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

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19

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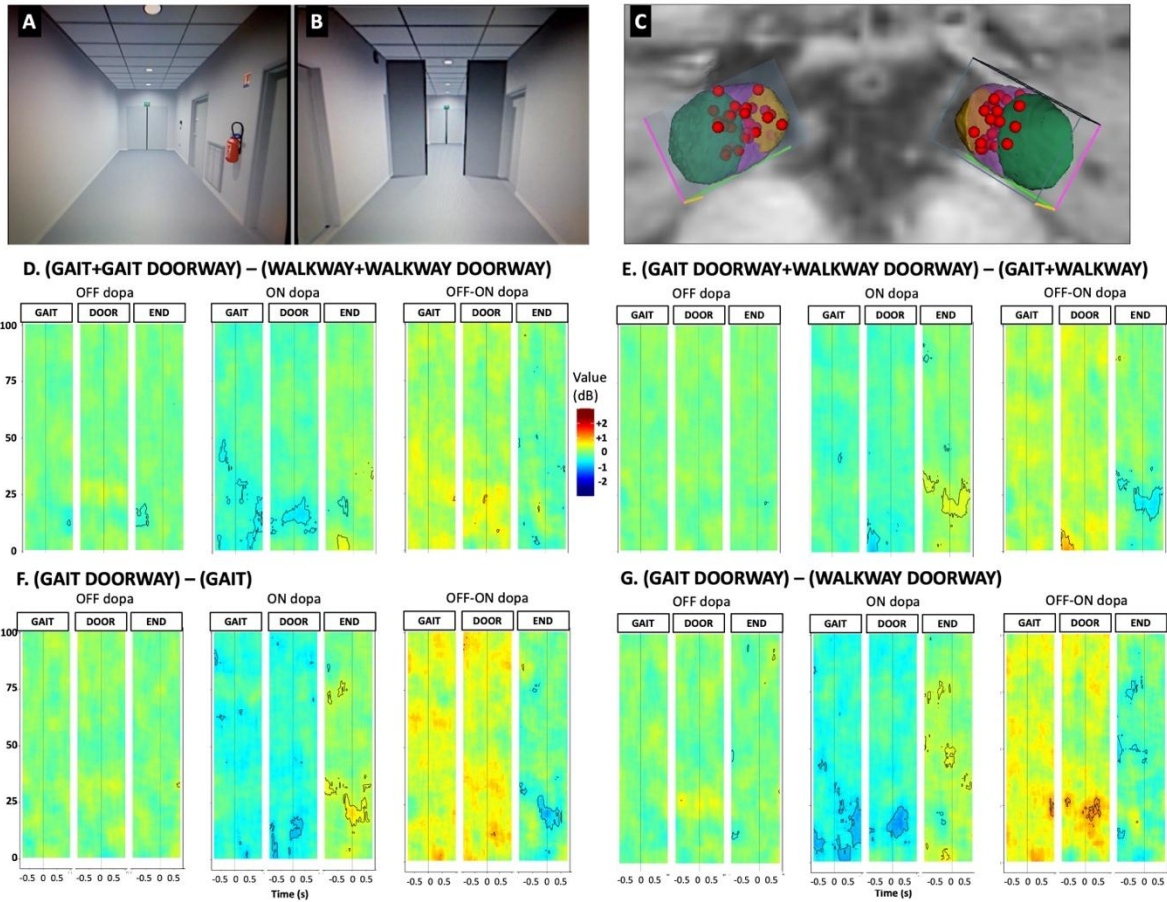
1 Letter to the Editor

2 Walking in humans requires continuous adjustment of locomotor patterns to internal and
3 environmental constraints. Walking often takes place under complex constraints, such as
4 navigating narrow passages, or multitasking. The neural mechanisms governing this
5 adaptation are not fully understood. Functional MRI studies show activation of various
6 cortical and subcortical brain regions during virtual walking tasks, passing through doorways
7 seems to engage the basal ganglia (BG) and mesencephalic locomotor region (MLR).¹
8 Individuals with Parkinson's disease (PD) often experience freezing of gait (FOG),
9 characterised by sudden walking blockage, especially during gait initiation or passing
10 through doorways. Abnormalities in the cortico-BG-MLR pathways have been implicated in
11 gait disorders in PD. Notably, subthalamic nucleus (STN) neuronal synchronization in the
12 beta frequency range (13-35 Hz) has been linked to on-the-spot stepping, with an alternating
13 low/high power related to contralateral leg heel-off/heel-contact, and higher beta band
14 activity with gait interruption²⁻⁴ This suggests that beta activity might contribute to FOG
15 episodes. To further understand the relationship between STN neuronal activity, gait, and
16 FOG in PD patients, we designed a virtual reality task (Figure A-B). Ten PD patients, who had
17 undergone STN deep brain stimulation (DBS), participated in the study (INSERM, C11-40,
18 N°IDRCD/GB-MOV) (eTable 1). All patients signed an informed consent form in accordance
19 with the Declaration of Helsinki, and the protocol received approval from the local ethical
20 committee (Paris 6, Pitié-Salpêtrière Hospital, see supplementary material). We recorded
21 STN local field potentials (LFPs) bilaterally while patients performed the virtual walking task
22 (Figures A-B-C). The task simulated walking through a hallway, with or without passing
23 through a doorway (Figures A-B).¹ As a control, we used a virtual moving walkway. Four
24 conditions were tested: 1) virtually walking ("GAIT" condition), 2) virtually gliding smoothly

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

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

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

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

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

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

1 (“WALKWAY DOORWAY”). Black lines delimit significant clusters (false discovery rate
2 corrected).

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1 **Supplementary material**

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

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5 **Patients**

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

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

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

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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		57.9	10.7	1000.5	35.2	8.5	77.5%
(SD)		(9.6)	(2.2)	(324.5)	(7.4)	(6.4)	(14.1)

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

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The virtual gait task

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

1 3D graphic software (Blender, The Blender Foundation, Amsterdam). Video game-like
2 oscillations reproduced the oscillatory movements of the head while walking from a first-
3 person perspective. These oscillations were absent for the control condition.

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

12 The motion speed of the virtual environment was adjusted for each patient's average
13 normalized natural gait speed for all four conditions. A PC running a 64-bit version of
14 Windows 7 Professional Edition controlled stimulus presentation. For the task, the patient
15 was seated approximately 50 cm in front of a computer screen. Before STN neuronal
16 recordings were started, the patients were trained to perform the virtual gait task using a
17 15-inch screen display of the virtual environment, with the instruction to fixate their gaze on
18 the end of the virtual hallway (Figure).

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

26 ***Subthalamic local field potentials recordings***

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

33 LFPs were bilaterally recorded using definitive stimulating electrodes with 4
34 platinum-iridium cylindrical contacts (Medtronic, model 33-89, 1.27 mm in diameters, 1.5
35 mm in length), separated by 0.5 mm. Signals were digitized at 2024 Hz using an
36 electroencephalogram amplifier (Porti system; TMSi, Oldenzaal, Netherlands) and re-
37 referenced to a bipolar montage between adjacent contacts of the same electrode, yielding
38 6 recordings channels per patient.

39 ***Data analysis and statistics***

40 The STN-LFPs were first segmented into trials (GAIT+REST), high-pass filtered at 1 Hz and
41 visually inspected. Each trial was then aligned according to the following events: Gait start,
42 Door, Gait end (Figure), from 2 s before to 2 s after the event, and transformed into the
43 time-frequency domain using a multi-taper estimation algorithm implemented in the
44 Chronux library (<http://chronux.org>). Power was calculated between 1 and 100 Hz using 3
45 orthogonal tapers with a time bandwidth product of 5, using 500 ms windows in steps of 30
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1 ms. The time-frequency (TF) signal for each trial were normalized by dividing all points by a
2 baseline spectrum obtained by averaging all time-points of the time-frequency maps over all
3 rest periods of the same medication condition. Power of each baseline corrected trial was
4 then log transformed ($10 \cdot \log_{10}$) to decibels for subsequent analyses.

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

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

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

27 **Supplementary References**

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29 subthalamic stimulation in patients with Parkinson disease. *Neurology*. 2014;82.
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