Virtual walking through a doorway promotes a beta-gamma power imbalance in the subthalamic nucleus in Parkinson's disease

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Marie-Laure Welter, MD, PhD,[1,2,3,4] Katia Lehongre, PhD,[1,5] Matthieu Faillot, MD, PhD,[1,6] Antoine Collomb-Clerc,PhD,[1] Hayat Belaid, MD, PhD,[1,6] Brian Lau,PhD,[1] Carine Karachi, MD, PhD.[1,5,6]

Affiliations:

1 Sorbonne Universités, Institut du Cerveau-Paris Brain Institute-ICM, APHP, Hôpital Pitié-Salpêtrière, Paris, France;

2 PANAM Platform, CENIR, ICM, Paris, France ;

3 Neurophysiology Department, Rouen University Hospital, CHU Rouen, Rouen, France;

4 University of Rouen, Rouen, France

5 STIM Platform, CENIR, ICM, Paris, France ;

6 Neurosurgery Department AP-HP, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, Paris, France;

Correspondence: ML Welter, Paris Brain Institute, France., ***Tel***: +33142165772, ***E-mail address***: marielaure.welter@icm-institute.org

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Letter to the Editor

Walking in humans requires continuous adjustment of locomotor patterns to internal and environmental constraints. Walking often takes place under complex constraints, such as navigating narrow passages, or multitasking. The neural mechanisms governing this adaptation are not fully understood. Functional MRI studies show activation of various cortical and subcortical brain regions during virtual walking tasks, passing through doorways seems to engage the basal ganglia (BG) and mesencephalic locomotor region (MLR).[1] Individuals with Parkinson's disease (PD) often experience freezing of gait (FOG), characterised by sudden walking blockage, especially during gait initiation or passing through doorways. Abnormalities in the cortico-BG-MLR pathways have been implicated in gait disorders in PD. Notably, subthalamic nucleus (STN) neuronal synchronization in the beta frequency range (13-35 Hz) has been linked to on-the-spot stepping, with an alternating low/high power related to contralateral leg heel-off/heel-contact, and higher beta band activity with gait interruption[2–4] This suggests that beta activity might contribute to FOG episodes. To further understand the relationship between STN neuronal activity, gait, and FOG in PD patients, we designed a virtual reality task (Figure A-B). Ten PD patients, who had undergone STN deep brain stimulation (DBS), participated in the study (INSERM, C11-40, N°IDRCD/GB-MOV) (eTable 1). All patients signed an informed consent form in accordance with the Declaration of Helsinki, and the protocol received approval from the local ethical committee (Paris 6, Pitié-Salpêtrière Hospital, see supplementary material). We recorded STN local field potentials (LFPs) bilaterally while patients performed the virtual waking task (Figures A-B-C). The task simulated walking through a hallway, with or without passing through a doorway (Figures A-B).[1] As a control, we used a virtual moving walkway. Four conditions were tested: 1) virtually walking ("GAIT" condition), 2) virtually gliding smoothly

on a moving walkway ("WALKWAY" condition), 3) and 4) virtually walking or gliding along the hallway through a narrow open doorway ("GAIT DOORWAY" and "WALKWAY DOORWAY" conditions). The motion speed of the virtual environment was adjusted to each patient's average normalized natural real gait speed in the hallway. Each run of the virtual gait task included 10 trials of each condition, being pseudo-randomized across trials. STN-LFPs recordings were performed OFF and ON-Dopaminergic medication (Dopa), segmented into trials and aligned according to the following events: Gait start, Door, Gait end (Figures D-G), from 2 s before to 2 s after the event and time to frequency domain transformed (see supplementary material). Power was calculated between 1 and 100 Hz, baseline corrected with rest periods and converted to decibels for subsequent analyses. We analyzed time-frequency data by fitting linear mixed models to predict estimated power at each time-frequency point. When testing task-induced modulations, we included as fixed effects the triple interaction for dopaminergic treatment (PD-OFF or PD-ON), task condition (GAIT or WALKWAY) and trial type (with or without DOORWAY). Our analysis revealed that comparing GAIT to WALKWAY conditions (Figure D), OFF-dopa, the low beta-band power significantly decreased after the start and before the end of the virtual GAIT. ON-dopa, low and high-beta band powers also decreased after the start of the virtual GAIT, during the doorway passage and at the end of virtual GAIT. We also found an increase in the low frequency activity at the end of the virtual GAIT. Comparing trials with and without DOORWAY (Figure E), we found no significant differences OFF-dopa. ON-dopa, the low-frequency activities decreased before the doorway passage and high-beta band activity increased at the end of the trials. During GAIT with *vs* without DOORWAY (Figure F), we found no significance differences OFF-dopa. ON-dopa, the low-beta band activity decreased during the doorway passage, accompanied by increased gamma band activity at the end of the trial. Lastly, during GAIT with DOORWAY

vs WALKWAY with DOORWAY (Figure G), we found no significant differences OFF-dopa. ON-dopa, the low-frequencies and beta band powers decreased after gait start, and the beta band at the door passage, while the low-frequencies and gamma band activity increased at the end of the trial. Our study sheds light on the dynamic nature of STN oscillations during walking tasks with decreased beta band activity at the doorway passage, increases at the end of the trial, and an additional increase in the low-frequency and gamma band activity at the end. This is in line with the recent reports showing an increased STN beta band activity during virtual gait or real walking in PD patients OFF-dopa, with increased beta and theta band activity found to be coincident to motor arrests or FOG episodes.[2,3] In our study, the greater decrease in theta and beta band activity found for trials with doorway, that started at gait initiation, may reflect the need for a higher cortico-subthalamic activity modulation to avoid motor blockage at the doorway passage. Increased beta band activity conversely occurred at the end of the trial, with an arrest of the virtual flow, and could correspond to a stop signal. Gamma band power was also higher ON- compared to OFF-dopa, as previously reported, and for gait trials with doorway. STN high frequency oscillatory activity was recently related to mesial cortical activity, and could thus reflect the anticipation of the end of walking flow when virtually walking.[5] Our study suggests a potential role of beta/gamma STN oscillations in modulating walking abilities, with imbalances in these power bands possibly contributing to gait impairments in PD, including FOG. Further research in this area could provide valuable insights into potential therapeutic interventions for managing gait disturbance in PD patients.

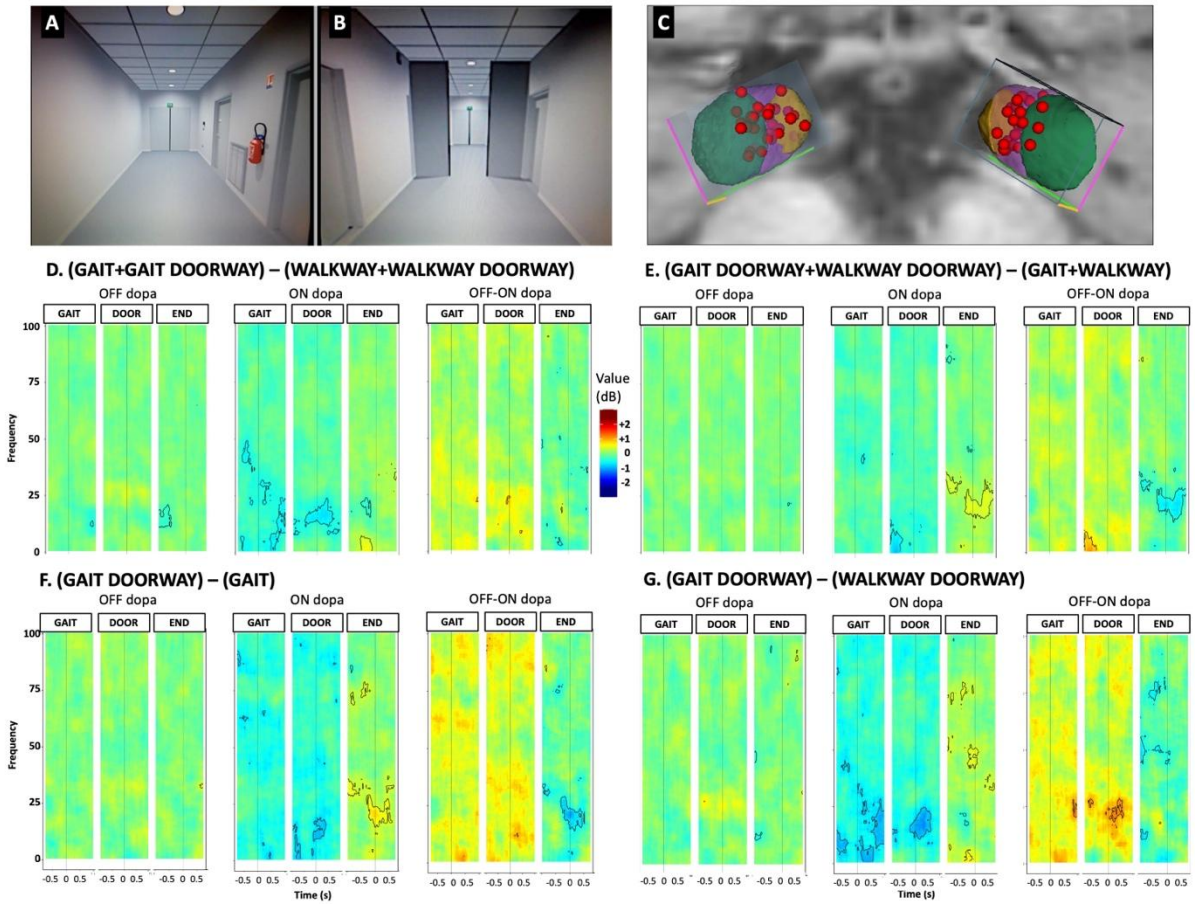

Figure. Effects of virtual gait task conditions on STN LFP neuronal activity

A. Virtual gait task without and B. with doorway.

C. Posterior view of the location of the STN LFPs dipoles,—reconstructed with the preoperative brain MRI and post-operative CT-scan. The STN subregions are represented in light green (posterior-motor), pink (central-associative) and yellow (anterior-limbic).

D. Averaged frequency maps of STN neuronal activity aligned with the start of the gait task (GAIT), door passage (DOOR), end of the gait task (END), recorded both OFF-(left) and ON-Dopa (middle), and the differences between treatment condition (right), for the differences between "GAIT" relative to "WALKWAY" trials, E. between "DOORWAY" relative "no DOORWAY" trials, F. between "GAIT with DOORWAY" relative to "GAIT" trials and G. between actively ("GAIT DOORWAY") relative to passively walking through doorway

("WALKWAY DOORWAY"). Black lines delimit significant clusters (false discovery rate corrected).

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Supplementary material

Virtual walking through a doorway promotes a beta-gamma power imbalance in the subthalamic nucleus in patients with Parkinson's disease. Welter et al.

Patients

Ten right-handed patients with Parkinson's disease participated in the study (eTable 1). The trial was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM, C11-40, N°IDRCD/GB-MOV) and received approval from the local ethical committee of Pitié-Salpêtrière Hospital. All volunteers signed an informed consent form in accordance with the Declaration of Helsinki.

Before surgery, all patients were familiarized with walking along a 10-meter-long hallway three times, at their natural speed, recorded with a stopwatch. For each patient, an average normalized gait speed (equal to gait speed/height) was calculated across trials.

Patients were then operated for STN DBS as usually performed at the Salpêtrière Hospital.[1] The STN was targeted using a combination of direct and indirect targeting as already described.[1] Quadripolar electrodes (model 3389-28, Medtronic, Minneapolis, MN) were implanted bilaterally with intraoperative microelectrode recordings and stimulation testing. Two external cables (model 3550-03, Medtronic, Minneapolis, MN) connected to the definitive DBS electrodes were placed following the electrode implantation. Definitive DBS electrode locations were determined by merging the postoperative CT scan and the preoperative MRI.

eTable 1. Demographic and clinical characteristics of PD patients

N°	Sex	Age	Disease duration	LEDD (mg/d)	UPDRS part III		
					OFF dopa	ON dopa	%improvement
P01	M	63	9	850	48	18	63
P02	M	71	8	1000	3	14	59
P03	M	42	10	1000	29	3	89
P04	M	48	11	700	37	10	73
P05	M	51	10	1260	27	4	85
P06	F	68	12	1000	30	4	87
P07	F	56	8	900	41	4	90
P08	M	65	14	1000	39	7	82
P09	F	64	14	1745	42	19	55
P10	F	51	11	550	25	2	92
Mean (SD)		**57.9 (9.6)**	**10.7 (2.2)**	**1000.5 (324.5)**	**35.2 (7.4)**	**8.5 (6.4)**	**77.5% (14.1)**

UPDRS = Unified Parkinson's Disease Rating Scale, OFF = Off dopa, ON= On dopa, LEED = levodopa equivalent daily dosage.

The virtual gait task

A virtual environment that closely mimicked the real hallway used for training was designed using 3D meshes with photorealistic textures and computer-generated lighting effects from

3D graphic software (Blender, The Blender Foundation, Amsterdam). Video game-like oscillations reproduced the oscillatory movements of the head while walking from a first-person perspective. These oscillations were absent for the control condition.

The virtual gait task consisted of four conditions.[2] The first condition was walking virtually along the hallway (Condition Gait, "GAIT"). The second condition consisted of virtually gliding smoothly on a moving walkway along the same hallway (Condition Walkway, "WALKWAY"). The third and fourth conditions were virtually walking or gliding smoothly along the same hallway through a narrow open doorway (Condition Gait with Open Doorway, "GAIT DOORWAY", and Condition Walking with Open Doorway, "WALKWAY DOORWAY"). The corridor was 7 m long and the position of the doorway within the hallway was fixed at 4.5m, with a width was of 83 cm.

The motion speed of the virtual environment was adjusted for each patient's average normalized natural gait speed for all four conditions. A PC running a 64-bit version of Windows 7 Professional Edition controlled stimulus presentation. For the task, the patient was seated approximately 50 cm in front of a computer screen. Before STN neuronal recordings were started, the patients were trained to perform the virtual gait task using a 15-inch screen display of the virtual environment, with the instruction to fixate their gaze on the end of the virtual hallway (Figure).

Each run of the virtual gait task included 10 trials of each condition (GAIT, WALKWAY, GAIT DOORWAY, WALKWAY DOORWAY). Conditions were pseudo-randomized across trials, ensuring that all conditions were presented, and two conditions of the same type never followed each other. Each trial began by displaying words on the screen to indicate the condition. When patients felt ready, they pressed a keypad with the right hand, which started the animation. At the end of each trial, the screen turned black indicating a 1-second rest period.

Subthalamic local field potentials recordings

We recorded STN LFPs 3 to 4 days after surgery, off and on levodopa. The off-levodopa recordings were done after an overnight withdrawal of dopaminergic medication. The on-levodopa recordings were done after administration of a suprathreshold dosage of dopaminergic medication (usual morning dosage plus 50 mg). For all patients, the experiment started with 2-minute recordings at rest while seated. The virtual gait task was then performed, with 1 to 4 runs per medication state.

LFPs were bilaterally recorded using definitive stimulating electrodes with 4 platinum-iridium cylindrical contacts (Medtronic, model 33-89, 1.27 mm in diameters, 1.5 mm in length), separated by 0.5 mm. Signals were digitized at 2024 Hz using an electroencephalogram amplifier (Porti system; TMSi, Oldenzaal, Netherlands) and re-referenced to a bipolar montage between adjacent contacts of the same electrode, yielding 6 recordings channels per patient.

Data analysis and statistics

The STN-LFPs were first segmented into trials (GAIT+REST), high-pass filtered at 1 Hz and visually inspected. Each trial was then aligned according to the following events: Gait start, Door, Gait end (Figure), from 2 s before to 2 s after the event, and transformed into the time-frequency domain using a multi-taper estimation algorithm implemented in the Chronux library (http://chronux.org). Power was calculated between 1 and 100 Hz using 3 orthogonal tapers with a time bandwidth product of 5, using 500 ms windows in steps of 30

ms. The time-frequency (TF) signal for each trial were normalized by dividing all points by a baseline spectrum obtained by averaging all time-points of the time-frequency maps over all rest periods of the same medication condition. Power of each baseline corrected trial was then log transformed (10.log 10) to decibels for subsequent analyses.

The anatomical localization of each dipole was assessed using a 3D histological and deformable atlas of the basal ganglia.[3] Only dipoles within the STN were kept for further analysis. For each trial and event realigned TF maps, dipoles with excessive noise were excluded after visual inspection of the TF map. Aborted rest periods and gait trials were also excluded from the analysis.

Statistical analyses were carried out to study the four main comparisons of interest: (GAIT+GAIT DOORWAY)-(WALKWAY+WALKWAY DOORWAY) to assess the effects of virtual gait versus walkway on STN neuronal activity, (GAIT DOORWAY+WALKWAY DOORWAY)-(GAIT+WALKWAY) to assess the effects of doorway versus no doorway, (GAIT DOORWAY)-(GAIT) to assess the effects of virtual gait with doorway versus gait without and (GAIT DOORWAY)-(WALKWAY DOORWAY) to assess the effects virtually actively versus passively-pass through the doorway.

We analyzed TF data by fitting linear mixed models to predict estimated power at each time-frequency point. When testing task-induced modulations we included as fixed effects the triple interaction for dopaminergic condition (PD-Off or PD-On), gait condition (gait or walkway) and trial type (with or without doorway). All models included random intercepts by dipole nested in patient. We used the false discovery rate to correct for multiple comparisons. Analyses were performed using MATLAB 2021a (The MathWorks, Inc., Natick, MA) and R version 4.2.2 (R Foundation for Statistical Computing Vienne, Austria) with lme4 package (v1.1-27.1, Bates et al., 2014, p.4) for GLMM fit, emmeans package (v1.7.2, Lenth, 2020) for post-hoc comparisons and model representation.

Supplementary References

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