TEMPORAL DISCRIMINATION IS ABNORMAL IN PARKINSON’S DISEASE

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SUMMARY

Temporal discrimination thresholds (TDT) for recognition of paired sensory (tactile, auditory and visual) stimuli given over a wide range of time intervals were assessed in 44 patients with Parkinson’s disease (PD) and 20 age-matched normal subjects. A significant increment in TDT for all three sensory modalities was found in PD patients compared with controls. This abnormality was greatly attenuated for about 2 h by a single levodopa/carbidopa (250/25 mg) tablet. A significant correlation was found between disease severity as assessed clinically and TDT. Patients with more severe PD had higher TDT values. The study of the peripheral median nerve and cortical somatosensory evoked potential recovery curves following double electrical stimulation of the index finger showed no differences between patients and control subjects, nor changes from ‘off’ to ‘on’ motor state which could explain the findings. These results indicate the existence of an abnormality of timing mechanisms in PD.

INTRODUCTION

The symptomatic manifestations of Parkinson’s disease (PD) are mainly motor (Marsden, 1982). Subjective sensory symptoms were described by earlier investigators such as Charcot (1887) and Kinnier Wilson (1940). In some recent studies, primary sensory symptoms were found in 43 out of 101 (43%) (Snider et al., 1976) and in 19 of 50 (38%) (Koller, 1984) patients with PD. Schneider et al. (1986, 1987) reported deficits on tests of sensory function and sensorimotor integration in the orofacial region and the arms. Disturbance of olfactory function has also been documented in PD (Ward et al., 1983; Quinn et al., 1987). Nevertheless, the meaning and origin of sensory and other non-motor clinical manifestations of PD is poorly understood at present. Marsden (1982) proposed a primary role of the basal ganglia in motor control while Snider et al. (1976) suggested that sensory symptoms in PD reflect participation of the basal ganglia in sensory function. Hassler in his scholastic review (1978) indicated that the basal ganglia served a sensorimotor integrative function, a view also held subsequently by other researchers (Cooke and Brown, 1979; Schneider et al., 1982; Rolls and Williams, 1987).

One approach to the study of sensory function is the assessment of temporal discrimination. Temporal discrimination (TD) is a measure of the minimum time interval required between two successive auditory, visual or somaesthetic stimuli for them to be perceived as separate. In a previous study (Lacruz et al., 1992) we found that patients with focal striatal and thalamic lesions had abnormal somaesthetic temporal discrimination thresholds (STDT), i.e. showed a prolongation of the time interval required for paired
stimuli to be perceived as separate on the hand contralateral to the lesion. Many of these patients also showed clinical features of parkinsonism. In a preliminary study we found an alteration of STDT in PD (Obeso et al., 1987). In this report we analyse in detail factors influencing STDT in a larger number of patients with PD and extend the investigation to visual and auditory TD.

SUBJECTS

The patient group consisted of 44 (30 males, 14 females) patients with PD with a mean age of 57.1 ± 9.3 yrs (41–77). None of the patients had clinical evidence of dementia or depression, and all had normal scores on the Mini Mental test (Folstein et al., 1975). At the time of study none of the patients had severe tremor at rest, dyskinesias or painful dystonic postures that might have interfered with the performance of the experiment. Mean illness duration was 7.7 ± 5.9 yrs (2–25). All patients were studied in the ‘off’ state, 12–24 h after withdrawal of anti-parkinsonian therapy. Eleven patients also performed the tests in the ‘on’ state following administration of 250/25 mg of levodopa/carbidopa (p.o.).

For the purpose of clinical comparisons patients were clinically classified into three severity groups (mild, moderate, severe) on the basis of their baseline (‘off’ medication) parkinsonian score and in accordance with the response to levodopa therapy. Those in the mild group (n = 15) had stable and adequate response to levodopa (‘long duration response’). Patients in the moderate category (n = 22) had ‘wearing off’ fluctuations with no or only mild ‘on’ dyskinesias. Patients with severe disease (n = 7) showed complex ‘on-off’ fluctuations with frequent and relatively unpredictable ‘off’ periods, and presence of various types of dyskinesias. The King’s College Hospital (KCH) Parkinson’s disease rating scale (range 0–117) was used for clinical evaluations. The mean KCH score for the clinically defined mild, moderate and severe groups was 20.7 ± 9.7, 37.8 ± 14.3 and 62.3 ± 16.2. The average age of the patients with mild, moderate or severe Parkinson’s disease was respectively 57.3 ± 8.7, 57.6 ± 10.6 and 55.1 ± 7.6 yrs.

Twenty normal controls (13 males, 7 females) were also tested. Their mean age was 61.9 ± 11.2 yrs (42–73). None of them had a history of physical or neurological disease.

PROCEDURES

Measurement of temporal discrimination threshold

Temporal discrimination thresholds (TDT) for somaesthetic (tactile), visual and auditory stimuli were studied using the ‘method of limits’ (Blackwell, 1953). The minimum time interval required for paired stimuli to be felt as separate in time was first assessed starting with an 8 ms interval for auditory stimuli and a 5 ms interval for the somaesthetic and visual stimuli, and then increasing the interval by 1 ms steps (ascending temporal discrimination threshold, ascending TDT). Subsequently, starting with an interstimulus interval 10 ms higher than the ascending TDT obtained in the ascending series, the intervals were reduced until the subject could only recognize one stimulus (descending temporal discrimination threshold, DTD). Each series was repeated six times. As a control, paired stimuli with zero time interval were randomly interposed in the series. On each trial, the subject indicated whether one or two stimuli were felt. For each subject the appropriate intensity of the stimuli was established by obtaining the individual sensory threshold (the point at which the stimulus was just noticeable) and then using a stimulus intensity above threshold. The method is also described in detail in a preceding paper (Lacruz et al., 1992). Somaesthetic temporal discrimination thresholds (STDT) were evaluated by applying a rectangular electrical pulse of 0.2 ms, with ring electrodes with an intensity three times the sensory threshold on the index finger of the hand. The two hands were tested separately. Auditory temporal discrimination thresholds (ATDT) were studied by presenting a 0.2 ms click, 60 dB above the subjective audiosensory level. The right and left ears were assessed independently. Visual temporal discrimination thresholds (VTDT) were assessed by exposing the right and left eyes separately to a red light-emitting diode (LED λ = 600 nm), 5 mm in diameter, positioned at a distance of 30 cm from the subject. This resulted in a monocular retinal stimulus of 1 degree arc.

Katzman’s test (Katzman, 1983) for attention was given at the beginning and end of the procedure, and found normal in all subjects included in this report.
Electrophysiological assessment

Sensory nerve action potentials (SNAPs) and cortical somatosensory evoked potentials (SEPs) from the scalp were recorded. The recovery curves of the peripheral nerve and cortical responses to paired pulse stimuli were measured in 15 control subjects and 15 age-matched parkinsonian patients during 'on' and 'off' periods. The characteristics of the electrical stimuli were identical to the ones used for assessing STDT. Sensory nerve potentials were recorded using surface silver-silver cup electrodes placed 2 cm apart on the wrist (over the region of the median nerve). Somatosensory evoked potentials were recorded from scalp electrodes (by the standard technique) over the contralateral parietal region with ear-linked references. Sixteen SNAPs were averaged following double stimulation at 17 different time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 100, 200 ms). The amplitude of SNAPs was taken as the largest negative-positive peak-to-peak amplitude. The SEPs were the result of averaging at least 128 potentials following paired stimuli of the index finger with interstimuli intervals of 20, 30, 40, 50, 60, 70, 80, 90, 100, 200 ms. For short (20–60 ms) interstimuli time intervals a computerized subtraction method was applied for better definition and easier measurement of the early N20-P25-N35 cortical potentials. The amplitude ratio of the second (Test Response, TR) and first (Conditioning Response CR) SNAP and SEP to paired stimuli were expressed in a curve as percentage of recovery (TR/CR×100) for each interstimuli interval.

Motor function tests

To obtain an index of slowness of movement in the patients the following motor tests were performed.

(1) A 40 degrees ballistic flexion movement of the wrist in response to a randomly presented auditory stimulus was used to calculate the average reaction time and movement time for 20 trials. Wrist position and the surface EMG rectified activity from forearm flexor muscles were recorded and averaged (in blocks of 10).

(2) Tapping. Patients were asked to tap with the index finger of each hand as fast as possible two white squares (2x2 cm) separated by a distance of 30 cm during 30 s. The arithmetic mean of the number of taps in six trials was calculated for analysis.

Statistics

Differences between TDT values in control subjects and patients and differences in TDT according to disease severity were analysed by the unpaired t test for unequal sample size and one-way ANOVA, respectively. The paired t test was applied to assess possible differences between right- and left-hand stimulation for somaesthetic TDT and between 'on' and 'off' motor states. Spearman's correlation was used to correlate the motor tests with TDTs. Results are given as the mean ±1 SD.

RESULTS

Somaesthetic TDT and electrophysiological studies

In control subjects STD values in the right hand were 39.5 ± 14.3 ms (ascending TDT) and 28.8 ± 11.1 ms (descending TDT). In the left hand STD values were 37.4 ± 13.5 ms (ascending TDT) and 27.7 ± 10.1 ms (descending TDT). In patients with PD, STDs were significantly increased (Fig. 1). Thus, STDs in the right hand were 118 ± 23 ms (ascending STD) and 95.2 ± 24 ms (descending STD). In the left hand, STD values were 117 ± 24.7 ms (ascending STD) and 90.3 ± 22.3 ms (descending STD).

No significant difference was found for STDs obtained by stimulating the right or left side of the body, in either controls or patients. As there were no left versus right differences in either group, the results are presented as the mean for both sides (Fig. 1). Results for both the ascending and descending series were significantly different in patients compared with controls (Fig. 1). Accordingly, the arithmetic mean of both values (mean threshold) is used for subsequent data presentation.
The recovery cycle of SNAPs was characterized by an initial phase of inhibition (refractory period) followed by a transient period of increased excitability (supranormal period) with interstimulus intervals between 5 ms and 10 ms; a second phase of relative inhibition was present with intervals between 20 ms and 50 ms (Fig. 2A).
Fig. 2. Recovery curves for nerve (A) and cortical (B) evoked potentials following paired median nerve electrical stimulation in the wrist in 15 patients with PD and 15 age-matched controls. No significant differences in either response was found between normal subjects (•) and parkinsonian patients (□).
A greater variability in the recovery curve of the primary response of the SEP was observed. Nevertheless, in most individuals the recovery cycle was characterized by inhibition (Fig. 2A) within the shorter intervals (between 20 ms and 50 ms) followed subsequently by a return to normal excitability (Fig. 2A). The time course of such curves is very similar to the ones previously described for a larger normal population (Gilliatt and Willison, 1963; Shagass and Schwartz, 1964). The amplitude and latency values of SNAPs and SEPs were normal in controls and patients (raw data not shown). In patients, no significant change in SNAPs and SEPs latency and amplitude was found between 'on' and 'off' periods.

Somaesthetic, auditory and visual TDT

The values obtained for somaesthetic, auditory and visual discrimination mean thresholds in 44 patients are shown in Table 1. The mean thresholds for somaesthetic, auditory and visual temporal discrimination were significantly higher for the patients compared with controls (Table 1). The difference between both groups was most marked for STDT. The values of TDTs for PD patients classified as mild, moderate or severe were also significantly different. Thus, for all modalities patients with more severe disease had higher TDTs (Table 1).

Motor tests and TDT

Mean reaction and movement times were respectively 288 ± 80.2 ms and 333.4 ± 45.6 ms in the 44 patients and 108 ± 16.4 ms and 102.5 ± 20.5 ms in the 20 control subjects (P < 0.01). The mean number of index-finger taps in 30 s was 53.3 ± 15.9 in patients and 83 ± 7.2 in controls (P < 0.01). A significant correlation between motor indices and TDT values was obtained in most instances (Table 2).

In the 11 patients in whom TD was evaluated before and after administration of 250/25 mg of levodopa/carbidopa, reaction and movement time were reduced, tapping frequency was increased (Table 3) and all TDT modalities, somaesthetic (P < 0.001), auditory (P < 0.001) and visual (P < 0.001) were significantly reduced (Fig. 3A, B, C) coinciding with the peak drug effect (around 90 min). The recovery curves of cortical and peripheral responses showed a similar pattern of 'on' and 'off' despite a reduction of STDT in the ‘on’ period (Fig. 3D).

### Table 1. Mean Temporal Discrimination Thresholds (ms) of Control Subjects and Patients With Parkinson's Disease Divided by Disease Severity and Disability (see Procedures)

<table>
<thead>
<tr>
<th>Temporal discrimination</th>
<th>Somaesthetic</th>
<th>Auditory</th>
<th>Visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 20)</td>
<td>33.9 ± 12</td>
<td>18.1 ± 7.2</td>
<td>68.7 ± 5.1</td>
</tr>
<tr>
<td>Parkinson's disease (n = 44)</td>
<td>104.1 ± 22</td>
<td>32.7 ± 8.8</td>
<td>85.6 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Degree of disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (n = 15)</td>
<td>89.8 ± 22.7</td>
<td>28.8 ± 7.4</td>
<td>81.6 ± 9.4</td>
</tr>
<tr>
<td>Moderate (n = 22)</td>
<td>104.0 ± 17.4</td>
<td>31.4 ± 9.1</td>
<td>83.3 ± 6.7</td>
</tr>
<tr>
<td>Severe (n = 7)</td>
<td>134.4 ± 24.7</td>
<td>38.0 ± 11.1</td>
<td>92.0 ± 10.6</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>
TABLE 2. SPEARMAN’S CORRELATION COEFFICIENT BETWEEN TEMPORAL DISCRIMINATION THRESHOLDS (TDT) AND RATING SCALE AND MOTOR INDICES IN 44 PATIENTS WITH PD

<table>
<thead>
<tr>
<th></th>
<th>Somaesthetic TDT</th>
<th>Auditory TDT</th>
<th>Visual TDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCH</td>
<td>0.29*</td>
<td>0.20</td>
<td>0.25*</td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>0.47**</td>
<td>0.38**</td>
<td>0.20</td>
</tr>
<tr>
<td>Movement time</td>
<td>0.61**</td>
<td>0.42**</td>
<td>0.32*</td>
</tr>
<tr>
<td>Index finger tapping</td>
<td>-0.33**</td>
<td>-0.24</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

TABLE 3. MODIFICATION OF MOTOR TESTS AFTER ORAL DOSE OF LEVODOPA-CARBIDOPA (250/25 mg)

<table>
<thead>
<tr>
<th>Case</th>
<th>Tapping*</th>
<th>Reaction time (ms)</th>
<th>Movement time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off</td>
<td>On</td>
<td>Off</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>96</td>
<td>328</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>60</td>
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<td>3</td>
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<td>78</td>
<td>350</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>77</td>
<td>274</td>
</tr>
</tbody>
</table>

i = 6.85  4.80  13.17  
P < 0.001  0.001  0.001

*Number of finger taps in 30 s.

DISCUSSION

The method used in this study is considered to be one of the most direct for exploration of sensory thresholds and allows repeated presentation of the stimuli (Engen, 1972). As temporal discrimination was the variable of interest, and to avoid confounding by other stimulus-related factors, the pairs of stimuli were identical with regard to other characteristics such as quality, intensity and duration. To overcome individual differences in sensory threshold, suprathreshold stimuli were used but none of the stimuli were disturbing or painful. The results obtained in the normal control group are comparable with previous studies using a similar technique (Uttal, 1959; Green et al., 1961; Green, 1984).

The main finding of this study is the impairment of temporal discrimination in three different sensory modalities in patients with PD. This deficit increased with disease severity and was partially ameliorated by administration of levodopa. The abnormality in temporal discrimination in PD reported here could be related to other clinical aspects such as age of the patients and presence of cognitive impairment, or arise from dysfunction of sensory receptors or pathways. However, significant differences in thresholds were
FIG. 3. Modification of somaesthetic (A), auditory (B) and visual (C) TDT from 'off' to 'on' in 11 patients with PD. The horizontal interrupted lines indicate the mean normal values for each modality. D, no change in the cortical SEP recovery curve occurred in either motor state.
obtained despite the fact that patients and normals were matched for age. Cognitive impairment is unlikely to have played a crucial role in the deficit of TD as one of the main selection criteria was integrity of intellectual function. Several studies have reported delayed visual evoked potentials (VEPs) (Bodis-Wollner and Yahr, 1978; Yaar, 1990) in PD. This abnormality was considered to arise as a consequence of dopaminergic deficiency in the retina (Bodis-Wollner and Yahr, 1978). However, the delay of VEPs in PD can hardly explain the impairment of visual temporal discrimination described here, which would necessitate an interference between the perception of the first stimulus and the second of each pair, not just a delay in the arrival of each of the two stimuli to the visual cortex. Furthermore, we found that abnormal STDT occurs in PD despite the presence of normal SNAPs and SEPs recovery curves following double stimulation. We believe therefore that impairment of TD in the somaesthetic, auditory and visual modalities is unlikely to be related to any abnormality along these sensory pathways.

The anatomical basis of abnormal TDTs in PD is not entirely clear. The findings that TDT increased with the severity of PD suggest that abnormal TD is linked to the disease process. Following administration of levodopa, TDT decreased significantly, although it did not attain normal values. This can be taken as an indication that the dopaminergic system may not be solely involved in the findings described here, but dose-response curves were not performed. It might therefore be considered that the failure to achieve normal TDT values after a single levodopa dose may merely reflect incomplete dopaminergic stimulation. Theoretically, faulty dopaminergic function in PD could disturb TD by directly impairing intrinsic cortical mechanism involved in the perception and temporal distinction of paired stimuli by changing strio-pallidal output to the cortex, or both. Experimental data suggest that the dopaminergic mesolimbic system is involved in the maintenance of attention (Piazza et al., 1988). Patients with PD have a deficit in attention, particularly during 'off' episodes (Gotham et al., 1980). We checked for defective attention during the tests by randomly introducing stimuli with zero time interval, and Katzman’s test did not reveal any major modification between ‘on’ and ‘off’. Taylor et al. (1986) demonstrated that recent visual memory is normal in patients with PD, which implies a normal attention span. The characteristics of the TD tests applied in this study required a simple decision between two fixed possibilities, making the participation of a memory retrieval deficit unlikely in our patients. Thus, it seems unlikely that a general and gross defect of attention could be the main explanation for our findings.

Somaesthetic TDT values similar to those of our patients with PD were found by Lacruz et al. (1992) in patients with focal striatal or thalamic lesions without disruption of somaesthetic pathways or cortical damage. In intact monkeys, extracellular recording shows that few pallidal neurons respond to afferent stimuli. In fact, Miller and De Long (1988) and Filion et al. (1988) have demonstrated that normally internal globus pallidus (GPm) neurons discharge almost exclusively in response to passive limb movements. Such selectivity is lost following blockade of the dopaminergic pathway by reserpine (p.o.) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (i.v.) administration, leading to an increased number of GPm neurons responding to a variety of somaesthetic stimuli (Filion et al., 1988; Miller and De Long, 1988). In addition, the magnitude and duration of the response is also greater (Miller and De Long, 1988). It may be deduced from such data that in PD, striato-pallidal responsiveness to peripheral stimuli is increased
in magnitude and reduced in specificity. In other words, the ‘noise’ level provoked by sensory afferents is augmented, and this could increase TDTs. Indeed, the striato-pallidal complex has been attributed with a ‘filtering’ function, capable of focusing attention on one single event whilst suppressing all other non-relevant stimuli (Hassler, 1978). A more attractive and complementary explanation is that increased pallidal inhibitory output to the thalamus, as it occurs in parkinsonian monkeys (Mitchell et al., 1989), provokes a reduction in the rhythmic neuronal firing of thalamo-cortical circuits acting as internal pacemakers. The existence of pacemakers or internal clocks in the CNS is well documented for many circadian functions, and presumably may also exist for time perception (Moore-Ede et al., 1982). In order to differentiate as separate in time two successive stimuli, the subject must have an internal representation of time which serves as reference for events occurring in the external world. Parkinsonian patients require a longer time interval to discriminate between paired stimuli and also show an abnormal performance in many tasks which depend upon appropriate internal time estimation or rhythm generation (i.e. reaction time, sequential and alternating movements, blinking, arm swinging). We believe, therefore, that abnormal TDTs indicate that the ‘internal clocks’ run slowly in PD. We found a significant although not very striking correlation between TDT and motor performance. This suggests that the proposed disorder of timing mechanisms in PD might take part in the pathophysiology of bradykinesia. Patients with PD are as good as normal control subjects in modulating the amplitude and duration of the first agonist burst during a ballistic movement according to the distance and the background, but movement speed remains abnormally slow. Berardelli et al. (1986) suggested that such findings may be explained as a defect in motor cortex activation due to a perceptual failure to select the muscle commands to match external force/speed requirements. Abnormal timing could be added to the abnormalities involved in slowness of movement in PD (Marsden, 1982).

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REFERENCES


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