminergic induced changes in cognitive and motor processing in Parkinson's disease: an electrophysiological investigation

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Abstract

Event-related potentials and reaction time measures to auditory discrimination tasks of graded difficulty were used to separate cognitive from motor processing time in 27 patients with newly diagnosed, previously untreated Parkinson's disease and later on optimal levodopa treatment. Before treatment event-related potential P3 and task performance were normal but the reaction time was prolonged compared with age matched controls. After treatment P3 latency was significantly prolonged and the reaction time reduced suggesting a dopamine induced dissociation between cognitive and motor processing. In early Parkinson's disease cognitive processing time remains normal but the motor processing time is prolonged. Dopamine replacement is followed by significantly reduced motor processing time despite increased cognitive processing time. Motor processing may reflect the dopamine status of the putamen whereas dopaminergic over-stimulation of other regions may adversely affect cognitive processing in patients treated with levodopa.

Parkinson's disease (PD) was originally considered to be a motor disorder without any impairment of mental function¹ but evidence^{2,3} is growing that some cognitive decline does occur although it is not clear whether this relates to basal ganglia pathology or cortical involvement.⁴ Some patients show specific focal cognitive deficits such as difficulties in strategy shifting,⁵ pattern tracking,⁶ and memory scanning,⁷ whilst others exhibit a general cognitive impairment.⁸ Performance IQ has been shown² to be impaired compared with verbal IQ but this may be due to motor deficits confounding assessment of performance. There is no "pathognomonic" cognitive profile for patients with idiopathic PD. Levodopa treatment initially improves psychometric performance⁹ but prolonged treatment is associated with deterioration.¹⁰

Planning of movements is considered a major defect in movement control in PD.¹¹ Reaction time experiments¹² support this view although Rafal *et al*¹³ found no evidence that bradykinesia is accompanied by slowness in assembling a motor programme but slowing in the later stages could not be ruled out. It is difficult on psychological testing to separate

cognitive from motor processing stages. This is particularly so in PD with the invariable presence of motor disability confounding evaluation of cognitive processing time.

The cerebral potentials associated with information processing, especially the timing of sensory stimulus discrimination and categorisation together with the reaction time measures, provide a unique means of separating decision processes from motor involvement. These event-related potentials (ERP) are insensitive to physical characteristics of the stimulus but are primarily affected by the task associated with stimulus discrimination which requires the subject to distinguish a particular target stimulus from a randomly presented sequence of two or more different types of stimuli. This paradigm yields an ERP complex comprising components N1, N2 and P3. N1, a negative potential occurring around 100 ms after stimulus onset is considered to represent the encoding of the auditory stimulus.¹⁴ N2 is a second negative peak occurring around 200 ms after stimulus which may represent the input stage of the stimulus evaluation process (see Discussion). P3, a positive potential with respect to the pre-stimulus baseline with a modal latency of 300 ms reflects motor-free speed of cognitive processing. P3 latency increases with advancing age and with the difficulty of target identification.¹⁵

After it had been shown that P3 is significantly delayed in patients with dementia,¹⁶ Hansch *et al*¹⁷ demonstrated a prolongation of P3 latency in patients with PD treated with levodopa (Sinemet). O'Donnell *et al*¹⁸ showed further that increase in P3 latency correlated with mental status decline. In contrast, Goodin and Aminoff¹⁹ observed no difference in P3 latency in non-demented, treated PD patients whereas PD patients with dementia showed a significant delay of N1 and P3. The discrepancy with the earlier studies^{17,18} was considered due to the mix of demented and non-demented patients. No study has considered the effect of drug therapy although in a recent study²⁰ of only seven patients with severe motor fluctuations, a significant decrement in P3 latency was shown in the "on" phase.

The purpose of this study was to evaluate whether the speed of cognitive processing, as measured by P3, is slower in an unselected group of newly diagnosed, non-demented patients with PD and by combining performance measures, and reaction time determine which stages of information processing are

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most affected especially for levodopa treatment.

Methods

Twenty seven consecutively referred newly diagnosed patients with idiopathic PD were studied before treatment started (*de novo*) and retested after optimal clinical response to treatment with levodopa + carbidopa (Sinemet). The mean total dose was 395 mg daily in a range of 150–800 mg for a mean period of 47 weeks in a range of four to 120 weeks. No other treatment was given. The patient group consisted of 12 male and 15 females in the age range of 29–76 years with a mean (SD) of 56 (10) years. A control group consisted of 27 (15 females) subjects with no known history of neurological or psychological illness in the age range of 35–74 years with a mean (SD) of 56 (11) years. Disease duration at initial testing varied from less than a year to six years with a mean (SD) of just under two years. The Hoehn and Yahr score did not exceed two and the laterality of major symptoms and signs was equally distributed to right and left across patients. On average the bradykinesia, tremor and rigidity levels scored on an arbitrary scale from normal (0) to severe (4) were in the mild (1) to moderate (2) range. The CT was only abnormal in one patient in whom WAIS and other psychometric assessments showed focal impairment. None had undergone thalamotomy.

All 27 patients were subjected to comprehensive neuropsychological examinations before initial electrophysiological testing. An index of general intellectual deterioration was obtained by assessing discrepancies between IQs and estimates of premorbid, optimal levels of functioning. A discrepancy of 15 IQ points or more indicated a significant deterioration. The IQs of 23 patients were obtained by using the WAIS.²¹ The reasoning skills of the remaining four patients were assessed with the Advanced Progressive Matrices, Set 1.²² Optimal levels of functioning were estimated on the basis of the patients' sight reading ability using the National Adult Reading Test²³ and/or the Schonell Reading Test.²⁴ Focal deficits were assessed on a variety of tasks, including tests of verbal and visual memory,²⁵ object naming and sentence comprehension,²⁶ perception,²⁷ visuospatial skills²⁸ and tests sensitive to frontal lobe dysfunction such as sorting tasks,²⁹ Cognitive Estimates,³⁰ word fluency³¹ and interpretation of common proverbs. Although some patients were assessed on all tests others received only a selection.

On the basis of the pre-treatment neuropsychological investigations the patient group could be defined as follows. Of the 27 patients 22 were normal, two showed a mild degree of intellectual deterioration (one of them also had significant perceptual and visuospatial deficits) and three had one or more focal cognitive deficits (frontal lobe deficits, selective verbal or visual memory impairments, perceptual difficulties).

Subjects were tested on two auditory tasks of graded difficulty as it was considered that the harder task may reveal subtle cognitive abnormalities. Task 1: Frequency discrimination: 1.5 kHz vs 1.0 kHz. A random series of high and low pitch tones of 100 ms duration were presented in a ratio of 30/70 and the subject identified by pressing a response button the high pitch target tone. Task 2: Duration Discrimination: 200 ms vs 100 ms at 1.0 kHz. In this task the subject identified the shorter tone burst presented randomly in the same target/non-target ratio. The order of presentation of the two tasks was randomised across subjects.

Subjects were presented 100 stimuli per test at 60 dBHL binaurally through TDH39 headphones at a rate of 0.3 Hz and were instructed to respond to the target as quickly as possible. Reaction time (RT) for correctly identified targets was measured to the nearest millisecond. Performance in terms of the number of targets correctly classified, missed and wrongly classified was assessed. On the basis of the control group performance a total of five or more targets missed or wrongly classified constituted impairment of performance. A preliminary run ensured that each subject understood the requirements of the task and was familiar with the target tone burst.

The cerebral potentials were recorded using standard silver/silver chloride EEG electrodes from mid-frontal (Fz), mid central (Cz) and mid-parietal (Pz) electrode placements on the scalp (according to the international 10:20 system) with reference to linked mastoids. Electrode impedance was reduced by skin abrasion to below 2 k ohms. This response activity was filtered so that the 3dB cut off points were 0.03 Hz and 32 Hz with a slope of 6 db/octave. Signals were amplified 50 000 times and averaged separately according to target and non-target stimuli. The analysis window was 768 ms duration sampled every 1 ms.

Patients and subjects were instructed to relax when performing the tasks avoiding any movement other than the button press in relation to the stimulus and were observed throughout the procedure for any overt orienting or stimulus related movements including any excessive or stimulus locked blinking but none was noted. However, any trials with large (> 50 μ V) artifactual excursions were automatically excluded by the computer from entering the average. The cerebral potential averages were independent of the patients' responses in that the error trials were not excluded from the averages. Only those trials in which the error was one of omission of overt response were included in the Target average as the subject may have classified the stimulus accurately but may have made a slow response which fell outside the response capture window of one second. Errors of commission were included in the Non-Target average. Furthermore, the total number of errors was computed and its relationship to P3 latency analysed. The data were averaged on-line using an HP 9836 computer with a Transera data acquisition system. The ERP component peaks of interest were N1, N2 and P3 which were identified from

the three electrode sites but the statistical latency comparisons were made for those measured from the Pz electrode position. In the case of a double peaked P3, P3a and P3b, the measurement of P3b was taken for computation. In the case of a flatter component the method of Goodin *et al*¹⁶ was adopted in that the leading and trailing slopes of the peak in the window of 280–600 ms were extrapolated and the point of their intersection was taken as the P3 latency.

Results

Comparison of the ERP component latencies and reaction time recorded initially from untreated PD patients and age matched controls, shown in table 1, revealed no significant differences in the mean latencies of components N1, N2, P3 or the mean RT for the frequency discrimination task. For the duration task the mean latency of N2 for PD was slightly prolonged compared to the control group although statistically falling outside the 5% significance level ($p = 0.052$). Mean P3 latency was not significantly different but the RT was ($p = 0.016$) prolonged compared with controls. The number of patients with significantly prolonged P3 latency beyond the normal 2SD limit are shown in fig 3. For some patients a delayed P3 on one task did not mean a delay on the other task. RT was prolonged beyond the 2SD normal limit in two patients for the frequency task and six for the duration task although only one of these patients had an absent P3 on the duration task, the others had a normal P3.

The classification errors were generally fairly small as indicated by the median figures although there was a certain skewness to the distribution as shown by the figures in table 2. The Mann-Whitney test showed no significant difference in the error scores between controls and patients. Of the 27 patients, three made more than five errors in target classification for the frequency task and six for the duration task. Only one of these patients had a delayed P3 and another prolonged RT whilst for the rest, the deterioration in performance did not appear to affect P3 or RT.

There were five patients who had focal or global impairment on psychometric assessment and their mean latency of P3 and RT did not differ significantly from the others with normal psychometry.

The treatment difference in RT and in the latency of N1, N2 and P3 for all patients for the frequency task is shown in fig 1 and for the duration task in fig 2.

The mean and SD of the latencies for peaks N1, N2, P3 and RT for all tasks are shown in table 1. Mean latencies of N1 and N2 remain unaffected by treatment whereas mean P3 latency is significantly ($p < 0.002$) increased from 347 ms to 373 ms for the frequency task and from 420 ms to 460 ms ($p < 0.001$) for the duration task. In contrast RT decreased from a mean of 400 ms to 379 ms for the frequency task and significantly ($p < 0.004$) from 515 ms to 460 ms for the duration task. After treatment the number of patients with significant prolongation of P3 latency (fig 3) had increased from four to 11 of the 27 patients (41%) for the frequency task and from six to 12 (44%) for the duration task. Those with an abnormal P3 on either task had almost doubled (16/27; 59%). In addition there were two patients with absent P3 on the duration task pre and post treatment. The five patients with psychometric impairment were not significantly differently affected by treatment from the others. Figure 4a, b and c show representative response waveforms for the frequency and duration tasks from three patients before and a variable time after treatment. The vertical lines delineate the N1 and the pre and post treatment P3 showing a clear prolongation after treatment. The RT, error scores and duration of treatment are given in the legend which indicate a general improvement in RT but a somewhat variable performance. Performance was measured in terms of the total number of errors which constituted missed targets and incorrect classification of non-targets. As there was no significant difference in the missed and wrongly classified non-targets as a function of treatment, further comparisons were made for the total error score. The correlation of P3 latency and RT with the error score revealed that increasing number of errors did not affect the latency of P3 or RT directly. Patients with a large number of errors did not necessarily have a prolonged P3 latency. A statistical comparison of performance between controls and patients before and after treatment shows no significant difference in either case (table 2). However, P3 latency is significantly prolonged after treatment despite any difference in the error scores as a result of treatment.

In an attempt to establish whether the change in P3 following therapy was due to progression of the disease over the treatment period (mean time 47 weeks) or the effect of dopaminergic treatment itself, the difference in latency before and after treatment was correlated with treatment duration. For ease of comparison the patients were divided into those having treatment for less than 30 weeks (with a mean of 14 weeks) and those more than 30 weeks (with a mean of 82 weeks). The former consisted of 15 patients and the latter 12 with no difference in their mean ages. The effect of treatment period on P3 and RT for both tasks is summarised in table 3 which shows that the mean change in P3 latency for the duration

Table 1 Pre and post-treatment peak latency mean (SD) for ERP components and reaction time (RT) for frequency and duration discrimination tasks

Component	N1	N2	P3	RT
<i>Normal Subjects</i>				
Frequency (pre)	107 (12)	230 (36)	339 (25)	367 (66)
Duration	107 (14)	277 (58)	420 (36)	453 (53)
<i>Parkinson's disease</i>				
Frequency (pre)	106 (14)	247 (48)	347 (56)	400 (97)
Frequency (post)	106 (14)	244 (36)	373 (55)*	379 (70)
Duration (pre)	106 (14)	310 (47)#	420 (58)	515 (112)##
Duration (post)	110 (17)	294 (56)	460 (62)**	460 (78)***

Comparison of normal subjects with pre-treatment PD

t-test independent samples (two-tailed): # $p = 0.052$ and ## $p = 0.016$

Comparison of pre and post treatment in PD

t-test repeated measures (two-tailed): * $p < 0.002$ and ** $p < 0.001$ *** $p < 0.004$

Figure 1 Frequency task treatment difference in reaction time and in the latency of event-related components N1, N2, P3 across all patients. Each bar represents the change in a patient's performance after treatment.

task for the group treated for a mean period of 14 weeks is significantly ($p < 0.02$) smaller (22 ms) compared to the group treated for a mean period of 82 weeks (58 ms). However, there was no effect of treatment period on the mean change in P3 latency for the frequency task and RT for both tasks.

Discussion

Only patients with early Parkinson's disease were examined and most had a normal neuropsychological assessment (22/27) with none overtly demented. Before treatment there was

no significant difference in the mean latency of N1, N2 and P3 between controls and patients for both tasks. Following treatment P3 latency was prolonged and RT was reduced. This is a surprising result as it implies that dopamine therapy produces a specific decline in cognitive information processing speed whilst improving the response processing. A clear dopamine induced dissociation is therefore indicated between P3 and RT.

Although Hansch *et al*¹⁷ and O'Donnell *et al*¹⁸ have reported in a mixed group of demented and non-demented PD patients, an increase in the mean latency of P3 to the "oddball" task, reaction times were not measured and only treated patients were tested. Thus the effect of therapy was not considered separately. Goodin and Aminoff¹⁹ also tested treated patients but separated demented from non-demented patients finding P3 latency to be normal in the non-demented group but delayed in the demented group. In contrast, in our study of non-demented patients, P3 was delayed after treatment which was particularly marked for the harder duration task. The difference in the results may be due to the differences in the level of difficulty of the tasks employed in each study. Their simpler task may not have been sensitive enough to detect abnormalities in the non-demented group.

Starkstein *et al*²⁰ reported a decrease in the latency of P3 without any change in RT in the "on" phase compared to the "off" in patients with fluctuating PD. Such apparent variation in the results from this study may relate to the differences in treatment and stages of the disease. Furthermore, the on/off situation is physiologically very different from that of this study.

Although the precise psychological correlate of P3 is not clear it is generally considered to cover stimulus evaluation stages of information processing whereas RT includes this as well as response selection and execution. From the comparison of RT and P3 it is evident that the stimulus and response stages are differentially affected by treatment. Prolongation of RT before treatment and its improvement on levodopa is in accord with a number of studies^{32,33} of choice reaction time which have either reported normal RT or improvement in RT after levodopa treatment. In contrast, sim-

Table 2 Comparison of Performance Error scores*

Performance Range	Frequency			Duration		
	Median	Skewness	Range	Median	Skewness	Range
Control	1.0	1.39	0-4	1.0	1.33	0-5
Pre-treatment	1.0	2.02	0-13	2.0	1.09	0-12
Post-Treatment	1.0	1.66	0-9	1.0	1.17	0-16

Mann-Whitney (MW) independent sample rank test and Wilcoxon (W) matched pairs signed rank test

Comparison	Frequency z-score†	p-value	Duration z-score†	p-value
Controls/Pre-Treatment (MW)	-1.69	0.09	-1.10	0.27
Controls/Post-Treatment (MW)	-0.966	0.33	-1.37	0.16
Pre/Post-Treatment (W)	-0.704	0.48	-0.845	0.39

*performance based on errors of omission and commission.

†p values non significant.

Figure 2 Duration task treatment difference in reaction time and in the latency of event-related components N1, N2, P3 across all patients. Each bar represents the change in a patient's performance after treatment.

Figure 3 Number of patients lying outside the normal upper limit for P3 latency before and after treatment. The hatched columns show the number of patients with abnormally prolonged P3 pre and post treatment whilst the clear columns indicate the significant increase post treatment.

Table 3 P3 and RT in relation to treatment time

	Treatment Time Mean (SD) weeks	Post minus P3 Mean (SD) ms	Pre Treatment RT Mean (SD) ms
Frequency Task	14 (9)	34 (42)	-29 (109)
	82 (25)	32 (53)	-10 (48)
Duration Task	14 (9)	22 (42)	-61 (97)
	82 (25)	58 (47)*	-54 (84)

*t-test (independent samples) P3 duration (14 vs 82 weeks) $p < 0.02$.

Figure 4 Event related potentials from three electrode sites for target stimuli for both frequency and duration discrimination tasks are shown for three patients (a: Disease duration four years, Hoehn and Yahr score 1, moderate tremor and rigidity, no bradykinesia, b: Disease duration three years, Hoehn and Yahr score 1, mild bradykinesia and rigidity, no tremor, c: Disease duration one year, Hoehn and Yahr score 2, mild bradykinesia and rigidity and moderate tremor) with PD tested both pre and post treatment. a) The responses from a patient treated for 27 weeks show that for the frequency task there was no change in the P3 latency but the reaction time (RT) was increased from 272 ms to 284 ms and the error score changed from 1 to 0 as a result of treatment. For the duration task there was a significant increase in P3 latency and decrease in RT from 401 to 359 with no errors before or after treatment b) The responses from a patient treated for 42 weeks show a prolongation of P3 latency for both tasks. RT for both tasks had also improved from 327 to 290 for the frequency task and 511 to 372 for the duration task. Performance had improved considerably from 12 errors before treatment and one post treatment for the frequency task but had deteriorated from one to six errors for the duration task. c) The responses from a patient treated for 68 weeks show a prolongation of P3 latency for both frequency and duration tasks. The reaction time had improved from 385 to 293 for the frequency task and 523 to 437 for the duration task. Performance figures show that on the frequency task there were no errors before treatment and one after treatment and on the duration task seven before and none after treatment.

ple reaction time (SRT) is prolonged in PD and remains unaffected by treatment.^{33,34} Thus SRT and CRT are also differentially affected by levodopa replacement.

In a similar fashion to SRT and CRT, P3 and RT are unlikely to follow a sequential process along a continuum, being differentially affected by treatment, they may indeed be mediated via separate parallel pathways. Prasher and Findley³⁵ have shown that with reaction time feedback, it is possible for patients to reduce their mean reaction time to below mean P3 latency. This infers that stimulus classification must occur before P3 for the response processing (RT) to be complete before P3 and again implies that generation of P3 and response processes follow parallel or more complex paths after N2.

If N2 is considered as the point in time where P3 and RT processes separate then the time from N2 to RT (RT minus N2) may be conceived as the "motor organisation time". From the data of table 1 it can be seen that the interval between mean RT and N2 before treatment for the frequency task was 153 ms and for the duration task 205 ms and both had improved after treatment to 135 and 166 ms respectively which are very close to normal figures of 137 ms and 176 ms respectively for the two tasks. This clearly shows the improvement in time required for motor organisation processes.

Gotham *et al.*³⁶ have observed similar treatment related dissociation in that certain cognitive functions (associative conditional learning and subject-ordered pointing) were adversely affected by treatment with levodopa whilst others (verbal fluency) showed improvement. They suggested that these conflicting findings may result from the beneficial effects of dopamine replacement in certain regions and adverse effects of dopamine overstimulation in the others. The overstimulation could occur in the pre-frontal cortex where the dopamine systems are relatively intact. Likewise, the adverse effect of dopamine therapy on P3 may be due to over stimulation of regions responsible for its generation rather than a replacement of dopamine in the depleted striatum which may account for changes seen in RT. This is consistent with the fact that in the initial untreated (dopamine depleted) state these patients have normal P3 but prolonged RT. Movement time (MT) and RT clearly reflect the extent of bradykinesia in PD which correlates well with striatal dopamine deficiency.^{37,38}

From these observations and our findings it could be argued that the speed of cognitive processing is unrelated to the extent of bradykinesia but is related to relative dopamine levels, though not necessarily in the striatum. Fluctuations in the plasma dopamine level have been shown to affect other cognitive functions such as state dependent memory performance.³⁹ Our electrophysiological findings are entirely consistent with the neuropsychological test results reported recently by Hurtig *et al.*⁴⁰ and Pillon *et al.*⁴¹ The former showed that levodopa treatment resulted in marked im-

provement in motor function and decline in performance on certain specific cognitive tests whilst the latter observed cognitive impairment in PD to be poorly correlated with levodopa responsive symptoms such as akinesia and rigidity but strongly correlated with levodopa resistive symptoms such as gait disorder and dysarthria.

This study has clearly shown that the combination of event related potentials and reaction time provides a powerful objective tool for monitoring the relative effects of dopaminergic therapy on both the cognitive and motor systems in Parkinson's disease. It is possible that the observation of increasing P3 latency with dopamine may be an early indication of eventual dementia seen in some long-term levodopa treated patients with PD.

It is clear that treatment effects must be taken into account in any assessment of cognitive function in Parkinson's disease.

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