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SEQUENCE LEARNING AND MULTI-STEP ACTIVITY IMPAIRMENT IN PARKINSON'S DISEASE

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SUMMARY

Background: Apraxia is rarely diagnosed in movement disorders. However, basal ganglia dysfunction may also lead to praxic disturbances. Our study aimed at showing selective motor sequence learning and multiple-step activity impairment in idiopathic Parkinson's disease (IPD) in the absence of other praxic disturbances. The study methodology was based on Luria's classification of apraxia.

Material/ Methods: Motor sequence learning, one-step vs. multiple-step activity, was assessed in 29 patients with IPD and 25 healthy controls against a background of global cognitive status (Mini-Mental State Examination), mood (Beck Depression Inventory), bradykinesia (Finger Tapping Test), motor impairment and disease severity (Unified Parkinson's Disease Rating Scale, Hoehn-Yahr staging) and other praxic dimensions according to Luria's classification (clinical trials assessing spatial, afferent, and frontal apraxia).

Results: The patients exhibited selective impairment on multiple-step tasks and second motor sequence learning. First motor sequence learning, limb-kinetic praxis and one-step activities did not differentiate between the groups. Therefore, the deficit cannot be attributed to bradykinesia or other purely motor deficit. Selective impairment on multiple-step tasks and second-sequence learning may be due to deficient procedural memory. Sequence learning impairment is related to disease severity in IPD.

Conclusions: Motor sequence learning and multiple-step activity impairment can be selectively impaired in IPD. The profile of praxic disturbances in IPD is consistent with the cognitive dysfunction observed in this disorder, namely procedural memory deficits.

Key words: movement disorders, apraxia, cognitive, motor, bradykinesia, basal ganglia

INTRODUCTION

Idiopathic Parkinson's disease (IPD) is a neurodegenerative disorder stemming from deficient dopaminergic transmission within the basal ganglia. IPD is diagnosed on the basis of motor symptoms, such as bradykinesia, rigidity and posture abnormalities. Major non-motor symptoms of IPD include cognitive impairment, psychiatric symptoms (e.g. apathy and depression; Friedman, 2005). The profile of cognitive dysfunction in IPD is characterized mainly by executive dysfunction, along with working and procedural memory impairment, with relative preservation of language function, even in the case of Parkinson's Disease Dementia-(PDD; Emre et al., 2007).

Apraxia, as a disorder of complex higher motor behaviour, cannot be attributed to primary motor and/or sensory deficits but represents the dysfunction of the cognitive component of motor behaviour. Recently, the relationship between apraxia and Parkinson's Disease and multiple system atrophy has been noticed (Zadikoff & Lang, 2005).

The presence of apraxia in IPD is still questioned by some clinicians. Apraxia testing is not routinely used in IPD diagnosis. Its assessment in IPD is difficult, as motor dysfunction itself may mask some of the praxic disturbances, especially for the inexperienced clinician. Nevertheless, in a methodologically well-designed study, Leiguarda et al. (1997) noted signs of bilateral ideomotor apraxia for transitive movements in about 27% patients with IPD. It was shown that the apraxic disturbance is related to executive dysfunction, which highlights a possible frontal lobe implication in generating praxic disturbances in IPD (Goldenberg et al., 1986). The cortical and particularly frontal origin of praxic dysfunction seems also probable because patients with lesions confined only to the basal ganglia are very unlikely to develop apraxia (Pramstaller & Marsden, 1996; Pąchalska 2008).

To our knowledge, most previous studies on praxis disturbance in IPD, such as those of Leiguarda et al. (1997), were based on Liepmann's system of classification, reconstructed into a new theoretical framework by Heilman (1985), and operationalized by Rothi and Heilman (1997). However, one of the latest studies also referred to Luria's classification of apraxia (Uluduz et al., 2010).

In our study, we aimed at showing the selective deficit of motor sequence learning and multiple-step activity execution in the absence of other praxic deficits in IPD according to Luria's classification of apraxia with reference to three factors implicated in gesture execution: visuospatial, kinaesthetic and sequential (Luria, 1966). Although this classification is less common than Liepmann's, it provides valuable insight into different aspects of motor actions. The kinesthetic factor dysfunction leads to afferent/kinesthetic apraxia, which may affect limbs (precise hand and finger movements) and / or mouth (the equivalent of orofacial/ buccofacial apraxia). Kinesthetic apraxia is caused by post-central lesions (Brodmann areas 1, 2 and partially 40), most often localized in the left hemisphere. The patient with kinesthetic apraxia cannot control precise movements despite preserved spatial organization of gestures (similar disturbances were described by

Foerster and Liepmann). Disturbance of proprioceptive feedback can be partially compensated by means of visual control.

The spatial disturbance causes spatial and/or constructional apraxia. Spatial apraxia is caused by (usually) left parieto-occipital lesions affecting the boundary between areas 19 and 39. In spatial apraxia, visuospatial feedback is disturbed. Spatial apraxia may appear even if visual function is preserved. However, most often it is accompanied by a visuospatial deficit, known as the apractognosis syndrome. Visual control of movement cannot improve performance.

Dynamic apraxia results from inferior premotor cortex damage (areas 6,8) and derives from disorganization of "kinetic melodies," the temporal organization of movement. Learning new motor sequences is impaired. Performance is very often disturbed by perseveration of single elements.

Regulatory or prefrontal apraxia stems from prefrontal lesions (mainly in the left hemisphere) and consists in a difficulty in performing purposeful actions and an inability to use inner speech to monitor one's own behavior (the regulatory function of speech). The patient may demonstrate echopraxia and/or perseverate entire motor programs. Regulatory praxis is closely linked to executive function, especially cognitive control.

Disturbance of spatial and kinesthetic factors represents simultaneous synthesis disorder: an inability to consider all the (spatial) relations between objects simultaneously. Dynamic and regulatory praxis disturbance is caused by impaired sequential synthesis, which is indispensable when a given goal-directed activity is organized in time. Simultaneous synthesis is performed by post-central brain areas, whereas sequential synthesis is dependent on pre-central areas. We hypothesized that the IPD group would show impaired performance only in a second sequence learning task, as it requires procedural set-shifting. Selective impairment of the second sequence learning task and multiple-step task execution would indicate a deficient sequential component of praxis, according to Luria's classification.

MATERIAL AND METHODS

Consecutive patients were recruited from an outpatient movement disorders clinic. Parkinson's Disease was diagnosed according to the United Kingdom Parkinson's Disease Brain Bank Criteria (Hughes et al., 1992). Only those with MMSE≥20 (Folstein et al., 1975) were included in the study, so as to assure comprehension of the instructions.

Twenty-nine right-handed outpatients with IPD and 25 healthy controls (24 right-handed and 1 left-handed), matched for age [$t = 0.569$; $P = 0.572$; n.s.] and education [$t = -0.740$; $P = 0.463$; n.s.], participated in our study.

The mean age of the patients was 66.72 ± 9.02 years (range: 52-82) and the mean duration of education was 11.72 ± 3.35 years (range: 5-17), while the control group averaged 68.52 ± 13.37 years of age (range: 48-92) and 11.08 ± 2.99 years of education (range: 2-15). Both groups were similar in terms of general

cognitive status, but there was a statistically nonsignificant trend towards lower cognitive functioning in the patient group. The Mini Mental State Examination scores were as follows: PD group - 27.41 ± 2.75 (range: 20-30); control group - 28.76 ± 2.17 (range: 20-30); $t = 1.977$; $P = 0.053$; n.s. The PD patients had higher depression scores in the Beck Depression Inventory (BDI) – 16.11 ± 8.41 (range: 3-30) than the control group – 6.57 ± 7.92 (range: 0-37), $t = -4.24$; $P < 0.001$. Among the PD patients there were 8 with predominant tremor, 6 in whom rigidity and akinesia were the most pronounced symptoms, and 15 with mixed symptoms. The patients averaged 8.60 ± 4.05 years from disease onset (range: 2-21). The patient's average age at the disease onset was 57.96 ± 9.21 (range: 43-74). The average stage of PD according to Hoehn-Yahr was 2.70 ± 0.55 (range:2-4) and the mean daily L-dopa dose was 732.14 ±331.16 mg (range: 300-1500). On the UPDRS Part II, the patients scored on average 13.46 ±5.27 (range:6-27), UPDRS part III: 16.71 ±9.21 (range:4-42) and UPDRS part IV: 4.93 ±2.72 (range:1-12). All the participants volunteered to take part in the study.

The neurological examination, including specific IPD scales, was performed by a clinician experienced in movement disorders (JS). The assessment consisted of the Hoehn and Yahr staging (Hoehn & Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS) – parts II-IV (Fahn & Elton, 1987).

The neuropsychological assessment consisted of:

- a global cognitive status examination using the Mini Mental State Examination (MMSE);
- a mood assessment by means of the Beck Depression Inventory (BDI) (Beck, 1978);
- a motor speed examination using the Finger Tapping Test (FTT) (Reitan, Wolfson, 1993);
- two sequence-learning trials (assessing efferent motor praxis according to Luria's praxis classification);
- one step and multi-step tasks, supplemented by a variety of control praxic trials, based on Luria's classification (Luria, 1966), which are presented in Figure 1.

In the FTT, taken from the Halstead-Reitan Neuropsychological Test Battery, the participant presses a button as rapidly as possible for 10 seconds (Reitan & Wolfson, 1993). There are 5 trials for each hand, with 30 seconds intervals between trials and one 60 second interval following the third trial. The average scores for right and left hand were used in the analysis.

Sequence learning (premotor/ efferent motor praxis) was tested with Luria's hand-position sequencing task. In the sequential hand movement tasks, the patient was shown the sequence by the examiner, then performed it with the examiner and at the end was asked to continue on his/her own. Each part consisted of 5 trials. The participant's performance was scored 0 if the three-step sequence was correct or 1 if it was incomplete or the order was mixed.

Four one-step and four multiple tasks were used, for which the time needed to perform the action was computed (measured in seconds). One-step tasks included putting on a glove, putting on a cap, fastening one button on a piece of

cloth, and inserting a plug into a socket. Multi-step tasks consisted of making a knot, preparing a letter to post, locking and unlocking a padlock, fastening a belt.

Spatial praxis was tested with five trials in which the patient imitated meaningless arm gestures performed by the examiner. For each of the trials the subject could score from 0 to 2 points, where correct performance was scored 0, difficulties in task execution or insufficient accuracy – 1, inability to perform an action – 2. Confounding left / right side was not scored as a mistake.

Kinesthetic praxis was tested in two dimensions. Limb-kinetic praxis was tested by means of five trials in which participants imitated meaningless palm/finger gestures performed by the examiner, without seeing their own hand. Orofacial praxis was assessed with 5 imitation trials. The scoring system for both afferent praxis tasks was the same as for spatial praxis.

Frontal praxis was tested by two tasks testing the regulatory function of speech. In the first trial the patient was asked to perform palmar flexion when the examiner performed dorsal flexion and vice versa. In the second task the patient was asked to tap a pencil on the table once when the examiner did it twice, and when the examiner tapped twice, the patient was asked to tap only once. The patient had to repeat the instructions carefully before the trial begun. In both tasks there were ten trials administered in random order. Faulty performance (imitating the examiner's behavior) was scored 1. The results of both trials were added.

Statistical analysis was carried out using the *t-Student* test, the *U-Mann-Whitney* test, or the χ^2 test to compare performance in both groups, depending on the data distribution. Correlations were computed using *r-Pearson* or *τ-Kendall* correlation coefficients according to the distribution of the variables.

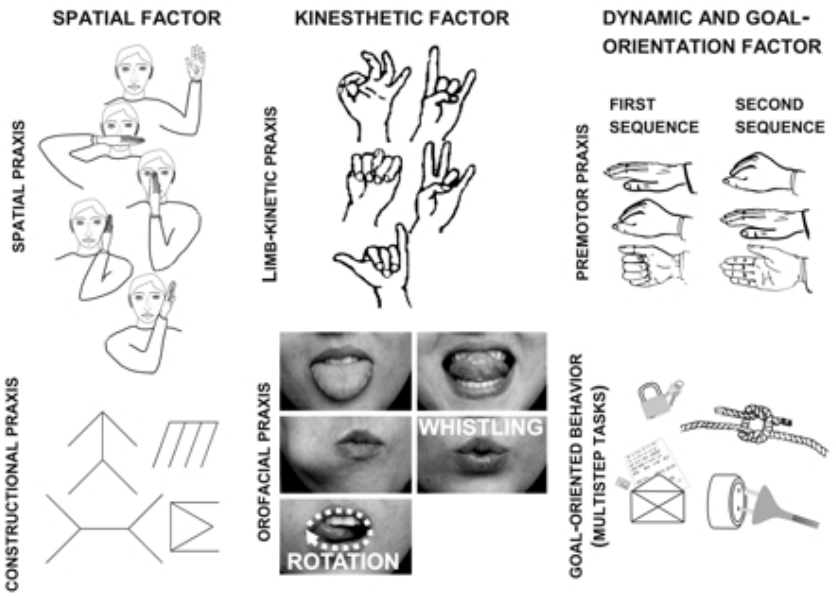

Figure 1. Methods of praxis assessment (Source: Wieczorek, Sławek & Mach, 2005)

RESULTS

The IPD patients' performance was poorer than that of the control group in second-sequence learning, multiple-step task execution and orofacial praxis. Neither spatial nor limb-kinetic praxis differentiated the IPD group from the controls. The results of intergroup comparisons are presented in Table 1.

Table 1. Results of intergroup comparisons

Variable	IPD patients mean (±SD)	Control group mean (±SD)	Inter-group differences
Bradykinesia			
tapping - right hand	31.83 (±10.91)	47.62 (±7.7)	t = 6.81; p <0.001
tapping – left hand	29.11 (±9.10)	44.90 (±7.21)	t =7.305; p <0.001
Sequence learning			
1st sequence	1.03 (±1.43)	0.92 (±1.44)	U = 347; z = -0.29683; p =0.77;n.s.
2nd sequence	3.17 (±3.30)	0.96 (±1.34)	U = 213.5; z = -2.67913; p =0.01
one-step tasks (in sec.)	31.83 (±16.08)	27.96 (±11.29)	t =-1.718; p =0.092; n.s.
multi-step tasks (in sec.)	119.72(±41.84)	87.20 (±13.80)	t =3.672; p =0.001
Spatial praxis	0.55 (±1.12)	0.2 (±0.41)	U =335; z= -0.656; p =0.511; n.s.
Bradykinesia			
limb-kinetic praxis	1.83 (±2.51)	0.92 (±1.61)	U=290.5; z=-1.375; p =0.169;n.s.
orofacial praxis	0.2 (±1.06)	0.04 (±0.2)	U = 287.000; z = -2.120; p < 0.034
Frontal praxis			
regulatory function of speech	0.17 (±0.76)	0.12 (±0.33)	U=345.500; z=-0.587; p=0.557; n.s.

Correlation of praxis results was measured with all clinical scales and L-dopa dose in the IPD group. MMSE performance correlated with multiple-step task execution (r=-0.469; p<0.05), one-step task execution (r=-0.371; p<0.05) and limb-kinetic praxis (r=-0.602; p<0.05). First-sequence learning was the only aspect of praxis that correlated with UPDRS global score (r=0.324; p<0.05) and UPDRS-III (r=0.327; p<0.05). The time to perform one-step actions [τ = 0.611; P = 0.00005] and multiple-step actions [τ = 0.492; P = 0.001] was related to the Hoehn-Yahr stage of the disease. Moreover, the second-sequence learning task correlated significantly with age at the time of testing [τ = 0.344; p = 0.01], age at disease onset [τ = e Hoehn and Yahr score [τ = 0.433; p =0.01], and the daily L-dopa dose [τ = 0.365; p =0.01]. None of the measures correlated with FTT scores. Oral praxis correlated with items 18 (speech: τ = 0.388; p=0.026) and 19 (facial expression: τ = 0.496, p=0.004) from the UPDRS motor examination.

DISCUSSION

Praxis impairment is not a novel finding in PD (Zadikoff & Lang, 2005; Leiguarda, 1997). Recent research on apraxia in PD and multiple system atrophy (Uluduz et al., 2010) has confirmed that apraxia might be a feature of both MSA and PD. In PD a specific impairment that cannot be explained by bradykinesia was noticed in the execution of sequential tasks. This last finding is in accordance with our results.

The results from our study show selective impairment of motor sequence learning and the execution of multiple-step activity in IPD, which cannot be explained by motor impairment itself. Firstly, no relationships were observed between motor impairment (the UPDRS III Motor Examination score) and those praxis results that differentiated between groups, as in previous studies (Uluduz et al., 2010). Similarly, none of the apraxia scores correlated with tapping, which is a measure of motor speed. In accordance with data from the literature, praxis disturbance was linked to global cognitive status rather than motor impairment. One shortcoming of our study was that MMSE was the only cognitive measure, which did not enable further insight into the cognitive deficits possibly underlying apraxia in IPD.

The impairment observed in the second motor sequence learning trial indicates that motor impairment cannot account for the deficits observed. If motor requirements were too high for the patients in the motor sequence learning task, they would have shown deficits in both sequence learning tasks, which was not the case. The second trial is similar in terms of motor demands, but requires procedural set-shifting. The learning of the second task was probably impaired due to proactive interference by the first learned sequence. These results are consistent with a specific sequencing deficit in IPD (Helmuth, Mayr & Daum, 2000) and the demonstrated relationship between apraxia severity and mental set-shifting impairment in PD (Goldenberg et al., 1986).

The comparison of one-step vs. multi-step task performance supports the above mentioned conclusion that praxis function and motor impairment are independent factors. If the slowing observed in the multi-step task was caused by

motor slowing, it would have correlated with tapping rather than MMSE. If motor slowing could account for the prolonged time of task execution, intergroup differences would also have been demonstrated in one-step tasks. Multi-step actions differentiated between the groups better than one-step tasks, possibly because of the sequential nature of the former. It seems that the results show planning and sequencing difficulty rather than motor slowing. As shown by Uluduz et al. (2010), performance on multi-step activities in PD may be not only slowed, but also poorly organized.

Leiguarda et al. (1997) provided further arguments to this discussion on the independence of praxis and bradykinesia, since in their study the apraxia scores did not differ in "off" and "on" states. This indicates that dopamine level decline induces the cardinal motor symptoms of PD, but not praxis deficits.

The oral praxis disturbance seems to be linked to motor dysfunction, since it correlated with motor examination results. Oral praxis trials are sensitive to hypomimia, the discrepancy between intention and range of movement. We suggest that in IPD impaired orofacial praxis should not be interpreted as a kinesthetic afferentation deficit in planning and adjusting movement parameters, since it may reflect efferent rather than afferent disturbance.

The results of our study indicate that some aspects of motor disability in IPD may be caused not only by the motor symptoms typical of PD, such as tremor and bradykinesia, but also by cognitive deficits, such as procedural learning problems and impairments in sequencing and set-shifting. It has previously been demonstrated that motor sequencing is related to executive function (Fama & Sullivan, 2002) and praxic performance is associated with visuospatial ability (Villardita et al., 1982). Therefore, praxic disturbance in PD should be analyzed in reference to cognitive impairment.

Procedural learning is crucial in daily life (e.g. driving a car, learning how to use a new mobile phone). Motor sequence learning, as a sensitive measure of procedural learning, can be easily incorporated into a comprehensive neurological examination. Further studies could shed light upon the usefulness of motor sequence learning trials in predicting procedural memory problems in daily life. e.g. driving problems.

CONCLUSIONS

Motor sequence learning and multiple-step activity impairment can be selectively impaired in IPD. Our results indicate that the profile of praxic disturbances in IPD is consistent with the cognitive dysfunction observed in this disorder, namely procedural memory deficits.

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