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Antoine Collomb-Clerc,[1,2,3,4,5] Marie-Laure Welter, MD, PhD.[1,2,3,4,5]

Affiliations:

1 AP-HP, Hôpital de la Salpêtrière, Département de Neurologie, F-75013 Paris, France; 2 Inserm, U1127, F-75013 Paris, France; 3 Sorbonne Universités, UPMC Univ Paris 06, UMRS 1127 F-75013 Paris, France; 2; 4 CNRS, UMR 7225, ICM, F-75013 Paris, France ; 5 Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France; 5

Correspondence: ML Welter, Département de Neurologie, Bâtiment Paul Castaigne, Groupe Hospitalier Pitié-Salpêtrière, 47-83 bd de l'Hôpital, 75013 Paris, France., ***Tel***: +33142161950, ***Fax***: +33142161958, ***E-mail address***: marie-laure.welter@psl.aphp.fr

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Summary

Deep brain stimulation (DBS) of the subthalamic nucleus and internal globus pallidus deep brain stimulation provides an efficient treatment for the alleviation of motor signs in patients with Parkinson's disease. The effects of DBS on gait and balance disorders are less successful and may even lead to an aggravation of freezing of gait and imbalance. The identification of a substantia nigra pars reticulata (SNr)-mesencephalic locomotor region (MLR) network in the control of locomotion and postural control and of its dysfunction/lesion in PD patients with gait and balance disorders led to suggestion that DBS should be targeting the SNr and the pedunculopontine nucleus (part of the MLR) for PD patients with these disabling axial motor signs. However, the clinical results to date have been disappointing. In this review, we discuss the effects of DBS of these basal ganglia and brainstem structures on the neurophysiological parameters of gait and balance control in PD patients. Overall, the data suggest that both STN and GPi-DBS improve gait parameters and quiet standing postural control in PD patients, but have no effect or may even aggravate dynamic postural control, in particular with STN-DBS. Conversely, DBS of the SNr and PPN has no effect on gait parameters but improves anticipatory postural adjustments and gait postural control.

Keywords: Deep brain stimulation, gait, balance, Parkinson's disease

Résumé

La stimulation cérébrale profonde du noyau sous-thalamique (NST) ou du globus pallidum interne (GPi) représente un traitement efficace des troubles moteurs de la maladie de Parkinson. Les effets de la stimulation cérébrale profonde (SCP) sur les troubles de la marche et de l'équilibre sont moins probants avec parfois une aggravation post-opératoire du freezing de la marche et/ou des chutes. L'identification du circuit

substantia nigra pas reticulata (SNr) –région locomotrice mésencéphalique (RLM), qui comprend le noyau pédunculopontin (NPP) comme ayant un rôle majeur dans le contrôle postural et la locomotion et de leur dysfonctionnement/lésion chez les patients parkinsoniens souffrant de troubles de la marche et de l'équilibre a permis d'envisager la SCP de ces régions cérébrales pour améliorer ces signes moteurs invalidants. Toutefois, les résultats cliniques ont été assez décevants. Dans cette revue, nous rapportons les effets de la SCP des ganglions de la base et du NPP sur les paramètres neurophysiologiques de la marche et du contrôle postural chez les patients parkinsoniens. En moyenne, la SCP du NST et du GPi améliore les paramètres locomoteurs et le contrôle postural en position statique, mais semble avoir peu ou pas d'effet sur le contrôle postural dynamique avec peut-être une aggravation, en particulier avec la SCP-NST. Inversement, la SCP de la SNr ou du PPN ne modifie pas les paramètres locomoteurs mais pourrait améliorer les ajustements posturaux anticipatoires et le contrôle postural dynamique.

Mots-clés: Stimulation cérébrale profonde, marche, équilibre, posture, maladie de Parkinson

Introduction

In 1987, high frequency stimulation of the thalamus was first proposed as a treatment for patients with tremor [7]. In accordance with experimental data obtained in animals models of Parkinson's disease (PD) [8], deep brain stimulation of the internal part of the globus pallidus (GPi-DBS), one of the major basal ganglia outputs, and subthalamic nucleus (STN-DBS) was employed for the treatment of PD and proved an efficient means of improving parkinsonian symptoms and alleviating levodopa-induced motor complications [111], with in addition a significant decrease of the dopaminergic drug treatment with STN-DBS [135]. Whereas the efficacy of DBS on segmental motor symptoms, i.e. rigidity, tremor and peripheral akinesia, is well established, its effect on axial disability remains controversial [36]. Published data mainly report an improvement of posture, gait and balance control after GPi or STN-DBS, with a greater improvement with STN-DBS providing that these symptoms were responsive to levodopa treatment before surgery [36,102,130]. However, the effects of DBS on balance (postural instability) and gait tend to decrease with time [23,38,105]. Moreover, some authors suggest that DBS may induce or aggravate freezing of gait and postural instability with falls in PD patients with DBS [46], but also in non-parkinsonian patients [139]. The role of stimulation parameter settings, in particular the frequency of stimulation has been suspected, freezing of gait being reported to be improved with low frequency STN stimulation (60-80 Hz) [88,103,138].

Besides the loss of dopaminergic nigrostriatal neurons, the neuropathological hallmark of PD, the role of additional brain dysfunction and/or lesions in the occurrence of balance and gait disorders has been recently pointed out. In PD patients, a loss of cholinergic neurons in the pedunculopontine nucleus (PPN), in the mesencephalic tegmentum, has been reported in fallers PD patients, with a decrease in thalamic

cholinesterase activity [12,13,60,67]. In normal and parkinsonian monkeys lesioning cholinergic neurons in the PPN induces gait and postural deficits resistant to levodopa treatment [51,67]. In line with these experimental data, low frequency PPN stimulation, thought to increase neuronal activity, has been tested in a few patients to improve freezing of gait and falls resistant to levodopa treatment and/or STN-DBS with disappointing and controversial results. In open label studies, PPN-DBS improved gait and balance in patients previously operated for STN-DBS, but also parkinsonian symptoms [69,121]. These first results have not been consistently confirmed in double-blind assessments [42,91,133]. However, a subjective improvement in the number of falls or freezing episodes has been frequently reported [42,127,133]. Lastly, high frequency stimulation of the substantia nigra pars reticulata (SNr), the other major basal ganglia output, has also been recently tested in PD patients to alleviate gait and balance disorders [25,132]. The combination of STN and SNr-DBS might specifically improve freezing of gait, whereas balance impairment remains unchanged [132].

In this review, we summarise the effects of DBS on neurophysiological parameters of balance and gait in PD patients. For this purpose, we first briefly describe the different DBS targets used in PD patients from an anatomical and functional point of view in relationship with known neural structures and networks involved in balance and gait control in humans. We then report the changes induced by DBS from a neurophysiological point of view on these two distinct, but interconnected, motor processes.

Deep brain targets and neural pathways for gait and balance control in human

Since the early experiments performed in invertebrate animals that revealed the predominant role of spinal cord central pattern generators (CPG), various brain cortical and subcortical areas have been identified as playing a major role in the control of gait and balance/posture in mammals. In mammals, cortical-basal ganglia-brainstem circuits modulate the central pattern generators (CPG) (see for review 95) that activate the organised and synchronised activation of forelimb muscles. In humans, the role of the CPG is still debated, gait being viewed as a higher-level motor activity (Figure 1).

At the subcortical level, in animals, postural muscle tone changes and/or locomotion can be induced by electrical or chemical modulation of the STN area, the brainstem reticular formation or mesencephalic locomotor region (MLR) that comprises PPN and the cuneiform nuclei (CN), the substantia nigra pars reticulata (SNr) and the cerebellum. Unilateral injection of GABAergic agents, producing functional lesions of the STN, induce postural asymmetry but not locomotion [33], whereas irreversible lesions produce both postural asymmetry and increased locomotor activity [2] . In both decerebrate cats and monkeys, electrical stimulation of the STN area generates locomotor activity while the animals' feet are in contact with a moving treadmill belt [34,52]. In freely moving rats, STN neuronal activity increases during locomotion, with some neural responses being related to the initiation and the termination of gait [116]. All in all, these data suggest that the STN is involved in postural control and locomotion. Similarly, electrical stimulation of the MLR or antagonist GABAergic agents injections induce suppression of muscle tone changes in forelimb muscles when performed into the caudal and medial part of the MLR, namely the PPN, and trigger quadrupedal locomotion when performed in its rostral and lateral part, namely the cuneiform nucleus (CN) [34,90,123,125]. These effects are abolished by concomitant electrical stimulation

of the SNr. When the SNr is electrically stimulated, postural muscle tone changes are generated and a delay in the initiation of locomotor activity is observed, with an interruption of walking at high stimulation intensities. These effects are abolished by the inactivation of the MLR (mainly in the PPN) [124]. This highlights the major role of the SNr-MLR system in promoting gait and postural control in animals, in particular for the automatic regulation of postural muscle tone and rhythmic limb movements during locomotion [124]. Finally, the MLR is thought to: 1) activate and control the level of activity of the CPGs, 2) control balance during gait, 3) adapt the on-going movement to external perturbations and 4) coordinate locomotion with other motor actions [96]. Beside its connection with the SNr, the PPN is widely connected with the basal ganglia system, in particular the STN and the parafascicular and centre-median (Pf-CM) of the thalamus, but also with the globus pallidus and the striatum. The PPN is also connected to the primary motor and premotor cortices, the supplementary motor area (SMA) and the frontal eye field (FEF). In the cerebellum, irreversible lesions produce abnormal locomotor pattern and imbalance, more specifically when performed in the vermis [134]. At the cortical level, the primary motor cortex has been reported to be mainly involved in complex gait tasks that require precise forelimb positioning (obstacle avoidance or direction changes) and the SMA for balance control during locomotion [6,32]. The posterior parietal cortex is also necessary to plan and execute gait pattern adaptations [6,84].

In human, the use of SPECT, TEP or NIRS allows real gait cortico-subcortical networks imagery. An activation of the premotor, primary sensorimotor, prefrontal, SMA, anterior cingulate, parahippocampal, fusiform and lingual gyri, precuneus and cuneus, superior parietal and visual cortices, cerebellar vermis with extension to the MLR and the thalamus has been reported after and/or during real gait [49,72,87]. At the

cortical level, perturbation of static balance induces dorsolateral prefrontal (DLPFC), medial precentral, SMA and posterior parietal cortex activation [85]. Mental imagery of standing position, swaying on a balance board, gait or running have been recently examined by using functional MRI or PET in healthy subjects. These studies demonstrated that imagining 1) standing in a static position induced preferentially vestibular, visual and somatosensory cortices, median thalamus, pallidum, striatum, dorsal pons, MLR and cerebellum vermis activation [63], 2) swaying on a balance board induced preferentially SMA, dorsal premotor, middle cingulate cortex, superior parietal lobule, putamen, ventrolateral thalamus, MLR and cerebellum vermis activation [43,68, 3) gait induced preferentially SMA, parahippocampical, fusigorm and lingual gyri, precuneus and cuneus, posterior cingulate and visual cortices, putamen, STN, MLR and cerebellar vermis and cortex activation with decreased activity in the vestibular and somatosensory cortices [63,66,72,79] (Figure 1) and 4) running induced preferentially cerebellar cortex and MLR activation with less cortical activity [63]. Lastly, neuronal recordings performed in PD patients demonstrate that mental imagery of gait [73,126], steps mimicking [99] and real gait [47] modulate MLR-PPN neuronal activity.

Finally, in humans and experimental animals, two distinct networks with : 1) the vermis-pons-MLR (lateral)-thalamus-vestibular-SMA-parietal posterior cortex and 2) the vermis-MLR (medial)-basal ganglia (putamen,STN)-fusiform, parahippocampic and sensorimotor cortices seem preferentially implicated in the control of balance and locomotion, respectively (Figure 1). In PD patients with gait, especially freezing of gait, and balance disorders these networks have been reported to be dysfunctional and/or lesioned, in particular the SMA, parietal posterior cortex, MLR and cerebellum with decreased cholinergic activity [11,44,56,112,114,119]. As previously briefly exposed, different structures of these two networks, i.e. the STN, GPi, SNr and MLR, have been

targeted for DBS to treat motor disability, including gait and balance disorders, in PD patients. In the subsequent part of this article, we report on the effects of DBS on neurophysiological parameters of gait and balance in PD patients.

Effects of deep brain stimulation on balance and gait control in PD patients

Balance and gait control can be assessed in humans by the use of specialised devices that enable kinematic (motion capture system), biomechanical (force platform) and electromyographic (surface electrodes) recording during standing, gait initiation or walking, under various conditions (quiet or perturbed standing, eyes open or closed, spontaneous or fast gait, etc…). In PD patients, many studies have reported changes in these various parameters in the absence of DBS or medical drug treatment, and the effects of levodopa treatment on them. Since the advent of deep brain stimulation in PD patients, relatively few studies have specifically dealt with the effects of DBS on balance and gait control parameters.

Effects of DBS on balance control

Effects of DBS in the quiet standing position

Body Position

Since it was first described, it has been reported that PD patients show an abnormal flexed posture when standing [97]. By precisely assessing the inter-segmental coupling and electromyographic activity, it has been reported that this abnormal posture is related to an abnormally high inter-segmental stiffness (in particular between the trunk and hip segments) [81] and higher background EMG activity with co-contraction [19,20,27,31]. An increased inclination of trunk, thigh and shank with respect to the vertical, with a related significant increase of external mechanical

moments acting at the hip and knee joints [27]. With levodopa treatment, all these parameters of standing body position are improved [20,27]. Similarly, STN-DBS reduces the forward trunk-bending with a trend toward a lower inclination of the thigh and significant decrease of the inclination of the shank, which induces a reduction of the mechanical moment at the hip and ankle. Leg muscles activity is also significantly reduced, with a similar effect on extensor and flexor groups [27]. Improvements are observed with both unilateral and bilateral STN-DBS [27,81], although changes are found to be more robust with bilateral DBS [27].

Centre of foot pressure displacement and velocity

The major parameters recorded to describe static posture and standing position are generally assessed by the use of a force platform which records the centre of foot pressure (CoP) displacements and velocities in the anteroposterior (AP) and mediolateral (ML) directions during quiet stance. Although in normal subjects without postural instability during quiet standing the CoP is perpetually in movement, it exhibits slow and short CoP displacements contained in a restricted area, preferentially oriented in the sagittal direction [136]. Among the postural sway measures yielded from CoP, the CoP velocity has been suggested to be most sensitive for detecting changes in balance ability due to aging and/or neurological diseases [80,108].

While in a standing position, PD patients as a result of their higher amplitude and faster upper and lower body displacements, AP and ML displacements and velocities of the CoP are increased to cover a large area. These abnormal parameters are frequently related to a history of falls and clinical imbalance 86. Both an abnormal anterior or posterior shift of the CoP average position has been reported in PD patients [27,53]. Dopaminergic replacement therapy appears ineffective in improving with these

parameters and as been reported in some cases to aggravate the situation with an increase in CoP displacements and area covered (Table 1) [53,76,107]. The effect of DBS on these parameters remains controversial (Table 1). Some studies report an improvement with a reduction in the CoP displacements and velocities, close to control values with both STN-DBS and GPi-DBS [26,53,107 27], whereas others report an aggravation with an increase in swaying [81] or no effect [76,93,94,128]. The posterior shift of the CoP in the standing position is also reduced by STN-DBS [27,53], but not to within the normal range, however. More recently, in relation to the clinical observations of an improvement in axial signs with low frequency STN-DBS, the effects of low (60 Hz) versus high (130 Hz) frequency of STN-DBS on CoP displacements and velocities during standing have been examined. Whatever the STN-DBS frequency or voltage, no significant change in the CoP velocities and ML displacements have been observed, although there was a decrease (improvement) in the AP direction with low frequency stimulation [128]. Lastly, the combination of levodopa treatment and STN-DBS results in an average effect of the two treatments taken separately, which may correspond to an improvement or a worsening [27,53,81].

Centre of foot pressure frequency

The increased stiffness and CoP velocities observed in PD patients lead to an increased CoP frequency in both AP and ML directions, in particular the 0.7-1.1 Hz range, with an asymmetrical mean CoP frequency between the two feet [81,107,109,131]. In addition, some patients exhibit a 5Hz power peak corresponding to postural tremor. Both levodopa, GPi and STN-DBS restored the CoP frequency values to the normal range [81,107,109,131] (Table 1). Conversely, the asymmetrical mean

frequency between the feet experienced is increased with levodopa but reduced by STN-DBS [107].

Effects of DBS on perturbed standing position

The sensory organization test is presumed to identify deficits in the processing of somatosensory, visual and vestibular information that contribute to dynamic postural control. The subject is placed on a force platform and by means of calibrated 'sway referencing' of the support surface and/or the visual surround, visual and somatosensory inputs are abolished creating sensory conflict situations. These conditions isolate the vestibular balance control, as well as stressing the adaptive responses of the central nervous system. In short, patients may display either an inability to make effective use of specific sensory systems, or inappropriate adaptive responses, resulting in the fallback use of less accurate sense(s). PD patients usually show difficulties in maintaining an upright stance when sensory feedback is limited, with increased sway [15], a reduced postural mean velocity and increased reaction times [26,118]. When the standing position is perturbed by an AP tilt or forward translation, PD patients are unable to move fast and react quickly enough to correct sudden perturbations, with increased and delayed destabilising medium and long latency response amplitudes resulting in an increase of the AP CoP displacements [10]. Finally, PD patients are unable to adapt their postural responses to functional demand with fixed gain [5]. Levodopa treatment has been reported to have no significant positive effect on these postural responses [10].

In PD patients, STN-DBS significantly improves postural control in the sensory deprived and incongruent conditions. The quality of postural sensorimotor strategies is improved, patient being able to provide better adapted responses to destabilisation with

increased agonist muscle activity duration [26,120], as well as during a rapid arm movement in standing position [9]. GPi-DBS also improves postural responses to platform perturbations [120]. The combination of STN-DBS and levodopa treatment induces a degradation of postural responses, whereas the combination of GPi-DBS and levodopa induces no such change [120].

Finally, conversely to that observed with levodopa treatment leading to a more or less severe degradation of static postural control, STN-DBS and GPi-DBS improve central integration of sensory feedback and reduce induced sensory conflicts [15,120] with an improvement in the processing of the sensory and internally generated signals necessary for postural control.

Effects of DBS on gait control

Effects of DBS on the initiation of gait (Table 2)

In healthy subjects, gait initiation comprises two parts: the preparation phase and the execution phase. During the preparation phase, different anticipatory postural adjustments have been described before raising the swing foot from the floor [28, 54,131]. From a biomechanical point of view, the CoP is first projected backward toward the swing leg (S1), then towards the heel of the stance leg (S2) to enable the contralateral foot to be raised from the ground and finally towards the tiptoe stance (S3). During this phase, the centre of mass (CoM) moves forward creating an AP disruption between the CoM and CoP positions. During the execution phase (swing phase), the vertical CoM velocity curve describes a V shape that corresponds to a forward fall that is restored before the foot hits the ground (braking index) [14,134]. Finally, just after the foot-contact, the CoP moves under the heel of the displaced foot, and then under the toe tips and so on… enabling the gait to smoothly progress [54,136].

In PD patients, in the absence of levodopa treatment, the APAs are perturbed with reduced AP and ML CoP displacement amplitude and velocity, longer duration and presence of atypical sequences of lateral and forward CoP displacements directed towards the stance leg [21,50,54]. The transition between the different phases (i.e. S1, S2, S3) is perturbed with high variability in the relative proportions of the 3 phases. These changes have been related to an abnormal interaction between the initial body fall and abnormal leg muscle baseline activity, i.e. persistent tonic activity in the triceps surae followed by activation of the antagonist tibialis anterior [28,54]. During the execution phase, the length and velocity of the first step are reduced with an increase in the double-stance duration [21]. Conversely, the cadence of the first step is not or mildly modified in PD patients, in comparison to age-matched controls [54]. The dopaminergic treatment improved APAs with a reduction of the APAs duration and an increase of the AP and ML CoP displacements and velocities [21,106]. The muscles activity pattern is also improved and the length and velocity of the first step significantly increased with levodopa treatment [21 ,106]. Conversely, the levodopa treatment does not significantly improve the balance control during the first step (as reflected by the braking index) [24,129].

The effects of STN-DBS on APAs differed from a study to another. It seems that STN-DBS generally induces an increase in the AP CoP displacement during the APAs whereas no change or an increase in the ML direction is seen [75,106,128]. Its effect on the APAs duration is also unclear with either a decrease [27] or no significant change being found [75,106,128]. Bilateral STN-DBS generates an improvement in the leg muscular imbalance coupling with a restoration of near normal patterns with a clearer inhibition of the triceps surae along with a more intense and synchronised recruitment of the tibialis anterior [27](Figure 2). Interestingly, unilateral STN-DBS produces similar

effects on the APAs of both the ipsi- and contralateral foot of the stimulated STN [27]. However, unilateral STN-DBS induces smaller changes in the AP and ML CoP directions compared to bilateral STN-DBS. The application of low-frequency (60 Hz) STN-DBS provoked no significant changes in the APAs in comparison to high-frequency (130 Hz), with an increased ML velocity during the S2 phase with both (low and high) frequencies at high voltages [128]. The combination of STN-DBS and levodopa treatment appears to improve both amplitude and duration of the APAs, that remain, however, significantly different from control values [106]. In addition to its positive effects on the APAs, STN-DBS significantly increased the length and velocity of the first step, similarly to levodopa treatment [25,27,75,106](Figure 2). Decreasing frequency of STN-DBS has no significant impact on step length and velocity of the first step [128]. The balance control during the execution of the first step (braking control) is also improved with bilateral STN-DBS in relationship with an increased stance leg soleus muscle activity during the swing phase [25](Figure 2).

When applied in the GPi, DBS appears to have little or no impact on the APAs (amplitude, velocity, duration) [106] but provokes an improvement of transfer of the CoP under the support leg with decreased shoulder amplitude, increased ankle velocity and time displacement [29]. The length and velocity of the first step significantly increases with a reduction in the double-stance duration [29,106]. Up to now, the effects of SNr-DBS on the APAs has not been reported but an improvement of balance control during gait initiation (braking index) has been observed in some PD patients with no significant change in length and velocity of the first step [25]. Low frequency unilateral PPN-DBS has been reported to increase the CoP displacement and velocity during the S2 phase with no change in the APAs phase duration [82]. This change was not significant when compared to the no-levodopa treatment condition, however [82]. Lastly, bilateral

PPN-DBS has been reported to significantly increase the ML CoP displacement during the APAs and decrease the double stance duration [133]. Conversely, the length and velocity of the first step were un-modified with PPN-DBS but increased after surgery, probably as a result of a lesioning effect [133].

Effects of DBS on automatic gait

In PD patients, in the absence of levodopa treatment, stride length and gait velocity are significantly lower than controls (reflecting gait hypokinesia) whereas the cadence has been generally reported unmodified or increased to compensate for the reduced length [1,92]. Other parameters have been also identified as of particular interest in PD patients: the stride-to-stride variability (or gait rhythm), the bilateral coordination of stepping and the double-stance duration, being related to freezing of gait and/or risk of falling [58,101]. Kinematic recordings also reveal a reduction in the angular excursion at leg joints, range of trunk torsion amplitude and lateral flexion, amplitude of arm and leg swing movements and forward bending of the trunk.

Both levodopa treatment and STN-DBS improve gait parameters with an increase in step length, gait velocity, angular leg excursion, reduced double-stance duration and normalisation of the leg muscles pattern [1,22,35,39,40,70,76,89,104,122,137] (Table 3). STN-DBS also reduces the spatial foot position asymmetry, stride-to-stride variability and inter-limb coordination, with a more physiological alternating gait cycle [57,64]. Decreasing frequency of STN-DBS has no or few significant impact on gait parameters [89,128]. The combination of levodopa treatment and STN-DBS produces a greater increase in gait velocity [35,40,57,78,122]. When applied in the GPi, DBS has been reported to also significantly increase gait velocity and decrease the double-stance duration [1,29], with also an increase or no change in step length, cadence and swing

time (Table 4). PPN-DBS alone induces no significant change in the gait velocity or upper and lower limbs movements [89,98] (Table 4). The combination of low frequency PPN (25 Hz) and STN (60 Hz) DBS seems to produce a higher increase in stride length and velocity than PPN or STN-DBS alone (with both 60 or 180 Hz) [89].

Discussion

Both STN and GPi DBS improve gait parameters and quiet standing postural control in PD patients. Its effects on dynamic and gait postural control, including the APAs, are still controversial, with on average a tendency to aggravate postural control with STN-DBS and with either no change or a small positive effect with GPi-DBS. Conversely, SNr and PPNa-DBS lead to no change in gait parameters but tend to improve APAs and gait postural control.

From a clinical point of view, the effects of DBS on gait and postural control have mainly been examined in relationship with their levodopa response. From a neurophysiological point of view, levodopa treatment has been reported to be ineffective at improving static and dynamic postural control, and may even worsen some parameters [10,24,48,81,107,120]. However, it is effective at improving APAs and the parameters of gait kinematics and biomechanics, with the restoration of leg muscle activity patterns to normal levels [24,27,106,128]. These data suggest that STN-DBS and levodopa treatment have similar positive effects on neurophysiological parameters of gait and postural control, with an additional improvement of gait velocity when both are combined [35,78,122,137]. This is in line with the strong relationship observed between the improvement of axial motor signs with levodopa treatment before surgery and STN-DBS after surgery [3,36,102,135]. Axial motor sign improvement is recognized as the major preoperative clinical parameter predicting best post-operative outcome [135]. Beside improvement, as well as with levodopa treatment, a disruption of APAs and both significant decreases and increases in the sway amplitude during quiet stance have been described with STN-DBS, with no or little effect on the poor compensation for external destabilising postural perturbation [61,81,104]. The APAs disruption and postural degradation could participate in both the occurrence or aggravation of freezing of gait

after surgery, as suggested for non-operated PD patients [62], and the increased fall rate reported in patients with STN-DBS but not with GPi-DBS [46]. These data suggest that STN-DBS operates on gait and postural control, at least partly, through the functional restoration of the dopaminergic systems [16,17]. How STN-DBS restores the dopaminergic transmission within the BG circuitry is not clearly established. In animals rendered parkinsonian and PD patients, STN-DBS decreases the increased STN neuronal activity, burst-type activity and abnormal oscillations [30], as well as the levodopa replacement therapy [74,77]. STN-DBS also provokes changes in other output and input structures with anti- and orthodromic activation resulting in a 'global' effect within the entire cortico-striato-pallido-thalamo-cortical system, with pattern regularisation and decreased abnormal oscillations [113]. However, some differences exist between the effects of STN-DBS and levodopa. Indeed, the dynamic and gait postural control have been reported to improve with STN-DBS whereas levodopa has no positive impact [25,120]. Moreover, the combination of STN-DBS and levodopa treatment induces greater increase in gait velocity compared to STN or levodopa treatment alone [35,41]. Conversely, a lower effect of levodopa treatment on APAs has been reported when combined with STN-DBS [106]. These observations suggest that the STN is *per se* involved in gait and balance control in human. In line with this hypothesis, electrical stimulation of the STN in normal animals induces locomotion [34]. In PD patients, modifying the electrical parameters or the site of the STN-DBS induced significant changes in dynamic postural and gait parameters. An increase AP CoP velocity during the unloading phase of gait initiation, regularisation of the cadence, improvement in leg coordination with reduced step length and velocity variability have been reported with lower frequency STN-DBS (60 Hz) [37,88,128] and greater increase in step length and velocity with dorsal *versus* ventral STN-DBS [65,83]. Lastly, recent imaging studies using

fMRI in healthy humans also show that the STN is activated during mental imagery of gait [72] and that PD patients with freezing of gait presented a disruption of the functional coupling between the STN (but also the GPi) and the sensorimotor and frontoparietal cortical regions [117].

The effects of GPi-DBS on postural and gait control are less clearly established. In the few studies reported, GPi-DBS seems to have little or no effect on static and dynamic postural control, with an improvement or no change in the APAs [29,106] but a significant increase in stride length, step length and velocity during active walking [1,71], but to a lesser extent than with STN-DBS [1,106]. Comparison of levodopa treatment and GPi-DBS revealed no clear relationship between the effects of these two treatments. This observation and the fact that in PD patients with GPi-DBS levodopa replacement therapy could not be reduced after surgery [45,110] suggest that GPi-DBS may act differentially on the cortico-BG-cortical network with no 'dopaminergic like' effect, maybe by the modulation of the descending pathways to the MLR. When DBS is applied in the SNr or in the PPN, dynamic postural control is improved with no significant impact on gait parameters [25,98,133]. These data suggest that 1) the GPi and the SNr, the two main basal ganglia output structures, are preferentially involved in locomotion and postural control, respectively and 2) the PPN is also preferentially involved in postural control, depending on their level of activity. This hypothesis is in line with data obtained in animals and humans. In normal primates, injections of GABAergic agents in the GPi induce dystonic and choreiform limb movements whereas it produces severe axial postural anomalies when injected in the SNr [18]. In decerebrate cats, local inhibition of the SNr by GABAergic agonist agents (eg muscimol) induces locomotion and lowers leg muscle tone with the reverse effects when excitatory high frequency electrical stimulation is applied [123,124]. In parkinsonian monkeys, SNr

lesions produce a reversal of body orientation, with no improvement in bradykinesia [59]. In PD patients, high frequency SNr also leads to axial motor changes with an improvement of clinical gait and postural stability [25,132] and an increase in dynamic postural control [25]. As the SNr projects GABAergic inputs to the MLR, the effects of the SNr-DBS on gait and postural control may be related, at least partly, to a modulation of the MLR-PPN activity. In PD patients, low frequency PNN-DBS does not affect gait parameters but improves postural control [98,133]. This could result from the partial restoration of the cholinergic pathway to the basal ganglia, thalamus and to the descending pathways to the spinal cord 55. Indeed, PPN-DBS generates cerebral blood flow increases in the thalamus, cerebellum and midbrain region [4] and restores the H-reflex [100]. PPN-DBS also improves the connectivity between the PPN and the SMA, shown to be defective in PD patients with freezing of gait [115].

Finally, all these data suggest that two main subcortical networks are involved in gait (gait length, velocity and rhythmicity) and balance (static and dynamic posture) control in humans, the first comprising mainly the subthalamo-pallidal-MLR pathway and the second the subthalamo-nigro-pedunculopontine pathway. These two subcortical networks are functionally connected with sensorimotor and frontoparietal cortices and a dysfunction across these two coordinated neural networks has been reported in PD patients with gait and balance disorders. Future studies are needed to further explore the specific role of these two networks in gait and balance control, in particular, high-resolution analyses with functional or metabolic brain imagery combined with precise neurophysiological assessment of balance and postural control.

Figure Legends

Figure 1. Anatomical structures and pathways involved in the control of gait and balance in human. *Left*: schematic representation of anatomical and cortico-subcortical networks; *Right*: Cortical and subcortical activations during mental imagery of gait in comparison to mental imagery of object movement (red: gait versus movement; blue: movement versus gait) in a healthy subject. Note an activation of the bilateral medial primary motor cortex (legs and trunk motor region), bilateral parietal cortex, cerebellum and the MLR. AC: Anterior Cingulate, BG: basal ganglia, CBL: cerebellar cortex, CBM: cerebellar vermis, FEF: frontal eye field, Fus: fusiform gyrus, GPe: external globus pallidus, GPi: internal globus pallidus, M1: primary motor cortex, MLR: mesencephalic locomotor region, PF: prefrontal cortex, pHip: parahippocampic gyrus, PreM: premotor cortex, SMA: supplementary motor area, RF: reticular formation, STN: subthalamic nucleus, Put: putamen, PPN: pedunculupontine nucleus, SNr: substantia nigras pars reticulata; S: somatosensorial cortex, Thal: Thalamus, V: visual cortices.

Figure 2. Effects of levodopa treatment and STN-DBS on biomechanical parameters of gait initiation in a Parkinsonian patient.

Curves represent from top to bottom, the mediolateral (ML) and anteroposterior (AP) CoP displacements, antero-posterior and vertical (V) CoM velocity. The mediolateral displacement of the CoP enables the measurement of the lateral displacement of the CoP before foot-off (mediolateral APAs) and the step width (W). The anteroposterior displacement of the CoP enables the measurement of the posterior displacement of the CoP before the foot-off (anteroposterior APAs) and the step length (L). With the anteroposterior velocity of the CoM, the maximum forward velocity (Vm) is measured at the end of the first step. The CoM vertical velocity curve enables the measurement of the position of V1 (negative peak of the CoM vertical velocity) and V2 (CoM vertical velocity

at the time of foot-contact) and the braking index ((V1-V2)/V1*100). Here, before surgery both wihtout (OFF) and with levodopa treatment (ON), the fall of the CoM is stopped when the foot touches the ground, i.e. no braking occurs (V1=V2). After surgery, with STN-DBS, vertical velocity of the CG describes a V shape indicating that an active braking occurs. Tibialis anterior (TA) and Soleus muscles activity of the stance and swing legs. t0: time of the first biomechanical event; HO = heel-off of the swing leg; FO1 = foot-off of the swing leg; FC = foot-contact of the swing leg; FO2 = foot-off of the stance leg.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Table 1. Effects of subthalamic nucleus deep brain stimulation on neurophysiological parameters of static postural control in PD patients

			Rocchi et al. 2002	Maurer et al. 2003	Rocchi et al. 2004	Vrancken et al. 2005	Colnat-Coulbois et al. 2005	Liu et al. 2005	Crenna et al. 2006	Guehl et al. 2006	Nilsson et al. 2009	Nantel et al. 2012	Vallabhajosula et al. 2015
n. of patients			6	8	5	14	12	11	10	7	7	28	19
Age (yrs)			61 ± 9	48 ± 8	60 ± 6	50 ± 8	59 (54-67)	54 ± 9	60 ± 5	57 ± 12	66 (59-69)	60 ± 8	62 ± 9
Disease duration (yrs)			16 ± 5	13 ± 7	19 ± 2	15 ± 4	112 (10-14)	14 ± 6	17 ± 6	13 ± 4	18 (10-22)	10 ± 5	14 ± 4
Time after surgery (months)			6	15 ± 11	6	18 ± 12	6	16 ± 10	10 ± 7	3	37 (15-70)	10 ± 2	35 ± 24
	LD	**DBS**											
Before surgery	OFF	-					X	X		X		X	
	ON	-					X	X		X		X	
After surgery	OFF	OFF	X	X	X			X	X	X	X		X
	OFF	ON	X	X	X			X	X	X	X	X	X
	ON	OFF	X	X	X	X		X	X	X			
	ON	ON	X	X	X	X	X	X	X	X		X	
UPDRS III	OFF	-					49 (44-58)	41 ± 7		37 ± 7		36 ± 13	
	ON	-					15 (11-22)	26 ± 10		11 ± 6		18 ± 9	
	OFF	OFF	58 ± 26	49 ± 16	64 ± 6				62 ± 11	35 ± 11	41 (35-84)		29 ± 2
	OFF	ON	36 ± 17	7 ± 3	40 ± 13			26 ± 10	21 ± 10	13 ± 5	22 (11-31)	11 ± 8	24 ± 2
	ON	OFF	26 ± 8	14 ± 7	26 ± 5	51 ± 10			24 ± 14	12 ± 7			(No difference 60 vs > 100
	ON	ON	25 ± 2	4 ± 2	20 ± 6	31 ± 8	14.0 (9-19)	21 ± 9	13 ± 7	6 ± 4		8 ± 7	Hz DBS-STN)
DOPA effect	No change			PF tilt response				CoP ML/AP D		CoP D CoP Area			
	Increase			CoP/UB/LB D (& var) CoP/UB/LB ML D (& var) CoP/UB/LB AP D (& var) CoP D RMS CoP A CoP/UB/LB D low Frequency CoP D mild Frequency UB-LB coupling	CoP AP&ML D CoP Velocity CoP RMS						CoP ML&AP D CoP ML&AP Velocity	
	Decrease			CoP/UB/LB Velocity CoP/UB/UL D high Frequency	CoP Frequency					CoP Post shift			
Effects of STN-DBS	No change		CoP D RMS asymmetry	PF tilt response		CoP ML/AP Velocity	CoP AP sway (Eyes open&close)	CoP ML/AP D	CoP L shift Thigh inclination Knee moment		CoP ML/AP D	CoP ML/AP D RMS CoP ML/AP Velocity	CoP ML/AP D, RMS CoP Amplitude CoP ML/AP Velocity & RMS (No difference 60 vs > 100 Hz DBS-STN)
	Increase			CoP/UB/LB D. CoP/UB/LB ML D. CoP/UB/LB AP D. CoP A CoP/UB/LB D low Frequency CoP D mild Frequency CoP/UB/LB V low Frequency UB-LB coupling								
	Decrease		CoP Velocity CoP V RMS asymmetry. CoP D RMS CoP D Frequency CoP D Frequency RMS asymmetry	CoP/UB/LB Velocity CoP/UB/UL D high Frequency	CoP Velocity CoP Frequency CoP AP&ML D CoP RMS	CoP ML/AP D CoP high Frequency	CoP area CoP ML D (Eyes open&close)		CoP P shift Trunk inclination Shank inclination Hip moment Ankle moment Limb extensors RMS Limb flexor RMS	CoP Post shift CoP D CoP Area			

Values are mean ± SD or mean (range); AP: anteroposterior; CoP: centre of foot pressure; D: displacement; DBS: deep brain stimulation; F: frequency; LB: lower body; LD: levodopa; ML: mediolateral; RMS: root mean square; STN: subthalamic nucleus; UB: upper body; V: velocity. An increase of the CoP displacements, velocities, RMS, asymmetry, frequency, body segment inclinations and muscles means an aggravation of static postural control. An increase in the upper-body/lower-body coupling means an improvement of body position.

Table 2. Effects of deep brain stimulation on neurophysiological parameters of gait initiation in PD patients

			Liu et al. 2005&2006	Crenna et al. 2006	Chastan et al. 2009	Rocchi et al. 2012	Vallabhajosula et al. 2015	Defebvre et al. 2002	Rocchi et al. 2012	Chastan et al. 2009	Mazzone et al. 2014	Welter et al. 2015
Target			**STN**	**STN**	**STN**	**STN**	**STN**	**GPi**	**GPi**	**SNr**	**Unilateral PPN**	**Bilateral PPN**
N of patients			11	10	7	15	19	7	14	7	10	4
Age (yrs)			54 (41-66)	60 ± 5	61 ± 7	61 ± 6	62 ± 9	58 ± 11	61 ± 8	61.0 ± 7	60 ± 7	62.0 ± 11.0
Disease duration (yrs)			13 ± 5	17 ± 6	18 ± 4	12 ± 5	14 ± 4	15 ± 3	13 ± 10	18 ± 4		15.8 ± 5.9
Time after surgery (months)			16 ± 10	10 ± 7	44 ± 20	6	39 ± 24		6	44 ± 20	12	4-6
	LD	**DBS**										
Before surgery	OFF	-				X		X	X	X		X
	ON	-				X		X	X	X		X
After surgery	OFF	OFF	X	X	X	X	X	X	X	X		X
	OFF	ON	X	X	X	X	X	X	X	X	X	X
	ON	OFF	X	X	X	X		X	X	X		X
	ON	ON	X	X		X		X	X		X	X
UPDRS III	OFF	-			31 ± 11	49 ± 12		50 ± 6	51 ± 18			48.5 ± 9.7
	ON	-			7 ± 5	21 ± 11		19 ± 6	29 ± 14			21.0 ± 6.2
	OFF	OFF	41 ± 7	62 ± 11	36 ± 14	51 ± 21	29 ± 2		47 ± 17	36 ± 14		45.5 ± 11.0
	OFF	ON	26 ± 10	21 ± 10	9 ± 7	34 ± 12	24 ± 2	31 ± 10	35 ± 18	9 ± 7	69.6 ± 21.4	48.3 ± 10.2
	ON	OFF	26 ± 11	24 ± 14	12 ± 6	35 ± 15			32 ± 13	-		26.0 ± 3.6
	ON	ON	21 ± 9	13 ± 7		21 ± 8		18 ± 6	23 ± 13	29 ± 15	2.8 ± 0.9	26.0 ± 10.2
Anticipatory Postural Adjustments												
Effects of LD	No change		APAs duration&amplitude Stance & swing leg shear forces CoP AP & ML D					S1 duration				
	Increase					CoP AP & ML D		S2 ankle peak Velocity S2 shoulder amplitude Velocity of transfer	CoP AP & ML D			CoP AP & ML D
	Decrease					APAs duration		S2 duration	APAs duration			APAs duration
Effects of DBS	No change		CoP ML D APAs duration			CoP AP & ML D APAs duration	S1&S2 duration S1&S2 CoP D&Velocity	S1 duration	CoP AP & ML D APAs duration		APAs duration S2 CoP ML D S2 CoP Velocity	APAs duration
	Increase		Co AP D	CoP AP & ML D TA reinforcement			S3 CoP AP Velocity S3 CoM distance Resultant CoM-CoP moment arm	S2 ankle peak Velocity S2 shoulder amplitude Velocity of transfer			S1 CoP AP D S1 CoP Velocity	CoP AP & ML D
	Decrease		Stance & swing leg shear forces	APAs duration				S2 duration				
First step execution												
Effects of LD	No change				Braking index TA and Soleus activity					Braking index TA and Soleus activity		
	Increase				Length and velocity	Length and Velocity			Length and Velocity	Length and Velocity		Length and Velocity Braking index
	Decrease				Fall in the CoM					Fall in the CoM		Double stance duration
Effects of DBS	No change		Cadence	Length and Velocity	Stance leg TA activity Stance & swing leg sole	Length and Velocity	Length and Velocity Var Time Var		Length and Velocity	Length and Velocity TA and Soleus activity		Length and Velocity Braking Index
	Increase		Velocity		Length and velocity Braking index Stance leg soleus activity		Length and Velocity (higher with 60 Hz vs > 100 Hz STN-DBS)			Braking index Stance leg soleus activity		
	Decrease				Fall in the CoM						CoP Velocity	Double stance duration

Values are mean ± SD or mean (range); AP: anteroposterior; APAs: anticipatory postural adjustments; CoP: centre of foot pressure; CoM: centre of mass; D: displacement; DBS: deep brain stimulation; F: frequency; LD: levodopa; ML: mediolateral; STN: subthalamic nucleus. An increase of the APAs amplitude, CoP displacements, velocities, cadence, braking index and lower limbs muscles activities and angles means an improvement in the spatiotemporal and kinematics parameters of gait initiation. An increase of the APAs duration and double stance duration means an aggravation of gait initiation.

Table 3. Effects of subthalamic nucleus deep brain stimulation on neurophysiological parameters of gait in PD patients

			Allert et al. 2001	Faist et al., 2001	Stolze et al., 2001	Xie et al., 2001	Ferrarin et al., 2002	Bastian et al., 2003	Krystkowiak et al., 2003	Ferrarin et al., 2005	Liu et al., 2005	Lubik et al., 2006	Hausdorff et al., 2009	Johnsen et al., 2009&2010	Cantiniaux et al., 2011	McNeely et al., 2011	Vallabhajosula et al., 2015
n. of patients			8	8	9	10	4	6	10	10	11	12	13	11	7	16	19
Age (yrs)			57 ± 3	48 ± 7	56 ± 7	56 ± 10	56 ± 3	54 ± 13	57 ± 8	52-68	54 (41-66)	62 ± 8	64 ± 9	61 (41 - 69)	65 ± 5	62 ± 9	62 ± 9
Disease duration (yrs)			12 ± 5	13 ± 7	13 ± 5	13 ± 5	19 ± 6		13 ± 5	17 ± 6	13 ± 5		13 ± 6	13 ± 4	13 ± 4	15 ± 6	14 ± 4
Time after surgery (months)			3	15 ± 11	3	6 (3-36)	11 ± 3	8 ± 2	3	10 ± 7	16 ± 10	23 ± 13	12 ± 7	19 (12 – 30)	10 ± 7		39 ± 24
	LD	**DBS**															
Before surgery	OFF	-	X		X				X		X					X	
	ON	-	X		X				X		X					X	
With STN-DBS	OFF	OFF		X	X	X	X	X		X	X	X	X	X	X	X	X
	OFF	ON	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	ON	OFF		X		X				X	X	X	X		X		
	ON	ON		X	X	X			X	X	X	X	X		X		
UPDRSIII	OFF	-	17 ± 4	50 ± 15	52 ± 8				52 ± 16		41 ± 7					36 ± 2	
	ON	-	6 ± 5	8 ± 3	18 ± 4				25 ± 8		26 ± 11					29 ± 2	
	OFF	OFF	15 ± 4	49 ± 16		43 ± 13	59 ± 8	47 ± 10		62 ± 11	19 ± 9	56 ± 12	31 ± 13	38 ± 13	37 ± 17		29 ± 2
	OFF	ON	6 ± 4	14 ± 7	27 ± 7	19 ± 10	18 ± 8	22 ± 13	26 ± 7	21 ± 10		31 ± 5	18 ± 1	17 ± 8	16 ± 13		24 ± 2 (>100 Hz)
	ON	OFF	9 ± 5	7 ± 3		19 ± 14				24 ± 14	18 ± 8	21 ± 5	20 ± 12		11 ± 8		25 ± 2 (60 Hz)
	ON	ON	6 ± 5	4 ± 2	20 ± 7	13 ± 9			14 ± 5	13 ± 7		20 ± 5	9 ± 5		9 ± 7		
Effects of LD	No change			Cadence (& Var) Stride Length Var Velocity Var SL Support	Cadence	Cadence Stride Time SL&DL Support			SL Support	Cadence SL/DL Support Pelvis yaw ROM Trunk pitch ROM & mean Ankle moment & power peak	Cadence Velocity	Cadence Step Length SL Support Asymmetry Index	Cadence Stride Time (&Var) SL Support Var		Cadence		
	Increase			Velocity Stride Length Swing Velocity Hip, knee, ankle ROM	Velocity Stride Length Step Height Hip, knee, ankle ROM	Velocity Stride Length			Velocity Cadence Stride&Step Length SL/DL ratio	Velocity Stride Length Hip, knee, ankle ROM Pelvis tilt&roll ROM Trunk roll&yaw ROM Hip moment&power peak		Velocity	Velocity Stride Length SL Support		Velocity Step Length		
	Decrease			DL Support					DL Support Stride&Step Time			Step Time DL Support					
Effects of STN-DBS	No change		Cadence Step Time Asymmetry Index DL Support Var	Cadence Stride Length Var Velocity Var SL Support	Cadence	Cadence Stride Time SL&DL Support	Cadence SL/DL Support Ankle ROM Pelvis roll ROM Trunk yaw ROM	Cadence Asymmetry Index SL Support		Cadence SL/DL Support Pelvis roll & yaw ROM Trunk-Pelvis roll ROM Trunk pitch ROM Hip moment peak Ankle moment & power peak	Cadence	Cadence Step Length SL Support	Cadence Velocity Stride Length Stride Time (& Var) SL Support Var	Cadence Stride Time	Cadence		Cadence Var Velocity Var Stride Time Stride Length SL&DL Support (& Var)
	Increase		Velocity Step Length SL Support SL/DL Support	Velocity Stride Length Swing Velocity Hip, knee, ankle ROM	Velocity Stride Length Step Height Hip, knee, ankle ROM	Velocity Stride Length Step Height	Velocity Stride Length Hip&Knee ROM Trunk pitch & roll ROM	Velocity Stride Length	Velocity Cadence Stride T & Length Step T & Length SL Support	Velocity Stride Length Hip, knee, ankle ROM Trunk-Pelvis yaw ROM Hip moment peak	Velocity	Velocity	SL Support	Velocity Step Length Stride Length Hip, knee, ankle ROM	Velocity Step Length	Velocity Stride Length	Velocity Step Length
	Decrease		Step T Var SL Support Var	DL Support	Stride Var				DL Support			Step Time Asymmetry Index DL Support		DL Support Asymmetry Index			

Values are mean ± SD or mean (range); DL: double-limb; SL: single-limb; Var: variability; ROM: range of motion, DBS: deep brain stimulation; LD: levodopa; TN: subthalamic nucleus; UB: upper body; An increase of the velocity, stride time, stride length, step time, step length, step height, SL Support, SL/DL ratio and cadence means an improvement of spatiotemporal and kinematics parameters of locomotion. An increase of the double limb support and asymmetry index means an aggravation of locomotion.

Table 4. Effects of deep brain stimulation of the GPi and PPN on neurophysiological parameters of gait in PD patients

			Allert et al., 2001	**Defebvre et al., 2002**	**Moreau et al., 2009**	**Peppe et al., 2010**	**Mazzone et al., 2014**
Target			GPi	GPi	Bilateral PPN*	Bilateral PPN*	Unilateral PPN
n. of patients			10	7	4	5	10
Age (yrs)			55 ± 10	58 ± 11		58 ± 9	60 ± 7
Disease duration (yrs)			11 ± 3	15 ± 3		16 ± 10	
Time after surgery (months)			3	3		3	12
	LD	DBS					
Before surgery	OFF	-	X				
	ON	-	X				
With DBS	OFF	OFF	X	X	X	X	
	OFF	ON	X	X	X	X	X
	ON	OFF		X	X	X	
	ON	ON		X	X	X	X
UPDRS III	OFF	-	17 ± 4.5	50 ± 6			
	ON	-	6 ± 5.5	19 ± 6			5.3 ± 3.0
	OFF	OFF				68 ± 5	
	OFF	ON		31 ± 10	28	43 ± 9	70 ± 21
	ON	OFF				37 ± 10	
	ON	ON		16 ± 8		25 ± 9	28 ± 9
Effects of LD	No change			Cadence		Mean velocity	
	Increase			Velocity Stride T Stride Length Step Length SL Support		Hip, Knee, Arm &Elbow angles	
	Decrease			DL Support			
Effects of DBS	No change		Cadence Step Time&Length Asymmetry Index SL&DL Support (&Var) SL/DL Support	SL Support	Cadence Mean velocity Step Time&Length SL&DL Support	Mean velocity Stride&Step Length SL& DL Support SL/DL Support Hip, Knee, Ankle, ROM	Step Width SL& DL Support IL pelvis tilt ROM Hip, knee ROM
	Increase		Velocity	Velocity Cadence Stride Time&Length Step Length			Velocity Cadence Stride Length
	Decrease			DL Support			

Values are mean ± SD or mean (range); DBS: deep brain stimulation; DL: double limbs; IL: interlimb; T: time, SL: single limb; ROM: range of motion; GPi: internal part of the globus pallidus; PPN: pedunculopontine nucleus. An increase of the stride time and length, velocity, step length, SL Support and ROM means an improvement of gait parameters.. An increase of the DL Support and Step Width means an aggravation.* In this study patients were previously operated for STN-DBS.

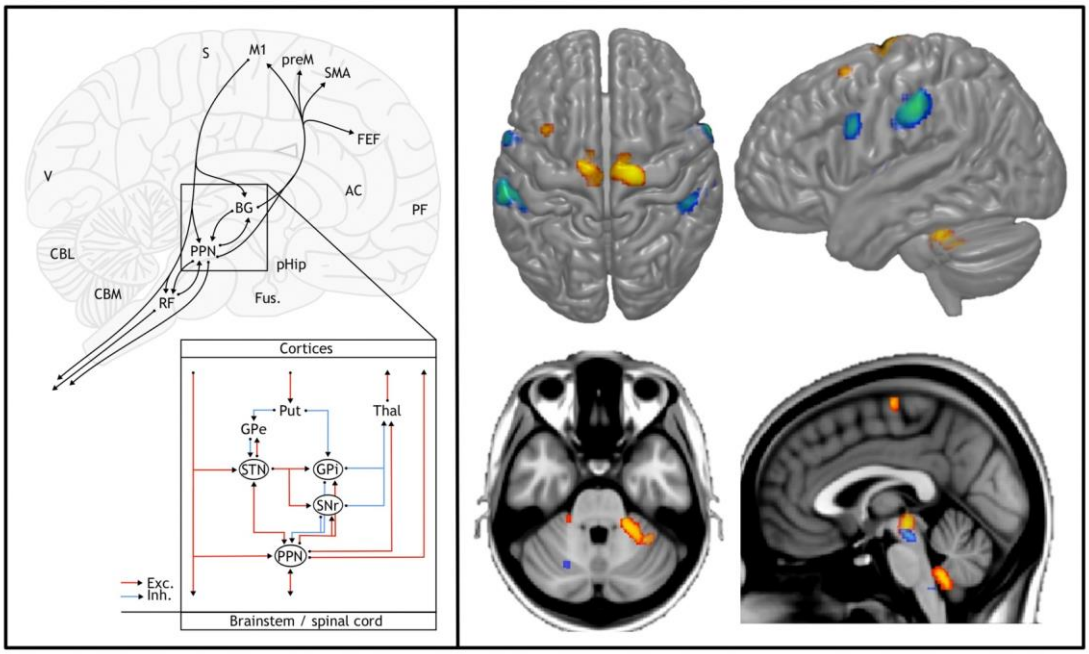
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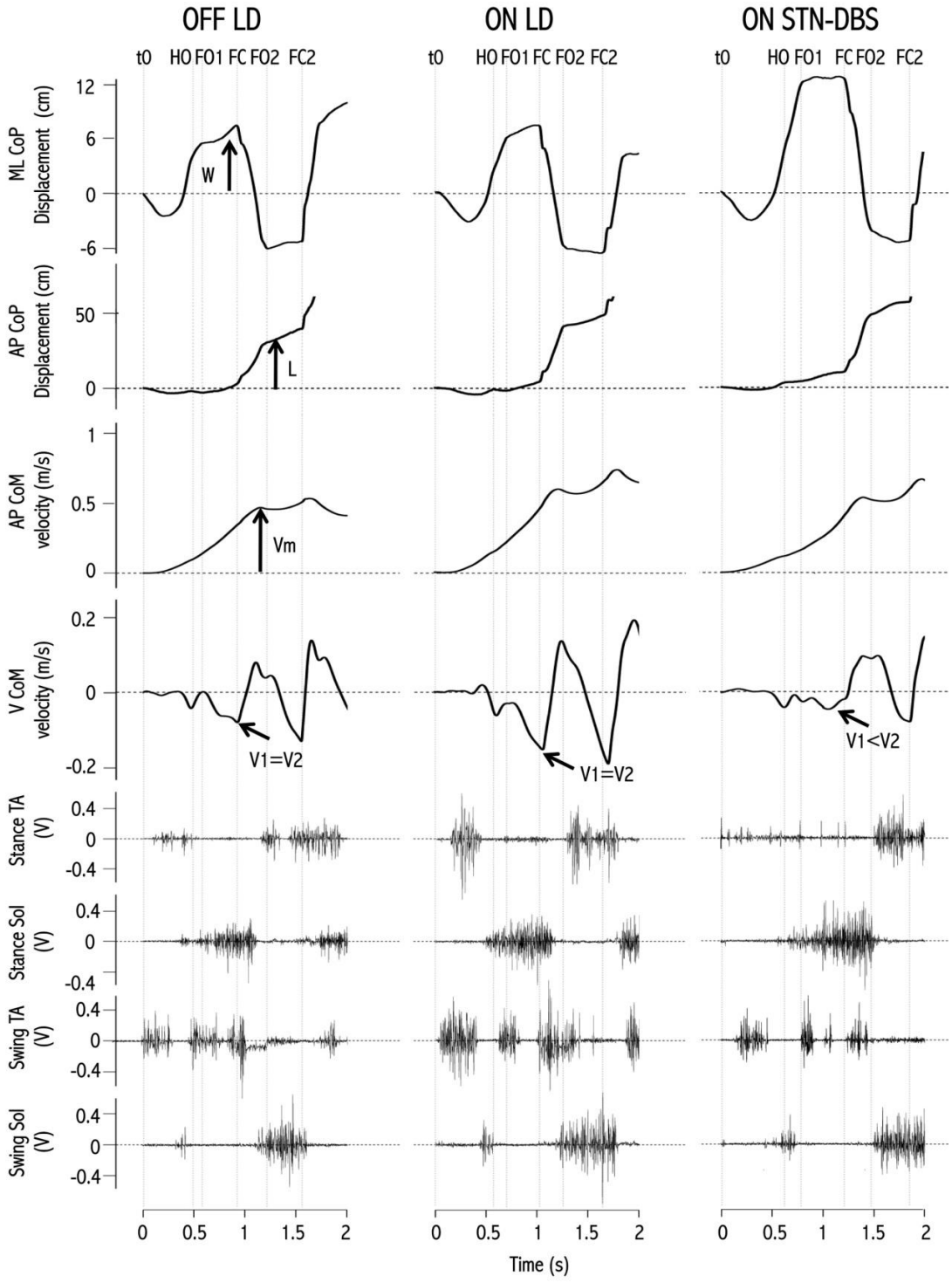
Figure 1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Swing TA (V)
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Time (s)

Figure 2