UNIVERSITÉ DU QUÉBEC À MONTRÉAL

IRRÉGULARITÉ MOTRICE DANS LES SYNDROMES PARKINSONIENS ATYPIQUES

MÉMOIRE PRÉSENTÉ
AU DÉPARTEMENT DE PSYCHOLOGIE
EN VUE DE L'OBTENTION
DU GRADE DE MAÎTRE ÈS SCIENCES (M.Sc.)

PAR
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MARS 2011

RÉSUMÉ

Le parkinsonisme est associé à des problèmes de mouvements volontaires importants. Dans des tâches de pointage, les personnes souffrant de la maladie de Parkinson montrent des trajectoires de mouvement fragmentées, avec des variations anormales de vélocité et d'accélération. Les syndromes parkinsoniens atypiques sont associés à des atteintes neuropathologiques distinctes de la maladie de Parkinson, mais sont difficiles à distinguer cliniquement de la maladie de Parkinson en début d'évolution. Nous avons examiné si des sujets atteints de la maladie de Parkinson et de syndromes parkinsoniens atypiques sont affectés différemment, comparés à des sujets contrôles, dans l'exécution de mouvements rapides sans feedback visuel effectués sur une tablette graphique. L'analyse des tracés de mouvement à l'aide d'un programme de reconnaissance d'événements irréguliers apparaissant dans la dérivée de l'accélération montre que le groupe de patients atypiques présente des temps de mouvement plus longs, des vitesses maximales plus basses et un nombre significativement plus élevé d'irrégularités par tracé que le groupe de sujets atteints de la maladie de Parkinson et que le groupe contrôle. Aucune différence significative n'est observée entre ces deux derniers groupes. Ces résultats montrent qu'il est possible, sur la base d'une mesure d'irrégularité du mouvement, de distinguer les syndromes parkinsoniens atypiques de la maladie de Parkinson.

TABLE DES MATIÈRES

INTRODUCTION

La maladie de Parkinson (MP) est une affection neurodégénérative qui se manifeste principalement par des troubles du mouvement dont la rigidité, le ralentissement, les troubles d'équilibre et le tremblement au repos (Bergman & Deuschl, 2002). Les syndromes parkinsoniens atypiques comme la paralysie supranucléaire progressive, l'atrophie multisystémique, la dégénérescence striatonigrique et la dégénérescence corticobasale sont des neuropathologies également associées à des problèmes de mouvements volontaires (Defebvre et al., 1999; Muratori, Reilmann, & Gordon, 2003). Les patients atteints de syndromes parkinsoniens atypiques présentent des atteintes neuropathologiques distinctes de la MP. Ces syndromes sont caractérisés par des atteintes striatales et pallidales importantes, alors que la MP est associée à une dégénérescence mésencéphalique. Les patients atteints de syndromes parkinsoniens atypiques ont peu ou pas de réponse au traitement à la levodopa, ce qui suggère qu'ils affectent les systèmes striataux par des voies autres que la déplétion dopaminergique de la substantia nigra typique de la MP en début d'évolution. Les déficits de motricité volontaire associés aux syndromes atypiques ont peu été documentés.

La présente étude visait à étudier les mouvements volontaires dans les syndromes parkinsoniens atypiques en examinant l'irrégularité motrice de mouvements de pointage balistique. L'irrégularité motrice est souvent opérationnalisée par des déviations observées dans le profil d'accélération du mouvement. Plusieurs études rapportent des troubles moteurs dans les mouvements précis ou complexes chez les patients atteints de la MP (Poizner et al.,

1998; Rand, Stelmach, & Bloedel, 2000). Les patients atteints de la MP présentent plusieurs irrégularités sur les tracés de vitesse et d'accélération du mouvement (Isenberg & Conrad, 1994; Poizner et al., 1998). Dans des mouvements balistiques, ces patients montrent un patron myoélectrique qui diffère de celui à trois phases observé chez des sujets sains (Hallett & Khoshbin, 1980). Ces irrégularités motrices sont généralement associées au dysfonctionnement des circuits striatocorticaux responsables du contrôle volontaire du mouvement (Albin, Young, & Penney, 1989; Alexander, Crutcher, & DeLong, 1990; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Hallett, 1993). Toutefois, dans des tâches de pointage simple sans rétroaction visuelle, les patients atteints de la MP (en stade OFF) montrent des trajectoires similaires à des sujets contrôles (Ghilardi et al., 2000). Peu d'études se sont penchées sur l'irrégularité motrice associée aux syndromes parkinsoniens atypiques. Une étude EEG rapporte des troubles de programmation motrice plus importants chez les patients atteints de paralysie supranucléaire progressive (PSP) que chez les parkinsoniens idiopathiques dans l'exécution de mouvements simples (Defebvre et al., 1999). Des troubles de coordination motrice et un ralentissement moteur plus sévère que dans la MP sont observés chez les patients atteints d'atrophie multisystémique (MSA) (Muratori et al., 2003; Testa et al., 1993). Étant donné les atteintes striatales, cérébelleuses et mésencéphaliques associées aux syndromes parkinsoniens atypiques, nous postulons que les patients atteints de ces syndromes pourraient montrer une irrégularité même dans les mouvements simples sans rétroaction visuelle.

Nous avons examiné l'irrégularité du mouvement chez les sujets atteints de MP (N=11) ou de syndromes parkinsoniens atypiques (N=11) et les avons comparés à des sujets sains du même âge. Les participants exécutaient des mouvements rapides d'extension du bras sur une tablette graphique sans rétroaction visuelle. L'absence de rétroaction visuelle empêche les sujets d'apporter des corrections à leur mouvement en cours d'exécution. Effectué en boucle fermée (*close-loop*), ce type de mouvement est beaucoup plus facile à réaliser qu'un mouvement nécessitant des corrections basées sur la rétroaction visuelle (*open-loop*). Les tracés étaient ensuite analysés à l'aide d'un programme de reconnaissance d'événements irréguliers apparaissant dans la dérivée de l'accélération (jerk) (Fimbel, Dubarry, Philibert, & Beuter, 2003).

MOVEMENT IRREGULARITIES IN ATYPICAL PARKINSONIAN SYNDROMES

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Abstract

This study measures the frequency of discrete motor irregularities in ballistic aiming movements in atypical parkinsonian syndromes (APS) compared to control and to idiopathic Parkinson's disease (PD) patients on standard medication. Eleven APS patients were compared to 11 controls and 11 PD patients on ballistic arm extension movements performed on a digitizing tablet without visual feedback and without accuracy constraint. Atypical patients showed a higher number of irregularities in the acceleration and jerk time series compared to PD patients and controls. No difference was found between control and PD groups. These discrete events were not associated with general motor impairment, tremor, akinesia, or rigidity. These results suggest that atypical parkinsonism is associated with discrete movement irregularities in ballistic movements.

Key words: movement disorders, basal ganglia, movement irregularity, parkinsonism.

Introduction

The lack of smoothness of movements in parkinsonism is a robust observation. This irregularity has been reported in a variety of tasks including: rapid aiming movements [1, 2], unconstrained remembered aiming movements [3], rapid reach-and-grasp movements [4], ballistic arm movements with indirect visual cues [5], rapid elbow flexion [6] and slow arm movements [7]. This irregularity may partly be due to task demands, as accuracy constraint and visual feedback require a high level of movement control. Previous work showed that accuracy constraints increased end-movement variability in Parkinson's Disease (PD) [2]. Precision demands also increase the reliance of PD patients on visual feedback for ongoing movement corrections [1]. This excessive reliance on visual information could accentuate bradykinetic impairments seen in PD [8]. The absence of visual feedback and/or accuracy constraints may improve PD patients motor performances. For instance, in the absence of visual feedback off-medicated PD patients showed movement paths similar to control in simple reaching movements [9]. Also, PD patients could normally regulate their movement speed when no target constraint was imposed [10].

Since atypical parkinsonian syndromes (APS) often produce early cortical or subcortical damage not present in early PD [11] these disorders may affect motor control differently. Imaging and neuropathological studies have reported brainstem and midbrain atrophy in progressive supranuclear palsy (PSP) [12-14], pontine and cerebellar atrophy in multiple system atrophy (MSA) [13, 14], and putaminal, pallidal and parietal atrophy in corticobasal degeneration (CBD) [15, 16]. These distinct patterns of atrophy affecting different components of the motor striato-thalamo-cortical loops could be associated with the motor impairment seen in APS. Deficits in sequencing movement phases have already been

reported in multiple system atrophy (MSA) patients [17]. Compared to idiopathic PD patients, MSA patients presented longer movements times in motor assesment tests [18]. An EEG study comparing clinically similar progressive supranuclear palsy (PSP) and PD groups on wrist flexion showed reduced primary sensorimotor cortical activation during movement preparation in the PSP group, suggesting a more severe motor programming impairment in PSP than PD [19]. However, there have been few researches of movement irregularity in parkinsonian syndromes.

The present study assesses movement irregularity in APS. We examined movements in which early PD patients present minimal deficits: short ballistic forearm movements with no specific target and no visual feedback [9, 20, 21]. Except for bradykinesia, no significant performance deficits have been reported for early PD patients in such movements. Whether movement irregularities are present in APS remains an open question. With the present study we wished to further characterize motor control in APS through the detection of discrete irregularities in ballistic aiming movements.

Methods

Participants

Participants included 11 patients diagnosed with APS (3 males), aged between 55 and 86 years (mean 68.6, SD 8.4). Atypical patients included 5 patients with PSP, 4 patients with MSA and 2 patients with corticobasal degeneration (CBD). The diagnosis of APS was made clinically by a movement disorders specialist on the basis of early distinctive neurological features including ophthalmoparesis, prominent axial manifestations, apraxia, cortical sensory loss, rapid progression, dopa-resistance or waning response to medication. The performance of APS patients was compared to that of 11 control subjects (6 males) aged between 46 and 80 years (mean 62.3, SD 10.0) with no history of neurological problems, and no observable motor deficits including essential tremor, and to 11 patients diagnosed with idiopathic PD (8 males), aged between 56 and 77 (mean 63.6, SD 5.6). All patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) [22]. APS and PD groups were clinically matched on the basis of the UPDRS motor score (section III). All patients were on standard optimized medication. Prior informed consent was obtained from all subjects. All subjects were right-handed and used their right hand to perform the task.

Task

Subjects executed rapid externally-triggered arm movements without visual feedback and with low precision requirements. Subjects were instructed to draw a diagonal line as fast as possible on a digitizing tablet (Wacom A4, X-Y spatial precision 0.025 mm, sampling frequency 100Hz.) after a signal. The corresponding forearm extension movement had average amplitude of 23 cm (angular variation of 30±5°). The elbow rested on the desk and remained partly flexed at the end of the movement. When overshooting occurred, the subject was instructed to reduce movement amplitude but undershooting was left uncorrected. In each trial a visual start signal, consisting of two flashing LED lights accompanied by a sound (800Hz, approximately 80 db), was emitted by a device placed in front of the subject after a random delay. Subjects maintained their gaze on the device and their arm was hidden from view. These conditions were chosen to avoid visual feedback and movement anticipation. A practice session was used to train the subjects to remain within the pad without visual feedback. After the initial training, subjects performed movements until approximately 30 correct movements (non anticipated start, end of movement in the limits of the pad) had been recorded. The digitizing pad was connected to a PC on which the investigator could monitor the movements in real time.

Data analysis

Linear displacement was determined from the X-Y positions of the stylus, and linear speed and higher order derivatives (acceleration and jerk, the derivative of acceleration) were calculated and filtered. Incomplete (i.e. final speed above 20% of the maximum speed V_{max}) and anticipated movements (i.e. 5% of V_{max} reached before the start signal) were discarded. The main speed peak was determined and the rest of the recording (threshold: 1% of V_{max}) was truncated. Computed movement parameters included reaction time (RT), movement time (MT), movement length (ML), and maximum linear speed (V_{max}). In addition, irregularities corresponding to qualitative changes in the acceleration and jerk time series (from positive to negative or vice versa) were detected by means of a qualitative pattern recognition software developed in our lab [23]. The sensitivity of the threshold used by the program was set to match the number of irregularities counted in a representative set of movement recordings by naive human judges (see [23] for details). Movement irregularity has often been quantified using total jerk [4, 24]. However, there is evidence that such global metrics may not be optimal in slow or ballistic movements [25, 26]. When velocity profiles are complex and variations in acceleration and jerk are linked to discrete motor irregularities, detection of these irregularities may give a more precise index of irregularity than global indicators of jerk. On each trial digitizing noise was removed using a trapezoidal convolution kernel filter [23]. After examining the distributions of the different measures, a logarithmic transformation was applied to the irregularity data in order to minimize skewness and statistical analyses were performed using the general linear model.

Results

Table 1 summarizes the demographic and clinical data for the APS and PD patients. Age and pre-test UPDRS motor score did not differ between patient groups. The PD group showed a slightly longer duration of illness than the APS group [$F(1,20) = 6.23$, $p = 0.02$]. Movement length (ML) was similar in the three groups. However, groups differed on maximum linear speed (V_{max}) [$F(2,30) = 5.2$, $p = 0.01$], atypical patients reaching lower V_{max} than both controls [$F(1,20) = 9.34$, $p = 0.006$] and PD patients [$F(1,20) = 6.5$, $p = 0.02$]. Groups also differed on movement time (MT) [$F(2,30) = 17.6$, $p = 0.00001$]. The atypical group showed longer MT than both control [$F(1,20) = 20.9$, $p = 0.0002$] and PD groups [$F(1,20) = 17.5$, $p = 0.0005$]. Reaction time (RT) was significantly different in the three groups [$F(2,30) = 3.8$, $p = 0.03$]. The APS patients showed RT comparable to PD patients [$F(1,20) = 3.3$, ns] but longer than controls [$F(1,20) = 4.7$, $p = 0.04$]. No significant differences were found on V_{max}, MT or RT between control and PD groups.

Figure 1 shows representative speed, acceleration and jerk profiles during individual movements in the three groups. Control subjects presented smooth bell-shaped speed profiles. Zero-crossings in the acceleration and jerk profiles reflected normal changes in velocity for such a simple ballistic task, movement length was covered by a single transport phase and no secondary corrections were needed as no target was specified. Medicated PD patients showed similar movement kinematics. However, irregularities were clearly present in the atypical group (see Figure 2). The average number of irregularities per trajectory in each group was significantly different between the three groups [$F(2,30) = 28.8$, $p < 0.0001$]. The atypical group differed from the control group ($F(1,20) = 50.37$, $p < 0.0001$) and from the PD

group ($F(1,20) = 25.6$, $p < 0.0001$). Controls and PD patients presented a similar number of irregularities ($F(1,20) = 3.8$, ns).

There was a significant correlation between the number of irregularities and age ($r = 0.38$, $p = 0.03$) in all subjects. There was no correlation between the number of irregularities and the motor score of the UPDRS ($r = 0.31$, ns) or illness duration ($r = -0.26$, ns). Tremor at rest was observed in only one APS patient and three PD patients. Also, action tremor was observed in only one APS patient and three PD patients. Moreover, the irregularities showed no predominant frequency (range 4.7-13.8 Hz, 95% confidence interval 5.2-12.2 Hz). This suggests that these results were not caused by tremor.

Predictably, PD and APS groups differed on the UPDRS gait-stability score [$F(1,17) = 10.2$, $p = 0.05$]. PD and APS groups did not significantly differ on the UPDRS rigidity score [3.6 vs 2.5, $F(1,17) = 0.6$, ns], the akinesia score [9.2 vs 11.0 $F(1,17) = 0.5$, ns] or the bradykinesia score [1.2 vs 1.4, $F(1,17) = 0.2$, ns]. No significant correlations were observed between the number of irregularities and the preceding UPDRS sub-scores except for the gait-stability score ($r = 0.53$, $p = 0.02$). When PD and APS patients were grouped on the basis of UPDRS cut-off scores (20 or less, and over 20) or on symptom duration (1-5 years, over 5 years), no significant differences were observed in the number of irregularities. Also, the number of irregularities was not linked to medication or gender.

In order to detect possible asymmetries in the time distribution of irregularities, the average time of occurrence of irregularities was determined and compared to the time of occurrence of the main speed peak for each group. No significant difference was found between the number of irregularities preceding and following the main speed peak [$F(2,30) = 0.07$, ns].

Discussion

Patients with atypical parkinsonians syndromes showed about three times more irregularities in movement trajectories than both controls and PD patients with comparable UPDRS motor scores (see Figure 2). Although APS patients were able to complete each trial in a single transport phase, their movements were fragmented and irregular. Figure 1 shows a large number of zero-crossings in the acceleration and jerk profiles of a representative APS patient. Irregularities seen in APS showed no predominant frequency, and they were not correlated with tremor, rigidity, akinesia or bradykinesia. Idiopathic PD patients with equivalent clinical motor deficits (UPDRS scores) did not show such irregularities. This suggests that irregularities seen in APS patients may not be attributed to core parkinsonian symptoms. These results cannot be attributed to medication since most patients in both groups received similar medications most often l-dopa and/or a dopamine agonist, and no medication was associated with a higher number of irregularities.

The irregularities observed cannot be described as feedback-based corrective commands since these were minimized by the absence of visual input during movement. Also, corrective commands internally generated are unlikely to contribute significantly to the irregularities observed since no constraining target was specified in the present task [30]. Moreover, irregularities did not present higher densities towards the end of the movement, as would occur with end-point corrections [1, 31]. It could be argued that the irregularities observed correspond to action myoclonus previously described in APS [32-35]. Indeed, discrete motor irregularities bear some similarities with the short-duration, small-amplitude, arrhythmic myoclonus described by Salazar et al [32]. Small amplitude myoclonus was also described in idiopathic PD [36]. Myoclonic jerks described by Salazar et al. were mainly

associated with posture and movement onset. In our study, irregularities were present throughout movement execution. Further investigations using neurophysiological measures will be necessary to clarify the origin of these discrete motor irregularities.

Atypical patients also showed longer MT and lower V_{max} than both controls and PD patients, confirming the severe bradykinesia observed in atypical parkinsonism [18]. However APS patients were as quick as PD patients in movement initiation. Performance of APS patients may have been improved by the provision of externally triggered auditory and visual cues. In contrast to APS patients, PD patients executed smooth movements in the absence of visual feedback and accuracy constraints. PD patients showed normal acceleration and jerk profiles, V_{max} and reaction time as compared to controls. These results support earlier findings showing that PD patients can achieve normal velocity profiles when tasks demands are minimal [9] and show reduced reaction time when movements were externally triggered [37, 38]. Pharmacological treatment may have normalized performance, still Ghilardi and colleagues obtained similar result with non-medicated PD patients [9].

The present results indicate that APS patients present slow and irregular ballistic movements even when tasks demands are minimal. In the same condition, control and medicated idiopathic PD patients show smooth movements. Although the UPDRS provides a valid general clinical assessment of motor functions in atypical parkinsonians syndromes, it was not sensitive to the motor irregularities that we observed in APS patients [41]. The irregularities detected were correlated with age when the three groups were considered together. This result is consistent with the well-documented effect of aging on movement control and execution [42]. However, no correlation was obtained between the number of irregularities and illness duration or severity in the patient groups, suggesting that APS

patients have a specific pathology which contributes to irregularities in simple ballistic movements. The correlation between irregularities and gait/stability can be explained by the fact that gait disorders and postural instability have frequently been observed in dopamine-resistant parkinsonians [27, 28]. These deficits are sometimes attributed to neuronal loss in brainstem structures such as the pedunculopontine nucleus (PPN) in APS patients [29].

The present data suggest that abnormalities in voluntary movements may be more closely linked to the striatopallidal damage associated with APS than to the midbrain damage typical of idiopathic PD. Current models of basal ganglia functions hypothesize a role of the basal ganglia in the integration of sensory inputs for movements guidance. Movement templates activated through different cortico-striatal loops are often hypothesized to help coordinate sensorimotor processing [43]. The integration of proprioceptive and visual information is often used to accurately guide movements. In our study the absence of accuracy constraint and the absence of reliance of visual information may have reduced the sensory integration processing in the basal ganglia motor loops for such stereotyped movements, possibly allowing medicated PD patients to perform smooth movements. The neural degeneration of the ganglia-thalamo-cortical loop described in APS patients [12-16] may be responsible for the slowness and abnormal movement path observed in ballistic movements.

Movement irregularities in such a low requirement task suggest a general motor programming or motor control deficit in APS, confirming previous suggestions [17, 18, 19]. These data also suggest that detection of discrete motor irregularities may be a useful tool in the characterization of the motor impairments in atypical parkinsonian syndromes. The

detection of discrete motor irregularities in ballistic movements could help in the early evaluation of several populations with basal ganglia dysfunction.

Acknowledgements

This study was supported in part by the Natural Sciences and Engineering Research Council of Canada. We would like to thank Wacef Guerfali for software development, Dr. Helene Masson for patient referrals, as well as the subjects who took part in this study.

No.	Sex	Age (yrs)	Disease duration (yrs)	Diagnosis	Motor UPDRS	Medication
APS						
1	F	57	3	MSA	35.5	L-dopa, Pramipexole, Orphenadrine
2	F	55	2	MSA	19.0	L-dopa, Pramipexole
3	F	68	6	MSA	23.0	L-dopa. Pramipexole, Entacapone
4	M	86	8	MSA	18.0	L-dopa, Midodrine
5	F	70	2	PSP	28.5	Pramipexole, Prolopa, triamterene
6	F	68	1	PSP	9.0	Bupropion
7	F	64	8	PSP	42.0	Bupropion
8	M	73	4	PSP	--	L-dopa, Pramipexole, Bupropion
9	F	68	6	PSP	--	L-dopa
10	M	71	1	CBD	29.0	L-dopa
11	F	75	2	CBD	--	L-dopa
PD				H&Y stages*		
1	F	56	11	3	15.5	L-dopa, Pergolide, Amantadine
2	M	61	5	2	32.0	L-dopa, Pramipexole
3	F	60	8	2	16.5	L-dopa, Pramipexole
4	M	77	7	3	38.0	L-dopa, Pramipexole
5	M	66	15	3	44.5	L-dopa, Pramipexole, Clozapine
6	F	66	11	2	22.5	L-dopa, Amantadine, Selegiline
7	M	67	7	2	28.0	L-dopa
8	M	64	1	1	10.0	Pramipexole
9	M	58	2	2	16.0	Entacapone, Gabapentin
10	M	58	11	2	5.0	L-dopa, Pramipexole, Amantadine
11	M	67	6	2	5.0	L-dopa, Amantadine, Entacapone, Ropinirole

Table 1 Clinical data for Parkinson's disease and atypical patients

*Hoehn & Yahr [44]

Figure Captions

Figure 1. Sample speed, acceleration and jerk profiles in a single ballistic movement in a control subject, a PD patient and an atypical parkinsonian patient.

Figure 2. Average number of movement irregularities per trajectory obtained in the three groups. Error bars are standard errors.

Figure 1

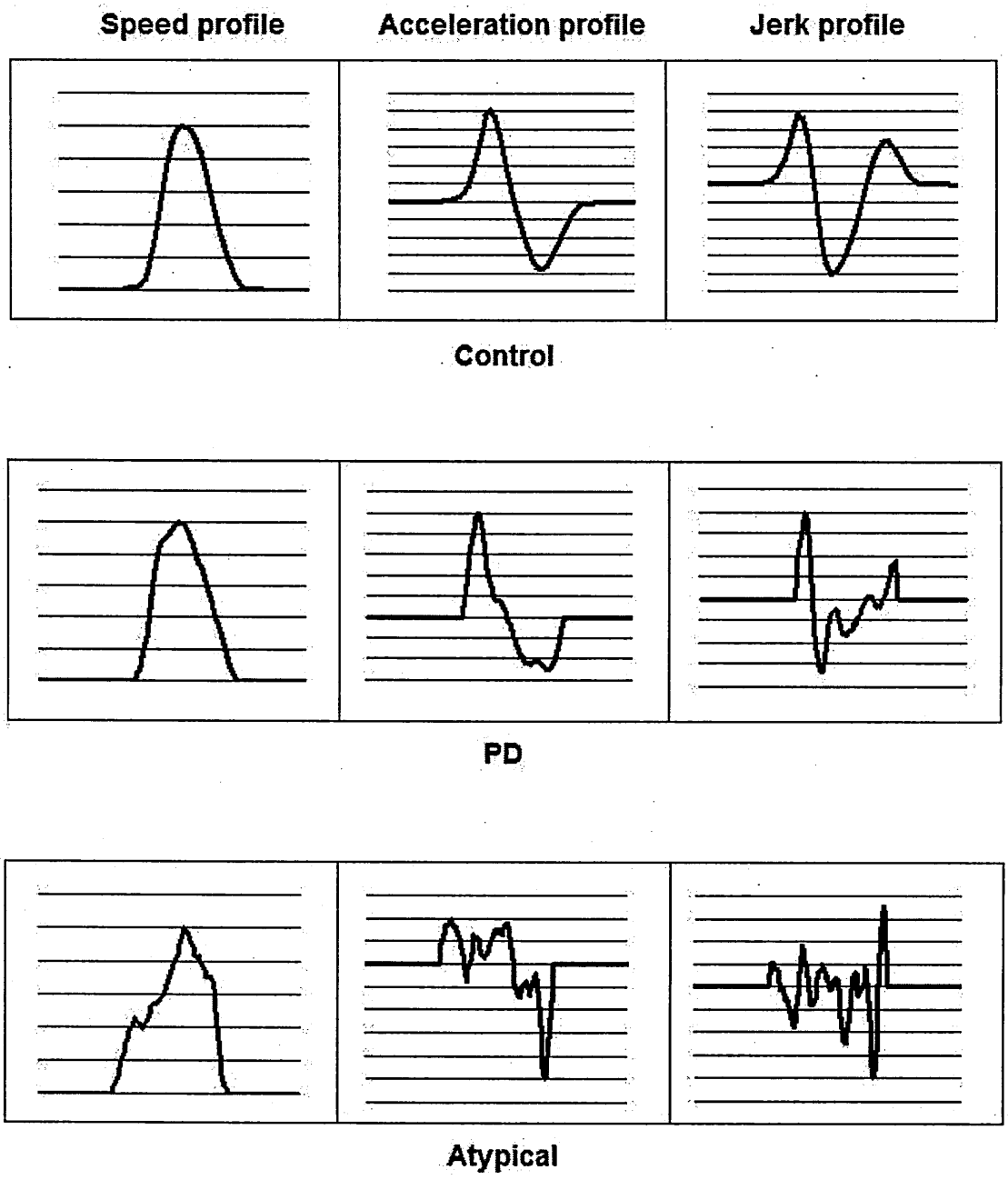
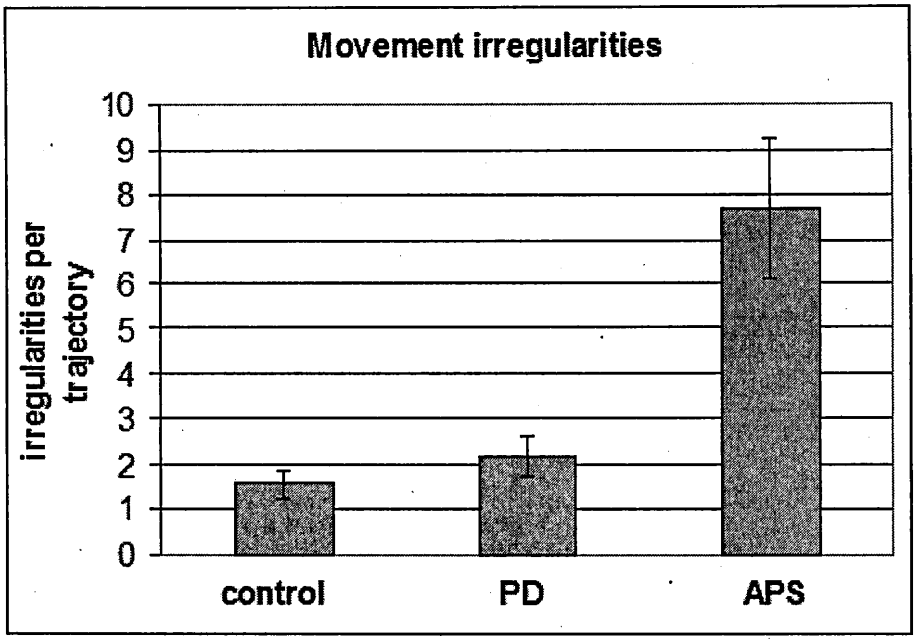

Speed profile
Acceleration profile
Jerk profile
Control
PD
Atypical

Figure 2


Movement irregularities
irregularities per trajectory
10
9
8
7
6
5
4
3
2
1
0
control
PD
APS

References

1. Flash, T., et al., *Kinematic analysis of upper limb trajectories in Parkinson's disease.* Exp Neurol, 1992. **118**(2): p. 215-26.
2. Rand, M.K., G.E. Stelmach, and J.R. Bloedel, *Movement accuracy constraints in Parkinson's disease patients.* Neuropsychologia, 2000. **38**(2): p. 203-12.
3. Poizner, H., et al., *Pointing to remembered targets in 3-D space in Parkinson's disease.* Motor Control, 1998. **2**(3): p. 251-77.
4. Alberts, J.L., et al., *Disruptions in the reach-to-grasp actions of Parkinson's patients.* Exp Brain Res, 2000. **134**(3): p. 353-62.
5. Hallett, M. and S. Khoshbin, *A physiological mechanism of bradykinesia.* Brain, 1980. **103**(2): p. 301-14.
6. Pfann, K.D., et al., *Control of movement distance in Parkinson's disease.* Mov Disord, 2001. **16**(6): p. 1048-65.
7. Isenberg, C. and B. Conrad, *Kinematic properties of slow arm movements in Parkinson's disease.* J Neurol, 1994. **241**(5): p. 323-30.
8. Abbruzzese, G. and A. Berardelli, *Sensorimotor integration in movement disorders.* Mov Disord, 2003. **18**(3): p. 231-40.
9. Ghilardi, M.F., et al., *Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease.* Brain Res, 2000. **876**(1-2): p. 112-23.
10. Teasdale, N., J. Phillips, and G.E. Stelmach, *Temporal movement control in patients with Parkinson's disease.* J Neurol Neurosurg Psychiatry, 1990. **53**(10): p. 862-8.
11. Schulz, J.B., et al., *Magnetic resonance imaging-based volumetry differentiates idiopathic Parkinson's syndrome from multiple system atrophy and progressive supranuclear palsy.* Ann Neurol, 1999. **45**(1): p. 65-74.
12. Lantos, P.L., *The neuropathology of progressive supranuclear palsy.* J Neural Transm Suppl, 1994. **42**: p. 137-52.
13. Paviour, D.C., et al., *Regional brain volumes distinguish PSP, MSA-P, and PD: MRI-based clinico-radiological correlations.* Mov Disord, 2006. **21**(7): p. 989-96.

14. Paviour, D.C., et al., *Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy.* Brain, 2006. **129**(Pt 4): p. 1040-9.
15. Groschel, K., et al., *Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration.* Neuroimage, 2004. **21**(2): p. 714-24.
16. Hauser, R.A., et al., *Magnetic resonance imaging of corticobasal degeneration.* J Neuroimaging, 1996. **6**(4): p. 222-6.
17. Muratori, L.M., R. Reilmann, and A.M. Gordon, *Coordination of fingertip forces during precision grasping in multiple system atrophy.* Neuropsychologia, 2003. **41**(11): p. 1498-508.
18. Testa, D., et al., *Cognitive and motor performance in multiple system atrophy and Parkinson's disease compared.* Neuropsychologia, 1993. **31**(2): p. 207-10.
19. Defebvre, L.J., et al., *Motor programming is more affected in progressive supranuclear palsy than in Parkinson's disease: a spatiotemporal study of event-related desynchronization.* Mov Disord, 1999. **14**(4): p. 634-41.
20. Sheridan, M.R. and K.A. Flowers, *Movement variability and bradykinesia in Parkinson's disease.* Brain, 1990. **113 (Pt 4)**: p. 1149-61.
21. Montgomery, E.B., Jr. and J. Nuessen, *The movement speed/accuracy operator in Parkinson's disease.* Neurology, 1990. **40**(2): p. 269-72.
22. Fahn, S., Elton, R., and Committee a.t.m.o.t.U.P.s.D.R.S.D., *Unified Parkinson's disease rating scale*, in *Recent Developments in Parkinson's Disease*, S. Fahn, Marsden, C.D., Calne, D., Editor. 1987, MacMillan: New York. p. 153-163.
23. Fimbel, E., et al., *Event identification in movement recordings by means of qualitative patterns.* Neuroinformatics, 2003. **1**: p. 239-258.
24. Schneider, K. and R.F. Zernicke, *Jerk-cost modulations during the practice of rapid arm movements.* Biol Cybern, 1989. **60**(3): p. 221-30.
25. Nagasaki, H., *Asymmetric velocity and acceleration profiles of human arm movements.* Exp Brain Res, 1989. **74**(2): p. 319-26.
26. Rohrer, B., et al., *Movement smoothness changes during stroke recovery.* J Neurosci, 2002. **22**(18): p. 8297-304.

27. Maher, E.R. and A.J. Lees, *The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy).* Neurology, 1986. **36**(7): p. 1005-8.

28. Rivest, J., N. Quinn, and C.D. Marsden, *Dystonia in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy.* Neurology, 1990. **40**(10): p. 1571-8.

29. Lee, M.S., J.O. Rinne, and C.D. Marsden, *The pedunculopontine nucleus: its role in the genesis of movement disorders.* Yonsei Med J, 2000. **41**(2): p. 167-84.

30. Bard, C., et al., *Deafferentation and pointing with visual double-step perturbations.* Exp Brain Res, 1999. **125**(4): p. 410-6.

31. Walker, N., D.E. Meyer, and J.B. Smelcer, *Spatial and temporal characteristics of rapid cursor-positioning movements with electromechanical mice in human-computer interaction.* Hum Factors, 1993. **35**(3): p. 431-58.

32. Salazar, G., et al., *Postural and action myoclonus in patients with parkinsonian type multiple system atrophy.* Mov Disord, 2000. **15**(1): p. 77-83.

33. Litvan, I., et al., *Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study.* J Neurol Neurosurg Psychiatry, 1996. **60**(6): p. 615-20.

34. Litvan, I., et al., *Clinical features differentiating patients with postmortem confirmed progressive supranuclear palsy and corticobasal degeneration.* J Neurol, 1999. **246 Suppl 2**: p. II1-5.

35. Collins, S.J., et al., *Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria.* J Neurol Neurosurg Psychiatry, 1995. **58**(2): p. 167-73.

36. Caviness, J.N., et al., *Small-amplitude cortical myoclonus in Parkinson's disease: physiology and clinical observations.* Mov Disord, 2002. **17**(4): p. 657-62.

37. Siegert, R.J., et al., *Self-initiated versus externally cued reaction times in Parkinson's disease.* J Clin Exp Neuropsychol, 2002. **24**(2): p. 146-53.

38. Georgiou, N., et al., *An evaluation of the role of internal cues in the pathogenesis of parkinsonian hypokinesia.* Brain, 1993. **116 (Pt 6)**: p. 1575-87.

39. Constantinescu, R., I. Richard, and R. Kurlan, *Levodopa responsiveness in disorders with parkinsonism: a review of the literature.* Mov Disord, 2007. **22**(15): p. 2141-8; quiz 2295.

40. Parati, E.A., et al., *Response to L-DOPA in multiple system atrophy.* Clin Neuropharmacol, 1993. **16**(2): p. 139-44.

41. Kroonenberg, P.M., et al., *Motor function in Parkinson's disease and supranuclear palsy: simultaneous factor analysis of a clinical scale in several populations.* BMC Med Res Methodol, 2006. **6**: p. 26.

42. Yan, J.H., J.R. Thomas, and G.E. Stelmach, *Aging and rapid aiming arm movement control.* Exp Aging Res, 1998. **24**(2): p. 155-68.

43. Alexander, G.E., M.D. Crutcher, and M.R. DeLong, *Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions.* Prog Brain Res, 1990. **85**: p. 119-46.

44. Hoehn, M.M. and M.D. Yahr, *Parkinsonism: onset, progression and mortality.* Neurology, 1967. **17**(5): p. 427-42.

DISCUSSION

Nous avons examiné l'irrégularité du mouvement chez les sujets atteints de syndromes parkinsoniens atypiques (MSA, PSP et CBD) et les avons comparés à des sujets sains du même âge, ainsi qu'à des parkinsoniens idiopathiques sous médication. Les patients atteints de syndromes parkinsoniens atypiques (SPA) montrent trois plus d'irrégularités dans leurs trajectoires de mouvement comparativement aux sujets contrôles et aux sujets atteints de la maladie de Parkinson idiopathique (MP). Nos données montrent que les mouvements des sujets SPA présentent une seule phase, mais que celle-ci est irrégulière et fragmentée. Ces irrégularités se traduisent par un nombre élevé de *zero-crossings* sur les tracés d'accélération et de jerk. Ces irrégularités ne montrent pas de fréquences prédominantes et ne semblent pas corrélées avec les mesures de tremblement, de rigidité, d'akinésie et de bradykinésie du l'*Unified Parkinson Disease Rating Scale* (UPDRS).

Les patients atteints de la MP appariés pour l'âge et pour le score clinique de déficits moteur de l'UPDRS ne présentent pas d'irrégularités motrices. Ce dernier résultat suggère que les irrégularités motrices détectées chez les patients SPA ne sont pas associées aux symptômes parkinsoniens typiques. De plus, il semble que l'écart de performance entre les patients MP et SPA ne peut être attribuable à la médication, puisque la grande majorité des patients des deux groupes sont traités à l'aide de L-dopa et/ou d'agoniste dopaminergique.

Les irrégularités observées chez les patients SPA ne peuvent être considérées comme des corrections motrices effectuées en cours de mouvement, étant donné l'absence

de rétroaction visuelle sur laquelle repose normalement ce type de corrections. L'absence de cible à atteindre diminue également le recours à des corrections une fois le mouvement amorcé (Bard et al., 1999). De plus, la présence d'irrégularités au début, au milieu ainsi qu'à la fin du mouvement suggère que celles-ci ne correspondent pas à des corrections de fin de mouvement comme on observe habituellement dans des tâches de pointage (Flash, Inzelberg, Schechtman, & Korczyn, 1992; Walker, Meyer, & Smelcer, 1993).

Ces irrégularités présentent des ressemblances avec les mouvements d'action myocloniques observés chez des patients SPA (Collins, Ahlskog, Parisi, & Maraganore, 1995; Litvan et al., 1999; Litvan et al., 1996; Salazar, Valls-Sole, Marti, Chang, & Tolosa, 2000) de même que chez des patients MP (Caviness, Adler, Beach, Wetjen, & Caselli, 2002). Quoique montrant certaines similitudes avec les mouvements myocloniques arythmiques présents en début d'exécution de mouvement décrits par Salazar et collègues (2000), les irrégularités observées dans notre étude sont présentes à travers toute l'exécution du mouvement. Des mesures neurophysiologiques supplémentaires seront nécessaires pour déterminer l'origine de ces irrégularités motrices.

L'analyse des paramètres du mouvement des patients SPA nous indique un ralentissement moteur important. Les patients SPA présentent des temps d'exécution de mouvement plus longs et une vitesse maximale plus basse que les sujets contrôles et les patients atteints de MP idiopathique. Ces résultats confirment la bradykinésie sévère observée dans le parkinsonisme atypique (Testa et al., 1993). Les patients SPA sont toutefois aussi rapides que les patients MP dans l'initiation du mouvement. Ce dernier

résultat peut s'expliquer par l'utilisation d'un signal externe indiquant l'initiation du mouvement.

Contrairement aux patients SPA, les patients MP évalués dans notre étude présentent des mouvements fluides et sans irrégularités. De plus, leurs temps de réaction ainsi que leurs patrons d'accélération et de jerk sont similaires à ceux des contrôles. Ces résultats appuient d'autres travaux de recherche montrant que les patients MP sont capables d'effectuer des mouvements normaux lorsque les demandes de précision sont minimales (Ghilardi et al., 2000) et qu'ils présentent des temps de réaction normaux lorsque leurs mouvements sont initiés à l'aide d'un signal externe (Georgiou et al., 1993; Siegert, Harper, Cameron, & Abernethy, 2002). La bonne performance de nos patients MP pourrait être attribuable à leur traitement pharmacologique, néanmoins Ghilardi et ses collègues (2000) ont obtenu des résultats similaires auprès de patients MP non médicamentés. Nos résultats suggèrent que les patients SPA présentent un ralentissement et une irrégularité importante dans l'exécution de mouvements simples sans cible à atteindre et sans rétroaction visuelle. Dans les mêmes conditions, les patients MP présentent des mouvements similaires aux sujets contrôles.

La comparaison de notre mesure d'irrégularité motrice aux différentes données nominatives et cliniques des participants nous permet d'identifier certains facteurs qui semblent influencer la présence d'irrégularités motrices. Les irrégularités corrèlent avec l'âge des participants de l'étude, confirmant l'effet bien documenté de l'âge sur le contrôle moteur (Yan, Thomas, & Stelmach, 1998). Cependant, aucune corrélation entre les irrégularités et la durée ou la sévérité de la maladie ou le score moteur de l'échelle clinique de l'UPDRS n'a été

obtenue dans nos groupes de patients. Cette dernière mesure de la sévérité de l'atteinte motrice ne semble pas sensible aux irrégularités détectées durant notre tâche. Nous notons toutefois une corrélation entre l'irrégularité et le score de stabilité et d'équilibre de l'UPDRS. Cette corrélation suggère un lien entre les irrégularités motrices ainsi que les troubles d'équilibre et l'instabilité posturale fréquemment observés chez des patients atteints de parkinsonisme résistant au traitement dopaminergique (Maher & Lees, 1986; Rivest, Quinn, & Marsden, 1990). Ces types de déficits sont souvent attribuables à des pertes neuronales des structures du tronc cérébral comme les noyaux pédoculopontins chez les patients APS (Lee, Rinne, & Marsden, 2000).

L'ensemble de nos résultats suggèrent un lien entre les déficits moteurs observés et l'atteinte striatopallidale présente chez les patients SPA. Ces déficits ne semblent pas associés à l'atteinte mésencéphalique caractéristique des patients MP. Selon les modèles actuels du fonctionnement des noyaux gris centraux, ces noyaux sont fortement impliqués dans l'intégration des entrées sensorielles nécessaires au guidage du mouvement. Il semble que les commandes motrices activent différentes boucles corticostriatales permettant la coordination sensorimotrice nécessaire au mouvement (Alexander, Crutcher, & DeLong, 1990). L'intégration de l'information proprioceptive et visuelle apparaît donc essentielle à l'exécution optimale du mouvement. Dans notre étude, l'absence de demande de précision et de rétroaction visuelle pourrait avoir minimisé cette intégration, diminuant l'activation des boucles frontostriatales et permettant aux patients MP médicamentés d'effectuer la tâche sans difficulté. Chez les patients SPA, la dégénérescence plus importante des boucles reliant le cortex, le striatum, le globus pallidus et le thalamus (Groschel et al., 2004; Hauser,

Murtaugh, Akhter, Gold, & Olanow, 1996; Lantos, 1994; Paviour, Price, Jahanshahi, Lees, & Fox, 2006a, 2006b) pourrait être responsable du ralentissement et de l'irrégularité du mouvement observé. La présence d'irrégularités motrices dans une tâche simple confirme l'hypothèse selon laquelle le parkinsonisme atypique entraîne des troubles de programmation motrice ou des déficits de contrôle moteur majeurs (Defebvre et al., 1999; Muratori, Reilmann, & Gordon, 2003; Testa et al., 1993). Les résultats de notre étude suggèrent que la détection d'irrégularités motrices constitue un indicateur utile des troubles moteurs caractéristiques des syndromes parkinsoniens atypiques. De plus, la détection d'irrégularités motrices pourrait permettre une meilleure évaluation du fonctionnement moteur dans différentes populations présentant des atteintes des noyaux gris centraux.

RÉFÉRENCES

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. Trends Neurosci, 12(10), 366-375.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res, 85, 119-146.

Bard, C., Turrell, Y., Fleury, M., Teasdale, N., Lamarre, Y., & Martin, O. (1999). Deafferentation and pointing with visual double-step perturbations. Exp Brain Res, 125(4), 410-416.

Bergman, H., & Deuschl, G. (2002). Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord, 17 Suppl 3, S28-40.

Caviness, J. N., Adler, C. H., Beach, T. G., Wetjen, K. L., & Caselli, R. J. (2002). Small-amplitude cortical myoclonus in Parkinson's disease: physiology and clinical observations. Mov Disord, 17(4), 657-662.

Collins, S. J., Ahlskog, J. E., Parisi, J. E., & Maraganore, D. M. (1995). Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria. J Neurol Neurosurg Psychiatry, 58(2), 167-173.

Defebvre, L. J., Derambure, P., Bourriez, J. L., Cassim, F., Guieu, J. D., & Destee, A. (1999). Motor programming is more affected in progressive supranuclear palsy than in Parkinson's disease: a spatiotemporal study of event-related desynchronization. Mov Disord, 14(4), 634-641.

Fimbel, E., Dubarry, A. S., Philibert, M., & Beuter, A. (2003). Event identification in movement recordings by means of qualitative patterns. Neuroinformatics, 1, 239-258.

Flash, T., Inzelberg, R., Schechtman, E., & Korczyn, A. D. (1992). Kinematic analysis of upper limb trajectories in Parkinson's disease. Exp Neurol, 118(2), 215-226.

Georgiou, N., Iansek, R., Bradshaw, J. L., Phillips, J. G., Mattingley, J. B., & Bradshaw, J. A. (1993). An evaluation of the role of internal cues in the pathogenesis of parkinsonian hypokinesia. Brain, 116 (Pt 6), 1575-1587.

Ghilardi, M. F., Alberoni, M., Rossi, M., Franceschi, M., Mariani, C., & Fazio, F. (2000). Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res, 876(1-2), 112-123.

Graybiel, A. M., Aosaki, T., Flaherty, A. W., & Kimura, M. (1994). The basal ganglia and adaptive motor control. Science, 265(5180), 1826-1831.

Groschel, K., Hauser, T. K., Luft, A., Patronas, N., Dichgans, J., Litvan, I., et al. (2004). Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration. Neuroimage, 21(2), 714-724.

Hallett, M. (1993). Physiology of basal ganglia disorders: an overview. Can J Neurol Sci, 20(3), 177-183.

Hallett, M., & Khoshbin, S. (1980). A physiological mechanism of bradykinesia. Brain, 103(2), 301-314.

Hauser, R. A., Murtaugh, F. R., Akhter, K., Gold, M., & Olanow, C. W. (1996). Magnetic resonance imaging of corticobasal degeneration. J Neuroimaging, 6(4), 222-226.

Isenberg, C., & Conrad, B. (1994). Kinematic properties of slow arm movements in Parkinson's disease. J Neurol, 241(5), 323-330.

Lantos, P. L. (1994). The neuropathology of progressive supranuclear palsy. J Neural Transm Suppl, 42, 137-152.

Lee, M. S., Rinne, J. O., & Marsden, C. D. (2000). The pedunculopontine nucleus: its role in the genesis of movement disorders. Yonsei Med J, 41(2), 167-184.

Litvan, I., Grimes, D. A., Lang, A. E., Jankovic, J., McKee, A., Verny, M., et al. (1999). Clinical features differentiating patients with postmortem confirmed progressive supranuclear palsy and corticobasal degeneration. J Neurol, 246 Suppl 2, II1-5.

Litvan, I., Mangone, C. A., McKee, A., Verny, M., Parsa, A., Jellinger, K., et al. (1996). Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry, 60(6), 615-620.

Maher, E. R., & Lees, A. J. (1986). The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology, 36(7), 1005-1008.

Muratori, L. M., Reilmann, R., & Gordon, A. M. (2003). Coordination of fingertip forces during precision grasping in multiple system atrophy. Neuropsychologia, 41(11), 1498-1508.

Paviour, D. C., Price, S. L., Jahanshahi, M., Lees, A. J., & Fox, N. C. (2006a). Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy. Brain, 129(Pt 4), 1040-1049.

Paviour, D. C., Price, S. L., Jahanshahi, M., Lees, A. J., & Fox, N. C. (2006b). Regional brain volumes distinguish PSP, MSA-P, and PD: MRI-based clinico-radiological correlations. Mov Disord, 21(7), 989-996.

Poizner, H., Fookson, O. I., Berkinblit, M. B., Hening, W., Feldman, G., & Adamovich, S. (1998). Pointing to remembered targets in 3-D space in Parkinson's disease. Motor Control, 2(3), 251-277.

Rand, M. K., Stelmach, G. E., & Bloedel, J. R. (2000). Movement accuracy constraints in Parkinson's disease patients. Neuropsychologia, 38(2), 203-212.

Rivest, J., Quinn, N., & Marsden, C. D. (1990). Dystonia in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Neurology, 40(10), 1571-1578.

Salazar, G., Valls-Sole, J., Marti, M. J., Chang, H., & Tolosa, E. S. (2000). Postural and action myoclonus in patients with parkinsonian type multiple system atrophy. Mov Disord, 15(1), 77-83.

Siegert, R. J., Harper, D. N., Cameron, F. B., & Abernethy, D. (2002). Self-initiated versus externally cued reaction times in Parkinson's disease. J Clin Exp Neuropsychol, 24(2), 146-153.

Testa, D., Fetoni, V., Soliveri, P., Musicco, M., Palazzini, E., & Girotti, F. (1993). Cognitive and motor performance in multiple system atrophy and Parkinson's disease compared. Neuropsychologia, 31(2), 207-210.

Walker, N., Meyer, D. E., & Smelcer, J. B. (1993). Spatial and temporal characteristics of rapid cursor-positioning movements with electromechanical mice in human-computer interaction. Hum Factors, 35(3), 431-458.

Yan, J. H., Thomas, J. R., & Stelmach, G. E. (1998). Aging and rapid aiming arm movement control. Exp Aging Res, 24(2), 155-168.