Influence of basal ganglia on upper limb locomotor synergies. Evidence from deep brain stimulation and L-DOPA treatment in Parkinson’s disease

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Clinical evidence of impaired arm swing while walking in patients with Parkinson’s disease suggests that basal ganglia and related systems play an important part in the control of upper limb locomotor automatism. To gain more information on this supraspinal influence, we measured arm and thigh kinematics during walking in 10 Parkinson’s disease patients, under four conditions: (i) baseline (no treatment), (ii) therapeutic stimulation of the subthalamic nucleus (STN), (iii) L-DOPA medication and (iv) combined STN stimulation and L-DOPA. Ten age-matched controls provided reference data. Under baseline conditions the range of patients’ arm motion was severely restricted, with no correlation with the excursion of the ipsilateral thigh. In addition, the arm swing was abnormally coupled in time with oscillation of the thigh. STN stimulation significantly increased the gait speed and improved the spatio-temporal parameters of arm and thigh motion. The kinetic changes as a function of gait speed changes, however, were significantly smaller for the upper than the lower limb, in contrast to healthy controls. Arm motion was also less responsive after L-DOPA. Simultaneous deep brain stimulation and L-DOPA had additive effects on thigh motion, but not on arm motion and arm–thigh coupling. The evidence that locomotor automatisms of the upper and lower limbs display uncorrelated impairment upon dysfunction of the basal ganglia, as well as different susceptibility to electrophysiological and pharmacological interventions, points to the presence of heterogeneously distributed, possibly partially independent, supraspinal control channels, whereby STN and dopaminergic systems have relatively weaker influence on the executive structures involved in the arm swing and preferential action on those for lower limb movements. These findings might be considered in the light of phylogenetic changes in supraspinal control of limb motion related to primate bipedalism.

Keywords: arm swing; subthalamic nucleus; deep brain stimulation; Parkinson’s disease; walking

Abbreviations: DBS = deep brain stimulation; ROM = range of motion; STN = subthalamic nucleus


Introduction

The pendular motion of the upper extremities is a basic, albeit non-obligatory, component of human gait. Rhythmic oscillations of arm and forearm segments have been described in some detail, with reference to movement kinematics (Murray et al., 1967; Donker et al., 2005), movement kinetics (Hinrichs, 1990; Li et al., 2001), shoulder muscle activity (Fernandez Ballesteros et al., 1965; Hogue, 1969; Jackson et al., 1983a), phase-relation to lower limb walking cycle (Muzii et al., 1984; Wagenaar and van Emmerik, 2000), mechanical effects on whole body motion (Jackson et al., 1983b; Eke-Oko et al., 1997) and physical models of varying complexity (Webb et al., 1994; Kubo et al., 2004; Gutnik et al., 2005). Unlike the rich kinesiological characterization, however, information on neural control of gait-related arm motion is still scanty and mainly based on indirect human evidence and extrapolation from animal models.

As for the basic mechanisms, locomotor swinging of the upper limbs is mainly an active phenomenon, driven by rhythmic commands delivered to the motor nuclei of...
arm extensor and outward rotator muscles (Fernandez Ballestreros et al., 1965; Craik et al., 1976; Jackson et al., 1983a). According to current thinking, cyclic drive is produced by pre-motoneuronal networks in the cervical cord, which can be regarded as central pattern generators, homologous to those accounting for lower limb locomotor rhythm (Hogue, 1969; Yamaguchi, 1992; Ballion et al., 2001; Zehr et al., 2004). Indirect evidence indicates that arm and leg pattern generators during walking operate in a stable and tightly coupled fashion. Interlimb coordination, for instance, remains stable despite changes of limb segment mass, suggesting independence from peripheral mechanics (Donker et al., 2005). Movements of the upper and lower limbs and related muscle activities, moreover, can be explained by a limited number of basic temporal profiles, indicating a partially shared neural drive (Ivanenko et al., 2003, 2004). Common limb coordination patterns are also maintained across kinematically and kinetically different locomotor tasks, which again suggests a common neural control (Wannier et al., 2001). Finally, modifying the natural coupling pattern (e.g. swinging ipsilateral upper and lower limbs in phase) is difficult, demanding considerable concentration, which suggests that the basic activity of tightly linked generators must be gated for the expression of unusual coupling modes (Crenna and Lee unpublished data). Based on the phylogenetic coherence of locomotor control mechanisms (e.g. Grillner, 1981), typical limb coupling patterns are thought to rely on reticulospinal systems (Shimamura et al., 1991; Matsuyama and Drew, 2000; Matsuyama et al., 2004; Davidson and Budford, 2006; Schepens and Drew, 2006) and long-axonated propriospinal connections linking the cervical and lumbosacral cords (Meink and Piesiur-Strehlow, 1981; Delwaide and Crenna, 1984; Nathan et al., 1996; Juvin et al., 2005).

Functional imaging studies indicate that higher-level control of locomotor limb movements, possibly entailing activation, amplitude modulation and changes in the interlimb phase-shift, can be mainly ascribed to the midbrain tegmentum, medial cerebellum, basal ganglia and related precentral cortices (Hellstrand, 1985; Fukuyama et al., 1997; Malouin et al., 2003; Jahn et al., 2004, 2008). Under minimally challenging conditions, such as steady linear walking over a flat terrain, engagement of cortical areas was shown to be relatively weak, so subcortical systems appear to take over most of the control function, possibly including regulation of arm rhythm (Hellstrand, 1985; Malouin et al., 2003; see also Carrol et al., 2005). Strong support for this comes from clinical and instrumental evidence in patients with idiopathic Parkinson’s disease, where primary dysfunction of the basal ganglia and related systems is one of the pathophysiological hallmarks (Braak and Del Tredici, 2008). Parkinson’s disease patients, but not patients with vascular parkinsonism (Zijlman et al., 1996), typically show little or no arm oscillation whilst walking, and this is often the first presenting feature of the disease (e.g. Buchthal and Fernandez Ballestreros, 1965; Stolze et al., 2001; Salarian et al., 2004). The arm swing reduction is not correlated with clinically tested shoulder rigidity, thus pointing to a motor disturbance specifically associated with active conditions and/or locomotor function (Buchthal and Fernandez-Ballestreros, 1965). Patients with Parkinson’s disease also have reduced flexibility in the adaptive coordination of arm/leg movements in relation to walking speed, and this was significantly correlated with the extent of degeneration of dopaminergic systems (Winogrodzka et al., 2005). Monoaminergically modulated basal ganglia structures therefore appear to be substantially involved in upper limb motion and limb coupling during human gait.

The deep brain stimulation (DBS) technique for treatment of the cardinal symptoms of Parkinson’s disease (e.g. Kringlebath et al., 2007) has provided new information on how basal ganglia subsystems influence locomotor control, with the internal pallidum (Siegfried et al., 1994; Limouzin et al., 1997), subthalamic nucleus (STN) (Hallet and Litivan, 1999; Krack et al., 2003; Kleiner-Fisman et al., 2006) and pedunculopontine nucleus (Mazzone et al., 2005; Plaha and Gill, 2005) as hitherto explored targets. Stimulation of the pallidum and STN, which in Parkinson’s disease show rhythmic neuronal discharge abnormally synchronized within and across the nuclei (Brown and Williams, 2005; Gatev et al., 2006), was reported to reset the overall temporal structure of network activity in a frequency-dependent fashion, by either suppressing aberrant firing or inserting new stimulation-driven patterns (Baev et al., 2002; Garcia et al., 2003; Meissner et al., 2005). These changes proved to be significantly correlated with consistent improvement in clinical motor deficits, mainly rigidity and akinesia (Silberstein et al., 2005; Kühn et al., 2006). With reference to gait function, in particular, high-frequency stimulation (>100 Hz) of the STN can dramatically improve stride dimensions (Allert et al., 2001; Krystkowiak et al., 2003), kinematic, kinetic and EMG locomotor parameters (Faist et al., 2001; Ferrarin et al., 2005, 2007) and dynamic axial posture (Ferrarin et al., 2004; Crenna et al., 2006), possibly through the involvement of extensive anatomical connections with gait-related neural structures in the dorsal meso-pontine tegmentum (e.g. portions of pedunculopontine nucleus and cuneiform nucleus; Papapill and Lozano, 2000; Takakusaki et al., 2003; Chen and Lemon, 2004; Aravanathan et al., 2007; Braak and Del Tredici, 2008). Interestingly, most of these beneficial effects replicate those produced by l-DOPA therapy (Maurer et al., 2003; Silberstein et al., 2005). In addition, when DBS and l-DOPA are administered jointly, effectiveness is further enhanced, which suggests synergistic, additive actions (Faist et al., 2001; Ferrarin et al., 2004). However, though the favourable impact of STN stimulation and l-DOPA on leg and axial locomotor movements is established, no specific studies have so far investigated how the two treatments affect the pendular motion of the upper extremities. In view of the tight arm/leg coupling, the hypothesis might be put forward that responsiveness of the
upper limb locomotor synergies to electrophysiological and pharmacological interventions might be closely linked to that of the lower limb segments. Alternatively, the two oscillatory movements might be affected to different extents, revealing differences in susceptibility to targeted treatments. In the latter case, partially different supraspinal influences on cervical and lumbar sensory-motor circuitry should be considered, possibly related to adaptive changes underlying the acquisition of human upper limb dexterity (Georgopoulos and Grillner, 1989; Dietz, 2002; Xiang et al., 2007). Distinguishing between these two conditions, which might help clarify unexplored aspects of higher-level control of locomotor automatisms, would entail comparing the effects of STN stimulation and L-DOPA therapy on spatiotemporal parameters of upper and lower limb locomotor oscillations, taking account of their relationship with walking speed, which clearly affects interlimb coordination patterns (Wagenaar and van Emmerik, 2000). The aim of the present study was to make such a comparative assessment, by providing the first quantitative analysis of arm and leg kinematics and their coupling in Parkinson’s disease patients with chronically implanted STN electrodes while without treatment, during therapeutic stimulation of the STN, after L-DOPA treatment and during combined STN stimulation and L-DOPA. Preliminary data from this study were presented at the meeting of the IEEE Engineering in Medicine and Biology Society (Carpinella et al., 2007).

Methods
Subjects
Ten patients with idiopathic Parkinson’s disease undergoing bilateral therapeutic STN stimulation (5M; mean age 60.2 ± 4.8 years; age range 52–68 years; Parkinson’s disease duration 8–26 years; clinical severity, Hohen and Yahr scale, 2.5–4.5; time post-surgery 3–28 months) and 10 age-matched controls (6M; mean age 61.4 ± 5; age range 55–69 years) voluntarily took part in the study. Seven patients were taking antiparkinson medication (L-DOPA, 75–300 mg/day) and dopamine agonists (0.54–15 mg/day). All subjects gave written informed consent to the experimental protocol, which conformed to the standards for human experiments set by the Declaration of Helsinki (last modified in 2004) and was approved by the local Ethics Committee.

Protocol
After a 12 h washout of antiparkinson medication, patients spent half a day in a gait laboratory for an assessment program involving four conditions: (i) no STN stimulation or medication (baseline), (ii) bilateral STN stimulation (monopolar cathodic stimulation delivered to the dorso-lateral, motor portion of the nucleus (see Lopiano et al., 2001 for details of surgical method); mean pulse duration 72.0 μs (SD 15.1), mean frequency 143.3 Hz (SD 17.4), mean intensity 3.1 mA (SD 0.4) [S+], (iii) L-DOPA medication (liquid L-DOPA preparation, 50% higher than the approved by the local Ethics Committee.

set by the Declaration of Helsinki (last modified in 2004) and was of patients as they arrived at the laboratory and was always tested first to minimize the duration of the session, by avoiding initial and post-trial washout phases, if not necessary. During the assessment periods patients were not informed of the on/off state of stimulation. For each condition subjects did eight walking trials at their preferred speed along a 10 m path, followed by a resting time of at least 60 min, which is considered enough for DBS washout, in accordance with the previous similar studies (Allert et al., 2001; Faist et al., 2001). Non-disabled controls did three sets of walking trials, at ‘preferred’ (eight trials), ‘slow’ (eight) and ‘fast’ (eight) speeds, in random order, following verbal instructions in the absence of external feedback. These trials enabled us to collect kinematic parameters related to a sufficiently large speed range to build up a normative database.

Set-up
Kinematics of body segments were measured during walking, using an optoelectronic system (ELITE, BTS, Milan, Italy, sampling frequency 50 frames/s), which computed the 3D coordinates of spherical markers (10 mm diameter) fixed to the following landmarks: sacrum, T7, C7 and, on both sides of the body, acromions, lateral humeral condyles, ulnar styloid processes, posterior superior iliac spines, lateral femoral condyles, lateral malleoli and fifth metatarsal heads.

Data processing
The marker coordinates were low-pass filtered (cut-off frequency 3–7 Hz, self-estimated by a linear-phase autoregressive model-based derivative assessment algorithm; D’Amico et al., 1990) and individual anthropometric parameters were used to estimate internal joint centres (Friso and Rabuffetti, 1998). For both sides of the body and for each gait trial, the time-courses of the angular displacement of the humerus segment of the arm and femoral segment of the thigh with respect to the vertical (positive forward) (Murray et al., 1967; Kubo et al., 2004; Donker et al., 2005; Gutnik et al., 2005) were computed in planes perpendicular to the inter-trochanter and inter-acromion lines, respectively. These measures were used to analyse the pendular behaviour of thigh and arm segments, independently from shoulder and pelvic girdle horizontal rotation associated with trunk torsion. Additional information on trunk mobility was obtained by computing the range of the angles between the inter-acromion and inter-trochanter lines projected in the horizontal plane, over the stride cycle. All the angular profiles were normalized in time as a percentage of the stride duration, and for each cycle the following parameters were automatically extracted: average speed (estimated from the marker attached to the sacrum), range of motion (ROM) of absolute arm and thigh angles, range of trunk torsion. For arm ROM larger than 3°, the interlimb phase-shift was further computed as the temporal delay between the positive peak of the arm angle and the negative peak of the ipsilateral thigh angle, between 20% and 80% of the stride cycle. When the upper limb produced two oscillations per stride, which could occur at the lower walking speeds (e.g. Wagenaar and van Emmerik, 2000), phase-shifts were computed using the first positive peak of arm oscillation and the negative peak of the ipsilateral thigh angle. For each control subject at each speed and for each Parkinson’s disease patient in each condition (baseline, S+, M+ and S+M+), all the above variables (gait speed, arm ROM, thigh ROM, phase-shift) were averaged over trials. To characterize the speed-related effects
on the main kinematic parameters, the slopes of the regression lines of arm ROM, thigh ROM and phase-shift as a function of the gait speed were computed for each control, considering all the trials in which walking speed was in the same range as Parkinson’s disease patients in the different conditions. Thereafter, for each patient, we measured the slopes of the lines passing through the points \((v \text{ baseline}, y \text{ baseline})\) and \((v \text{ s+}, y \text{ s+})\), through the points \((v \text{ baseline}, y \text{ baseline})\) and \((v \text{ m+}, y \text{ m+})\), and through the points \((v \text{ s+/m+}, y \text{ s+/m+})\), where \(v\) is the average gait speed and \(y\) is the average arm ROM, thigh ROM and phase-shift for that patient in the given condition (slope was expressed as \(\circ/(\text{m s}^{-1})\)). This meant that the range of speeds spanned was comparable across subjects and conditions, and large enough to reliably compute a slope line, as demonstrated by the statistically significant increase of gait speed observed in Parkinson’s disease patients in each therapeutic condition with respect to the baseline (see ‘Results’ section). Finally we compared the slopes obtained in patients for each therapeutic condition with the slope for the control group.

**Statistics**

Distribution was non-normal for most of the variables, as assessed by Shapiro–Wilks’ W-test (SWt, where \(P < 0.05\) indicates non-normal distribution) and by skewness analysis (where skewness \(\neq 0\) stands for non-normal distribution, and positive values indicate data clustering in the lower or negative range). Accordingly, descriptive statistics and comparisons were always based on median/range values and non-parametric tests, respectively. Differences in gait speed, ROM, phase-shift indexes and slope parameters between control and Parkinson’s disease groups were analysed using the Mann–Whitney test (MWt). Differences between the four conditions (baseline, S+, M+, S+/M+) were evaluated by repeated-measures analysis of variance (non-parametric ANOVA for multiple dependent samples, Friedmann test, Ft). If significant differences were found (\(P < 0.05\)), Bonferroni post hoc (Bt post hoc) comparisons were systematically applied.

**Results**

**Baseline conditions**

In the absence of treatment the Parkinson’s disease patients’ walking speed was significantly lower than controls [median 0.64 m/s; range 0.20–0.80 m/s (patients) and 1.05 m/s; 0.84–1.31 m/s (controls); \(P_{(MWt)} < 0.0005\)]. In view of the speed-dependence of gait kinematics, the two groups were compared using reference values from controls walking at low speed, which was not significantly different from the patients’ baseline speed (median 0.62 m/s; range 0.44–0.83 m/s). Results, summarized in Fig. 1, indicate that the patients’ arm ROM was significantly less than age-and speed-matched controls [median 3.2\(^\circ\), range 1.4–10.2, 20 arms (patients) and 9.5\(^\circ\), 4.0–15.0, 20 arms (controls); \(P_{(MWt)} < 0.0001\)]. Likewise, the thigh ROM was substantially lower [median 26.8\(^\circ\), range 16.0–40.9, 20 thighs (patients) and 33.3\(^\circ\), 29.9–42.0, 20 thighs (controls); \(P_{(MWt)} < 0.001\)]. At variance with normal controls, where thigh and arm ROM were significantly correlated with the self-selected walking speed (thigh: \(r = 0.60; P < 0.01\); arm \(r = 0.59; P < 0.01\)), correlation in Parkinson’s disease patients was significant for the thigh (\(r = 0.66; P < 0.005\)), but not for the arm ROM.

![Fig. 1 Baseline condition. (A) Arm and thigh angle ROM for controls walking at low velocity (CO) and Parkinson’s disease patients. Bars: median. Whiskers: non-outlier min–max. Horizontal lines: statistically significant differences (Mann–Whitney U-Test). (B and C) Scatter plots of right and left arm ROM (squares) and thigh ROM (black circles) as a function of walking speed for Parkinson’s disease patients (B) and controls walking at low speed (C). (D) Phase-shift between arm and thigh angles in the sagittal plane for controls walking at low speed (CO) and Parkinson’s disease patients. Bars: median. Whiskers: non-outlier min–max. Horizontal lines: level of statistical difference (Mann–Whitney U-test).](image-url)
Analysis of individual angular profiles indicated that in healthy controls rhythmic oscillations of the arms had a frequency of one cycle per stride in 60% and two per stride in 40%, whereas in patients 25% of arms showed no regular swinging and 75% swung at one cycle per stride. Interlimb phase-shifts in the latter group indicated significant anticipation of maximum arm flexion (forward motion) in relation to ipsilateral thigh extension (backward motion), compared to controls [median –33.0% stride; range –44 to –4.9, 15 arms/thighs (patients); –14% stride; –3.1 to –7.8, 20 arms/thighs (controls); \( P_{(MWt)} < 0.001 \)]. Representative limb coupling patterns in controls and Parkinson’s disease patients are reported in Fig. 2 as angle–time (A, B, C) and angle–angle (D, E, F) diagrams. Measurement of trunk rotation in the horizontal plane in patients under baseline condition showed reduced ROM with respect to speed-matched controls (median baseline Parkinson’s disease 4°, range 3.3–10.8 versus median controls 8.8°, range 5.3–15; \( P_{(MWt)} < 0.001 \)).

**STN stimulation (S+ condition)**

STN stimulation achieved an overall improvement in locomotor function with respect to baseline. Walking speed rose considerably (median 1.04 m/s; range 0.48–1.15 m/s; \( P_{(FT, BT post hoc)} < 0.05 \), attaining the same average as controls walking at natural speed, which were therefore used as a reference (median 1.05 m/s; range: 0.84–1.31 m/s; no significant difference between controls and patients). As shown in Fig. 3A, the average arm ROM became more pronounced (median 5.9°; range 2.0–52.3°; \( P_{(FT and BT post hoc)} < 0.05 \), although still significantly lower than in speed-matched controls (median 17.3°; \( P_{(MWt)} < 0.01 \)). The slope of ROM changes in relation to the walking speed, reported in Table 1, did not significantly differ in the two groups and the distribution of the effects, detailed in Fig. 4 (top histogram, left column), was clearly skewed toward lower values (\( P_{(SWt)} < 0.0005 \); skewness = 1.86), with an average change of 2.7° (delta of median arm ROM\(_{(S+ – basal)}\)). STN stimulation had more marked effects on thigh movements. The average thigh ROM (Fig. 3B) was significantly larger (median 39.9°; range 25.8–48.1; 20 thighs, \( P_{(FT and BT post hoc)} < 0.05 \)) and attained values not significantly different from controls (median 38.3°). The slope of thigh ROM changes in relation to speed was steeper than for healthy controls, and the distribution of the effects showed a normal profile (\( P_{(SWt)} \); NS; skewness = 0.43), with an average improvement of 13.2° (delta of median thigh ROM\(_{(S+ – basal)}\)). Comparative analysis of the slopes of the arm and thigh angle changes as a function of the gait speed in Parkinson’s disease patients showed that, unlike the healthy controls, the slope of the arm changes was significantly lower than the slope of the thigh changes (median arm slope 12.2°/(m s\(^{-1}\)), range –1.2 to 35.5; median thigh slope 28.9°/(m s\(^{-1}\), range 13.1–59.4, \( P_{(MWt)} < 0.05 \)). Finally, the phase-shift between arm and ipsilateral leg motion, reported in Fig. 3C was significantly reduced in patients undergoing STN stimulation, attaining average values not significantly different from controls [median –9.7% stride, range –37.5 to –1.2, 17 arm/thighs (patients) versus median –5.8% stride, –12.1 to –1.1, 20 arm/thighs (controls); \( P_{(MWt)} \); n.s.]. Analysis of axial mobility in the horizontal plane showed a significant increase in the angular range of trunk torsion upon STN stimulation compared with baseline (median STN stimulation 9.2°, range 3–15 versus median baseline: 4°, range 3.3–10.8; \( P_{(FT and BT post hoc)} < 0.05 \). As a consequence, this parameter attained values not significantly different from

![Fig. 2](image-url) Baseline condition. Arm and thigh angles in the sagittal plane for each stride cycle of one representative control subject CO6 (A) and two representative Parkinson’s disease patients PD3 (B) and PD7 (C). Lissajous graphs representing arm angle as a function of thigh angle for each stride cycle of one representative control subject CO6 (D) and two representative Parkinson’s disease patients PD3 (E) and PD7 (F).
speed-matched controls (median 11.5°, range 8.4–20.5; \(P_{(MWt)}\) NS).

**L-DOPA (M+ condition)**

The effects of L-DOPA were not significantly different from those of STN stimulation. Medication significantly increased the spontaneously adopted walking speed compared to baseline (median 1.03 m/s; range 0.35–1.27; \(P_{(Ft and Bt post hoc)} < 0.05\). As shown in Fig. 3A, the arm ROM was significantly greater as well (median arm ROM 10.2°; range 2.5–49.6; \(P_{(SWt)} < 0.0005\); skewness = 1.50), with an average change of 7.0° (delta of median arm ROM(M+ – basal)). Similarly to the condition with DBS, the thigh ROM increased more (median thigh ROM M+: 41.4°; delta of median thigh ROM(M+ – basal) = 14.6° (20 thighs);

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**Table 1** Slopes of the regression lines

<table>
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<tr>
<th></th>
<th>Controls</th>
<th>Parkinson’s disease baseline/S+</th>
<th>Parkinson’s disease baseline/M+</th>
<th>Parkinson’s disease baseline/S+M+</th>
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<tbody>
<tr>
<td>Slope arm ROM (\text{[°/(m s(^{-1})]})</td>
<td>19.4 (31.3–31.2)</td>
<td>12.2 (NS) (–1.2 to 35.5)</td>
<td>20.5 (NS) (–4.1 to 49.0)</td>
<td>15.0 (NS) (0.7–50.5)</td>
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<tr>
<td>Slope thigh ROM (\text{[°/(m s(^{-1})]})</td>
<td>12.7 (3.3–18.4)</td>
<td>28.9 ((P &lt; 0.0001)) (13.1–59.4)</td>
<td>22.8 ((P &lt; 0.001)) (6.3–70.2)</td>
<td>21.2 ((P &lt; 0.001)) (14.1–50.3)</td>
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<tr>
<td>Slope phase shift ROM (\text{[°/(m s(^{-1})]})</td>
<td>18.9 (3.9–270)</td>
<td>34.4 ((P &lt; 0.05)) (–12.0 to 100.0)</td>
<td>32.1 ((P &lt; 0.05)) (6.5–136.3)</td>
<td>31.2 ((P &lt; 0.01)) (2.5–41.1)</td>
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Slopes of the regression lines between walking speed and arm ROM, thigh ROM and phase shift for control subjects (controls) walking at low and self-selected speed and for Parkinson’s disease patients under baseline and S+ conditions (baseline/S+), baseline and M+ conditions (baseline/S+) and baseline and S+M+ conditions (baseline/S+M+). Median values, non-outlier min-max, and levels of statistical difference with respect to control values (Mann–Whitney U-test) are reported.
0.05] and reached amplitudes not significantly different from healthy controls. Again, the interlimb phase-shift was significantly reduced [median – 5.3% stride (range –36.5 to +2.11), \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \)], eventually attaining the control values. Likewise, axial mobility in the horizontal plane was significantly greater than at baseline (median trunk torsion range with L-DOPA: 9.4\(^\circ\), range 3.4–16.4; \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \), showing no significant difference with respect to speed-matched controls.

**STN stimulation and L-DOPA (S+ M+ condition)**

The combination of STN stimulation and L-DOPA significantly increased the walking speed, compared to both baseline and each treatment on its own (median 1.25 m/s; range: 0.70–1.79; S+M+ versus baseline, S+M+ versus S+, S+M+ versus M+, \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \)). The effects on the arm ROM were significant compared to baseline [median arm ROM\(_{S+M+}\): 13.2\(^\circ\) (range 3.0–54\(^\circ\)); \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \)], as shown in Fig. 3A, but not compared with stimulation and medication singly. There were therefore no additive effects. In fact the average arm S+M+ ROM was significantly lower than reference values, the slope of the effect in relation to speed was not different from controls, and changes in the arm excursion were skewed toward lower effects, averaging 10.0\(^\circ\) [delta of median arm ROM\(_{S+M+ - \text{basal}}\)]. Unlike the upper limbs, the effects on thigh ROM were significant in relation to baseline [median thigh ROM\(_{S+M+}\): 43.4\(^\circ\) (range 29–55.5\(^\circ\)); delta of median thigh ROM\(_{S+M+ - \text{basal}}\) = 16.7\(^\circ\); \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \)] to the S+ condition \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \) and to M+ \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \). There was therefore an additive effect. Finally, the interlimb phase-shift significantly improved with S+M+ compared with baseline (median: –4%; range –33.7–0.4; \( P_{(Ft \text{ and } Bt \text{ post hoc})} < 0.05 \)), but not compared to each individual treatment. In summary, both the S+ and M+ conditions significantly increased the arm and thigh ROM and reduced the phase-shift, while the two treatments combined had additive effects for the thigh ROM, but not for the arm ROM and phase-shift.

**Discussion**

At baseline Parkinson’s disease patients adopted a slow walking speed, with less excursion of thigh segments than speed-matched controls. In view of the correlation between thigh excursion and stride length, therefore, patients’ gait
appeared to combine shorter strides and higher cadence, as typically reported in Parkinson’s disease (e.g. Murray et al., 1978; Knutsson and Mårtensson, 1986; Morris et al., 1999). The arm swing pattern associated with this gait presented spatial and temporal abnormalities. The most obvious was a marked reduction of arm excursion which was less than 3° in a quarter of the subjects. This local kinematic defect may well be related to abnormal activation of shoulder muscles, which in Parkinson’s disease present a spectrum of EMG profiles ranging from discrete, wrongly timed recruitment, up to continuous, rhythmic activity, involving the posterior deltoid in 90% of cases (Buchthal and Fernandez-Ballestreros, 1965). Parkinson’s disease patients also had impaired limb coupling. Normal adults walking slowly (generally at <0.8 m/s) tend to swing their arms at twice the stride frequency, a pattern that becomes more obvious when they walk bent forward (Webb et al., 1994; van Emmerik et al., 1998; Wagenaar and van Emmerik, 2000).

This coupling mode was observed in age- and speed-matched controls, but never in patients, in spite of their slow gait and forward-bent posture. In addition, patients had an increase in phase-shift between the time of maximum forward motion of the arm and the time of maximum backward motion of the ipsilateral thigh. Changes in the arm ROM were not significantly correlated with the self-selected walking speed, which demonstrates that they are not a direct consequence of abnormal scaling of spatio-temporal parameters of the stride. Moreover, the dissociation between arm and leg locomotor impairment indicates that the two rhythmic movements are not necessarily susceptible to parallel hindering in Parkinson’s disease.

STN stimulation caused overall improvement in Parkinson’s disease patients’ locomotor performance. On average, the walking speed and the thigh ROM rose significantly, in keeping with previous studies where STN stimulation affected the stride size mainly by acting on the length (Krystkowiak et al., 2003; Salarian et al., 2004; Ferrarin et al., 2005). Recording locomotor EMG output in lower limb muscles (Ferrarin et al., 2007) revealed that the above kinematic changes are paralleled by substantial increase in amplitude and degree of synchronization of myoelectric activity, especially in leg muscles during the stance phase. Effects of DBS were also significant for the arm swing, in terms of increased average ROM and reduction of abnormally wide interlimb phase-shift. These findings indicate that interfering with the activity of the dorso-lateral (motor) portion of the STN by high-frequency stimulation can drive toward a physiological operational range not only the neural networks responsible for lower limb locomotor movements, but also those involved in the concurrent oscillation of the arms. In view of the main mechanical action ascribed to arm swing (i.e. application of a horizontal torque to the upper trunk, aimed at counteracting the opposite torque induced by pelvis and limb swing rotation around the supporting foot; Li et al., 2001; Park, 2008), enhanced arm ROM might be expected to cause more horizontal rotation of the trunk. Indeed, trunk torsion ROM during walking was increased by STN stimulation and L-DOPA (see also Ferrarin et al., 2004), meaning that both treatments improve axial mobility. The evidence that DBS and L-DOPA have little effect on trunk stiffness assessed under static (upright standing) conditions (Wright et al., 2007; see also Maurer, 2003), suggests that beneficial actions are mainly related to dynamic conditions occurring during locomotion.

Further examination of the impact of STN stimulation showed that the effects on arm and leg movements, although significant in both cases, were different in the majority of subjects. Changes in the arm ROM were largely skewed toward minor effects, attaining a median increase of approximately 3° and lower than 5° in most patients. Changes in the thigh ROM were more substantial, amounting to a median of ~12° and values larger than 5° in the majority of patients. The slopes of the limb ROM changes in relation to the walking speed confirmed that the ‘gain’ of the effects of stimulation was significantly smaller for the arm than for the thigh swing. As a result, the arm ROM failed to reach the reference values for the speed-matched controls, whereas the thigh ROM did, thus contributing to recovery of normal stride length and walking speed. This situation was just the opposite of that observed in healthy individuals, where at higher walking speeds the changes in the arms were greater than the thigh ROM (see Table 1, controls). As a consequence, STN stimulation appeared to improve the walking pattern of Parkinson’s disease patients by producing weaker action on the executive systems involved in upper limb swinging than lower limb motion. The limited responsiveness of gait-related arm movements to therapeutic procedures interfering with the activity of basal ganglia in Parkinson’s disease is in keeping with results from Buchthal and Fernandez-Ballestreros (1965), who reported that electrocoagulation of the VL nucleus of the thalamus (an important relay within the basal ganglia-thalamo-cortical circuits) did not restore the arm swing in the majority of patients.

Additional analysis of the effects of anti-parkinson treatment showed that the actual figure achieved with stimulation was maintained after administration of L-DOPA. Moreover, comparison of isolated and combined stimulation and medication indicated additive effects for the leg movements, but not for the upper limb ROM and phase-shift. The evidence of uncorrelated impairment upon dysfunction of the basal ganglia, and the different susceptibility to electrophysiological and pharmacological interventions, supports the general conclusion that human upper and lower limb locomotor automatisms can be viewed as oscillatory movements coupled according to discrete coordination modes by heterogeneously distributed, possibly partially independent, supraspinal control channels. In particular, it would appear that STN and related structures, with dopaminergic motor-related systems, have relatively lower influence on the executive
circuitry responsible for locomotor movements of the arms, and preferential action on those subserving the gait cycle of the lower limbs.

The evidence of different supraspinal influences on locomotor automatisms at the shoulder and pelvic girdles is new, and can be possibly related to current knowledge of the descending pathways responsible for the control of fore/upper limb movements, obtained from animal and human studies. These pathways include: (i) phylogenetically older, indirect connections involving brainstem relay stations, such as the para-lemniscal pontine and medial bulbar reticular formation, subserving postural support and most automatic forms of locomotion (Shimamura et al., 1991; Matsuyama et al., 2004, Davidson and Budford, 2006); (ii) more recent projections employing cervical (C3–C4) propriospinal systems, activated by motor cortices and other descending tracts during target reaching, and possibly used for accurate foot placement while walking (Georgopoulos and Grillner, 1989; Pierrot Deseilligny, 2002; Alstermark et al., 2007); (iii) recent control systems employing direct corticospinal pathways, preferentially active during skilled actions, possibly including walking in challenging conditions (Lemon and Griffiths, 2005). Several lines of evidence indicate that phylogenetic evolution of fore/upper limb dexterity associated with primate bipedalism was paralleled by extensive reorganization of these control pathways, with the appearance and subsequent reinforcement of direct cortical projections to cervical motor nuclei, including those related to proximal muscles responsible for the arm swing (Georgopoulos and Grillner, 1989; Alstermark et al., 1999; Turton and Lemon, 1999; see also Dietz, 2002). This rewiring process has most probably played a role in the changes in use of fore/upper limbs during locomotion, i.e. in the transition from ‘front driving’ in quadrupeds, to ‘back driving and front steering’ in the monkey’s quadrupedal gait, to ‘back driving with arm swing as a stabilizing mechanism’ in the monkey’s bipedal gait, and eventually to ‘lower limb driving with facultative arm swing’ in human walking (Xiang et al., 2007). Various authors have proposed that the strengthening of direct corticospinal control on fore/upper limb muscles and the related behavioural achievements were obtained at the expense of indirect control systems, i.e. by functional limitation (e.g. active inhibition) and/or actual anatomical restriction of their access to the upper limb motor nuclei (Nathan and Smith, 1982; Nicolas et al., 2001; Nielsen, 2003; Lemon and Griffiths, 2005). If that were true, phylogenetically dependent, selective loss of effectiveness of indirect pathways projecting to cervical cord [which are the main candidates for controlling basic locomotor automatisms of upper limbs by conveying downstream commands from basal ganglia (see Jordan, 1998; Takakusaki et al., 2003; Matsuyama et al., 2004; Aravamuthan et al., 2007; see also Dietz, 2002)] would be expected to render human arm synergies specifically prone to dysfunction in Parkinson’s disease, thus accounting for their early and rather severe impairment, as well as for their relative resistance to targeted treatments. Persistence of more powerful and/or more consistent, indirect connections with lumbo-sacral segments, on the other hand, might be regarded as a greater ‘safety factor’, possibly explaining the lower impairment of thigh compared with arm motion observed in Parkinson’s disease, and the more favourable response of lower limb motion to therapeutic interventions aimed at the basal ganglia. A corollary of this working hypothesis would be that selective lesions of the direct corticospinal systems will possibly shift the balance toward a relative increase in the effectiveness of indirect channels, which typically subserve tight interlimb coordination. Indeed, recent evidence in stroke patients indicates that arm–leg coupling may be paradoxically augmented after corticospinal injury, and this was ascribed to reduced cortical inhibition on reticulo–spinal systems controlling the upper limb flexion synergies and limb coordination (Kline et al., 2007).

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