

# **Entrainning stepping movements of Parkinson's patients to alternating subthalamic nucleus deep brain stimulation**

Running title: Entrainning stepping to alternating STN DBS

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## 1    **Abstract (<250 words)**

2    Patients with advanced Parkinson's can be treated by deep brain stimulation of the subthalamic  
3    nucleus (STN). This affords a unique opportunity to record from this nucleus and stimulate it in a  
4    controlled manner. Previous work has shown that activity in the STN is modulated in a rhythmic  
5    pattern when Parkinson's patients perform stepping movements, raising the question whether the  
6    STN is involved in the dynamic control of stepping. To answer this question, we tested whether an  
7    alternating stimulation pattern resembling the stepping-related modulation of activity in the STN  
8    could entrain patients' stepping movements as evidence of the STN's involvement in stepping  
9    control. Group analyses of ten Parkinson's patients (one female) showed that alternating  
10   stimulation significantly entrained stepping rhythms. We found a remarkably consistent alignment  
11   between the stepping and stimulation cycle when the stimulation speed was close to the stepping  
12   speed in the five patients that demonstrated significant individual entrainment to the stimulation  
13   cycle. Our study provides evidence that the STN is causally involved in dynamic control of step  
14   timing, and motivates further exploration of this biomimetic stimulation pattern as a basis for the  
15   development of specific deep brain stimulation strategies to ameliorate gait impairments.

## 16    **Keywords**

17    Rhythmic stimulation, gait problems, freezing of gait, closed-loop control, basal ganglia

18

## 19    **Abbreviations**

20    **DBS**            Deep brain stimulation  
21    **altDBS**        Alternating deep brain stimulation  
22    **contDBS**       Continuous deep brain stimulation  
23    **STN**            Subthalamic nucleus  
24    **UPDRS**        Unified Parkinson's Disease Rating Scale

25

## 26 **Introduction**

27 Some of the most challenging symptoms for patients with Parkinson's disease are gait and  
28 balance problems as they can cause falls (Bloem, Hausdorff, Visser, & Giladi, 2004; Walton  
29 et al., 2015), loss of mobility and strongly reduce patients' quality of life (Walton et al., 2015).  
30 Deep brain stimulation of the subthalamic nucleus (STN) is an effective treatment for tremor,  
31 rigidity and bradykinesia in Parkinson's disease (Kleiner-Fisman et al., 2006). However, the  
32 impact of STN DBS on gait control is less consistent and can even result in deterioration of  
33 gait (Barbe et al., 2020; Collomb-Clerc & Welter, 2015). Conventional high-frequency DBS is  
34 provided continuously and is thought to attenuate beta activity (Kühn et al., 2008). Several  
35 reports describe changes in STN beta activity or its phase locking between hemispheres during  
36 gait (Arnulfo et al., 2018; Hell, Plate, Mehrkens, & Bötzl, 2018; Storzer et al., 2017), and our  
37 previous work has shown rhythmic modulation of STN activity when patients perform stepping  
38 movements (Fischer et al., 2018): Beta (20-30 Hz) activity briefly increased just after the  
39 contralateral heel strike during the stance period, resulting in alternating peaks of right and left  
40 STN activity. Auditory cueing, which also helps improve gait rhythmicity, further enhanced  
41 this alternating pattern (Fischer et al., 2018). However, whether such patterning helped  
42 organise the stepping behaviour or was secondary and afferent to it could not be discerned.  
43 Here we investigate whether STN activity is causally important in the dynamic control of  
44 stepping by assessing the entrainment of stepping by alternating high-frequency stimulation  
45 delivered to the two nuclei at a given individual's preferred stepping speed. We also studied  
46 whether their stepping speed could be manipulated by accelerating the rhythm of alternating  
47 stimulation.

48

49 **Materials and methods**

50 **Participants**

51 We recorded 10 Parkinson's patients (mean age  $67 \pm$  (STD) 7 years, disease duration  $14.2 \pm 4$   
52 years, time since DBS implantation  $3.8 \pm 1.3$  years, 1 female) with chronically implanted STN  
53 DBS electrodes, who had received DBS surgery 1-5 years previously at University College  
54 London Hospital (UCLH) in London (n=9) or at the Hadassah Hospital in Jerusalem, Israel  
55 (n=1). All patients were implanted with the Medtronic Activa-PC neurostimulator and the 3389  
56 macroelectrode model to alleviate their motor symptoms, and all patients were recorded in the  
57 UK. We considered patients younger than 80 years for this study. None of the participants had  
58 cognitive impairments, which were assessed with a mini mental score examination ( $\geq 26/30$  see  
59 **Table 1**). Interleaved stimulation as a DBS setting was an exclusion criterion because the  
60 streaming telemetry system Nexus-D (Medtronic, USA) that was used to control alternating  
61 stimulation cannot deliver interleaved stimulation.

62 The study was approved by the South Central - Oxford A Research Ethics Committee  
63 (17/SC/0416) and patients gave informed written consent before the recording.

64 Our main objective for this study was to find out if participants would entrain to the alternating  
65 DBS pattern and how their step timing would align to the stimulation pattern. Therefore, we

**Table 1 | Clinical details and stimulation parameters for all patients.** Patients who were significantly entrained to alternating DBS are highlighted in bold. No distinct differences between the group of responders and non-responders were apparent with respect to the stimulation intensity boundaries, location of the active contact, severity of motor symptoms or gait problems. The only criterion that stood out was the stimulation frequency, which was either 80 or 100 Hz in the group of responders. The four contacts on each electrode are labelled as 0-3 (ventral-dorsal) on the left electrode and 8-11 on the right electrode. The clinically effective stimulation intensity during standard continuous stimulation was set as *Upper threshold* (rounded to the first decimal place). *Stim threshold diff* was the difference between the upper threshold and the intensity during the periods of lower or absent stimulation during the alternating mode. This difference was the same in the two sides. All patients received stimulation with a pulse width of 60 $\mu$ s. GFQ = Gait and falls questionnaire (Giladi, 2000). LED = Levodopa equivalent dose.

Age	Disease duration (y)	Months since DBS	Preop. UPDRS OFF med	Preop. UPDRS ON med	Recording day UPDRS cont. DBS	Recording day UPDRS alt. DBS	GFQ	Freezing Yes/No	Mini-Mental Score	LED	Le STN contact location	Le Active contact	Le Upper threshold (V)	Ri STN contact location	Ri Active contact	Ri Upper threshold (V)	Stim. frequ. (Hz)	Stim. threshold diff. (V)	
P01	70	19	64	25	9	22	17	12	No	29	1413 mg	ventral STN	1	4	ventral STN	9	4	80	4
P02	71	13	54	29	12	35	30	21	Yes	29	384 mg	N/A	2	2.5	N/A	9	2.5	100	2.5
P03	69	10	16	41	11	21	29	34	Yes	29	739 mg	ventral STN	1	3.5	ventral STN	9	3.5	100	3.5
P04	57	18	42	49	9	28	33	42	Yes	28	1223 mg	dorsal STN	1	2	dorsal STN	9	2	100	2
P05	73	14	38	33	10	22	23	29	Yes	28	1333 mg	dorsal STN	1	2.5	dorsal STN	9	2.5	130	2.5
P06	66	20	41	64	22	23	24	13	Yes	30	645 mg	dorsal STN	2	3.5	+ dorsal STN	9+10	2.5	100	1
P07	70	9	69	35	4	16	18	8	No	27	966 mg	N/A	1+2	1	N/A	9	1	170	1
P08	69	9	38	92	31	26	27	3	No	30	1169 mg	dorsal STN	1	3	dorsal STN	9	3	80	3
P09	50	15	41	29	11	25	26	15	Yes	26	907 mg	N/A	1	1.8	N/A	9	1.8	130	1.8
P10	73	15	52	46	24	33	38	5	Not anymore	28	379 mg	midline STN	2	2.5	dorsal STN	9	3.5	80	1.2

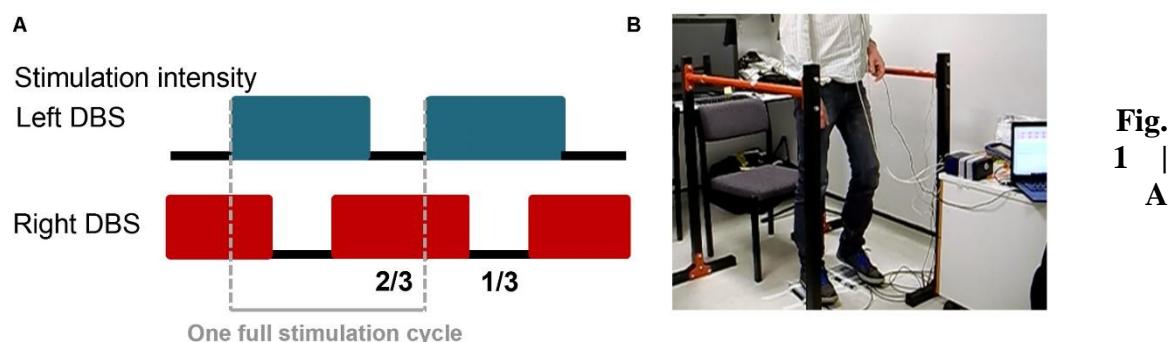
67 did not specifically recruit patients with severe gait impairments but also included patients  
68 that experienced no gait impairments such as freezing or festination. Patients' severity of gait  
69 impairments was assessed at the beginning of their visit with a gait and falls questionnaire  
70 (GFQ, Giladi *et al.*, 2000).

71

## 72 **Stimulation conditions and setting the DBS parameters**

73 All patients performed stepping in place while standing during three stimulation conditions:  
74 Conventional continuous DBS, alternating DBS at their preferred stepping speed and  
75 alternating DBS 20% faster than their preferred speed. We will refer to the latter as *fast*  
76 *alternating DBS* in the following sections. Some patients also performed the stepping  
77 movement when stimulation was switched off (n=5), but because time constraints allowed this  
78 only in half of all patients, this condition was not further analysed. All recordings were  
79 performed on medication to limit fatigue. Before changing DBS to the alternating pattern,  
80 patients' preferred stepping speed was measured during ~30s free walking and during ~20s  
81 stepping in place (while DBS was on continuously) with a MATLAB script that registered the  
82 time interval between key presses performed by the experimenter at the patient's heel strikes.  
83 Because of the highly predictable nature of the heel strike within the continuous stepping cycle,  
84 this measurement method provided a high accuracy, verified by comparing it to force plate  
85 measurements that resulted in nearly identical estimates. The key input method was chosen  
86 because it did not require any additional manual processing steps to obtain the final estimate  
87 and was thus faster. The final estimate was needed for the programming of the test conditions  
88 and was therefore needed as quickly as possible (on average, as it is, the study took 2.5 hours  
89 to complete). The key inputs were always performed by the same experimenter. The preferred  
90 duration of one full gait cycle was 1.2s in most cases (stepping in place: mean =  $1.27 \pm 0.22s$ ,  
91 ranging between 1.1-1.8s, free walking: mean =  $1.18 \pm 0.17s$ , ranging between 0.94-1.4s).

92 There was no significant difference between the two conditions ( $t_6 = 0.5$ ,  $p = 0.664$ ;  $df = 6$   
93 because the preferred speed of free walking was only measured in the final six patients). The  
94 median interstep interval from the stepping in place measurement was used to determine the  
95 duration of the stimulation cycles in the two alternating DBS conditions during stepping in  
96 place. The stimulation intensity and timing delivered by the chronically implanted pulse  
97 generator were remotely controlled by the Nexus-D device, which communicated via  
98 telemetry. The stimulation intensity was at the clinically effective voltage for two thirds of the  
99 stimulation cycle and was lowered intermittently only for one third of the full stimulation cycle  
100 (**Fig. 1A**). This rhythm was provided with an offset between the left and right STN such that  
101 the pauses occurred at opposite points within one full stimulation cycle. This 67/33% pattern  
102 was chosen because the technical limitations of Nexus-D would have not allowed a 50/50%  
103 pattern as the device requires gaps of at least 100ms to reliably send two consecutive commands  
104 (left up, right down, right up, left down, see **Fig. 1A**). We opted for 67% instead of 33% for  
105 the high-intensity stimulation period to keep the overall stimulation intensity relatively high in  
106 comparison to continuous DBS.



111 **Alternating DBS pattern.** DBS was set to the clinically effective voltage for 2/3 of the  
112 stimulation cycle and reduced for 1/3 of the cycle. For the reduced period, stimulation intensity  
113 was set to 0V in eight patients and it was reduced by -1V and -1.2V relative to the clinically  
114 effective threshold in the remaining two patients. The pattern was offset between the left and  
115 right STN such that the pauses occurred at exactly opposite points of the stimulation cycle.  
116 **B** Recording setup. Patients performed stepping while standing on force plates and were  
117 allowed to hold on to parallel bars positioned next to them if they felt unstable or if they felt  
118 more comfortable resting their arms on the bars.

120 A typical alternating stimulation cycle thus consisted of 0.8s (= 2/3 of 1.2s) of standard  
121 intensity stimulation (drawn from the clinically effective voltage during chronic continuous  
122 stimulation) and 0.4s (= 1/3 of 1.2s) of lowered intensity or no stimulation. The lower limit of  
123 alternating stimulation was determined by reducing the clinically effective voltage in steps of  
124 -0.5V and evaluating if the patient noticed a change until reaching 0V. If troublesome  
125 symptoms appeared before reaching 0V, the lower limit remained above the side effects  
126 threshold. In 8 of 10 patients the lower limit was set to 0V with patients reporting that  
127 alternating stimulation was well tolerated. In one patient (P06), reducing the lower limit by  
128 more than 1.2V resulted in reappearance of tremor and in another patient (P10) it caused  
129 headache at the forehead and slight tingling of the lips, which immediately disappeared when  
130 stimulation was switched back to the continuous mode. These two patients were the only  
131 participants with an upper stimulation threshold (based on their clinical stimulation settings)  
132 that differed between the left and the right STN (see P06 and P10 in **Table 1**). Their lower  
133 limits were set separately for the left and right STN to -1V (P06) and -1.2V (P10) below the  
134 upper thresholds, so that the patients were spared tremor and tingling. Other minor side effects  
135 in other patients were slight dizziness in one case and increased clarity, ‘as if a fog has been  
136 lifted’, in another case. Patients were informed of each change in stimulation intensity whilst  
137 the lower threshold for stimulation was sought.

138 Note that before using Nexus-D to switch to the alternating stimulation mode, the amplitude  
139 limits of the patient programmer option in the stimulator were adjusted with Medtronic  
140 NVision: We set the upper limit to ‘+0V’ relative to the clinical amplitude (drawn from the  
141 clinically effective voltage during chronic continuous stimulation) and the lower limit to ‘-  
142 clinical amplitude’ to ensure that the stimulation amplitude could never be increased above the  
143 clinically effective amplitude.

144

145 **Task**

146 Patients were asked to perform stepping in place on force plates (Biometrics Ltd ForcePlates)  
147 at their comfortable speed and maintain a consistent movement throughout the recording. Two  
148 parallel bars were placed to the left and right of the force plates to allow patients to hold on to  
149 them if they wanted more stability (**Fig. 1B**). Most patients rested their arms on the bars  
150 throughout the stepping in place recordings. P02 did not use the bars, and two patients (P06  
151 and P08) used them only intermittently as they found it less comfortable to hold on than to  
152 stand freely. The experimenter asked patients to ‘Start stepping whenever you are ready’. After  
153 about 20s they were prompted to stop and pause. For the first three patients the prompt was  
154 given verbally, and for the subsequent patients a mobile phone countdown triggered an auditory  
155 alarm after 20s to prompt the pause. The duration of the pauses was randomly varied (the  
156 shortest pause was 2.7s) and they could extend up to several minutes as patients were allowed  
157 to sit down and rest between the 20s sequences whenever they wanted. To control for any  
158 effects of fatigue that may increase with time, we chose to record the three conditions  
159 (continuous DBS, alternating DBS and fast alternating DBS) in the following order: A B C C  
160 B A, with 5-6 stepping sequences per block (except in patient P05 who completed only A B C  
161 as he was too tired to complete the full set). The order of the stimulation conditions was  
162 balanced across patients, so that A would in turn refer to continuous DBS, alternating DBS or  
163 fast alternating DBS. The stimulation was set to one mode for the whole duration of each  
164 experimental block without any pauses or resets between stepping sequences or rest intervals.  
165 Patients were not told what stimulation condition was active. They also did not report any  
166 conscious rhythmic sensations and thus could not discern the rhythm of the alternating  
167 stimulation. The experimenter controlled the stimulation modes using custom-written software  
168 and was thus aware of the stimulation conditions but was unaware of the precise timing of the  
169 stimulation onset when prompting patients to start stepping any time again. Either before or

170 after the stepping task, a blinded clinical research fellow performed the UPDRS-III motor  
171 examination (on medication), once during continuous DBS and once during alternating DBS.  
172 The order was randomized across patients so that continuous DBS was the first condition for  
173 half of all patients. Stepping in place provides only a proxy measure of stereotypical gait, but  
174 as part of the clinical examination a 20m free walking assessment was also performed in a  
175 corridor. For the first patients, Bluetooth communication was not yet available and one  
176 experimenter had to walk next to the patient carrying the laptop connected via USB with the  
177 Nexus-D. For the final six patients, Bluetooth communication between the laptop and Nexus-  
178 D allowed the patients to walk freely during both alternating DBS and continuous DBS.  
179 Alternating DBS was set to the individual's preferred speed that was recorded during free  
180 walking. In these six patients, we also measured the time and number of steps needed to  
181 complete a 10m straight walk, turn and return to the starting point. Note that the step timing  
182 relative to stimulation was not recorded during free walking, and thus the strength of  
183 entrainment could not be assessed. The complete visit lasted up to 2.5 hours including extended  
184 pauses between individual assessments.

185

## 186 **Recordings**

187 A TMSi Porti amplifier (2048 Hz sampling rate, TMS International, Netherlands) recorded  
188 continuous force measurements from the two force plates, which were taped to the floor, to  
189 extract the step timing. Triggers indicating the onsets of high-intensity stimulation were  
190 recorded with a light-sensitive sensor attached to the screen of the laptop that controlled  
191 stimulation timing via the Nexus-D. The screen below the sensor displayed a grey box that  
192 briefly turned black at the onset of high-intensity stimulation in the left electrode and white for  
193 the onset in the right electrode. DBS artefacts that captured if stimulation was on, and in which  
194 mode, were recorded with two bipolar electrodes attached to the back of the neck slightly below

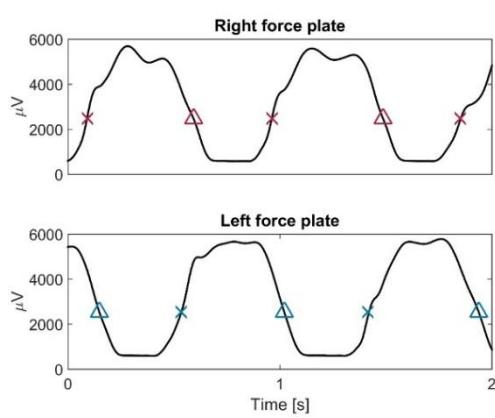
195 the ears. This measurement provided a simple check during the experiment that allowed us to  
196 see if the stimulation protocol was working.

197

## 198 **Data processing**

199 Heel strikes were identified in Spike2 (Cambridge Electronic Design Limited) based on the  
200 force measurements by setting a threshold for each patient to capture approximately the  
201 midpoint of each force increase (**Fig. 2**). The force measurement increased whenever weight  
202 was transferred onto a force plate. Note that the foot touched the force plate already slightly  
203 earlier, about 100ms before the heel strike event, however, considerable weight was only  
204 transferred on the leg by the time of the event. We used the same threshold for identifying when  
205 the leg was lifted, which was captured by a force decrease. Note here again that the foot was  
206 fully lifted off the plate only slightly after the event, however, the process of lifting the leg up  
207 was initiated already before then.

208 To avoid biasing the entrainment results by sequences that were several seconds longer than  
209 other sequences, which occurred occasionally when verbal prompts were used to prompt  
210 stopping, steps at the beginning and end of the longer sequences were removed, such that the  
211 remaining number of steps did not exceed the median number of steps of all the sequences.



**Fig. 2 | Force measurements and step cycle events.** x = heel strikes. The force increased during heel strikes. Δ = when the foot was raised from the force plate the force decreased.

212

213

214 Freezing episodes were very rare and were excluded from the analyses. They occurred in two  
215 patients (P03, P04) towards the end of the recording session without any apparent difference  
216 between conditions.

217

## 218 **Statistical analysis**

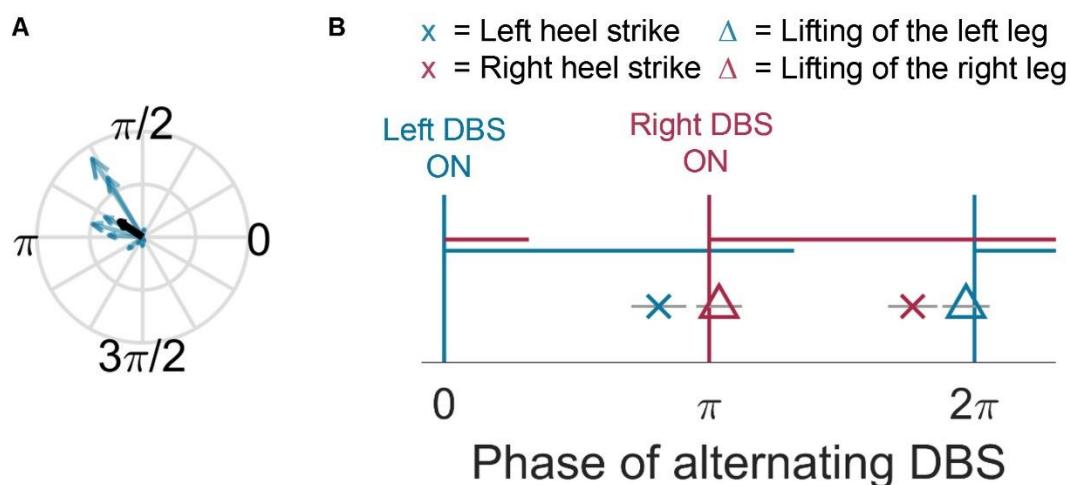
219 All analyses were performed with MATLAB (v. 2016a, The MathWorks Inc., Natick,  
220 Massachusetts). Here we define entrainment as significant alignment of the timing of steps to  
221 the rhythm of the alternating stimulation pattern. This alignment was evaluated with a  
222 Rayleigh-test (using the MATLAB toolbox CircStat; Berens, 2009) for each individual patient  
223 and with a permutation procedure at the group level that considers each individual's average  
224 timing and entrainment strength.

225 Whenever a heel strike occurred (tests are only reported for the left heel strikes, because p-  
226 values were highly similar for the right heel strike), the coincident phase of the rhythmic  
227 alternating DBS pattern was extracted. The uniformity of this resulting phase distribution was  
228 then assessed with a Rayleigh-test to test if individual patients showed significant entrainment.  
229 An additional permutation procedure was used to compute a group statistic across all ten  
230 recorded patients. For the group statistic, the vector length was calculated first for each patient

231 according to the formula  $\left| \frac{\sum_{s=1}^N e^{i\phi_s}}{N} \right|$ , where  $\phi_s$  is the phase of alternating DBS at each left heel

232 strike and  $N$  the number of all heel strikes. The grey dashed lines in Fig. 1A show the start and  
233 end of one full stimulation cycle, and the x-axis in Fig. 3B shows the phase of one alternating  
234 stimulation cycle. Note that whenever we show arrows representing phases, they always refer  
235 to the phase of alternating stimulation at the time of the patients' heel strikes and not to the  
236 phase of their stepping cycle, which was another cyclic measurement. The circular mean of

237 these phases was then computed to obtain the average ‘preferred’ phase for each patient. This  
238 resulted in ten vectors (one for each patient) with their direction representing the average  
239 preferred phase, and their length representing the strength of entrainment (blue vectors in **Fig.**  
240 **3A**). Next, they were transformed into Cartesian coordinates and the average of the ten vectors  
241 (black vector in **Fig. 3A**) was computed. The length of this average vector was obtained using  
242 Pythagoras’ theorem and was our group statistic of interest. It takes into account both the  
243 strength of entrainment and the consistency of the preferred phases across patients. If all  
244 patients would have shown strong entrainment, but with different preferred phases, the length  
245 of the group average vector would be close to zero. Only if the vectors representing individual  
246 patients pointed into a similar direction, the group average vector would be significantly larger  
247 than the one obtained from our permutation data.



**Fig. 3 | Entrainment at the group level.** **A** Blue vectors show the average phase of alternating DBS at all left heel strikes and the strength of entrainment for individual patients ( $n=10$ ). Long arrows show strong entrainment. The group average vector (black arrow) shows the average of the blue vectors. The length of this vector was significantly larger than in the surrogate data, demonstrating consistent alignment of stepping to the alternating DBS pattern across the group. **B** Group-averaged timing of key events of the gait cycle ( $\times$  and  $\Delta$ ) relative to the stimulation pattern. The blue and red horizontal lines indicate high-intensity stimulation of the left and right STN, respectively. The left heel strike (blue  $\times$ ) was made just before contralateral stimulation (right STN DBS shown in red) increased. Grey horizontal bars indicate the standard error of the mean phases across the patients.

255 We computed a permutation distribution of 1000 surrogate vector lengths by shifting,  
256 separately for each patient, each of their 20s long stepping sequences in time by a random offset  
257 drawn from a uniform distribution ranging between -1.5s and +1.5s. This way the rhythmic  
258 structure within the 20s stepping sequences remained intact and only their relative alignment  
259 to the stimulation pattern was randomly shifted. Once all sequences were randomly shifted, we  
260 computed the surrogate vector length and preferred phase for each patient as described above  
261 for the unpermuted data. The resulting ten surrogate vectors were again averaged in the  
262 Cartesian coordinate system to compute the average length as described above. After repeating  
263 this 1000 times, we obtained a p-value by counting how many of the surrogate group vector  
264 lengths ( $L_p$ ) were larger or equal to the original group vector length ( $L_{orig}$ ) and dividing this  
265 number by the number of permutations ( $N_p$ ). The number 1 is added to both the nominator  
266 and the denominator to avoid p-values of 0 and be consistent with the exact p-value, which  
267 must be at least  $\frac{1}{N_p}$  (see section 4.2 from Ernst, 2004):

$$268 \quad p\_value = \frac{1 + \sum_{p=1}^{N_p} f(L_p)}{1 + N_p}, \quad f(L_p) = \begin{cases} 0, & L_p < L_{orig} \\ 1, & L_p \geq L_{orig} \end{cases}$$

269 As we expected entrainment to be strongest when the stimulation speed matches the patient's  
270 stepping speed as closely as possible, the group statistic was based on the data from the  
271 alternating DBS condition that matched the patient's stepping speed most closely. All patients  
272 that showed significant entrainment indeed did so in the condition that was closest to their  
273 stepping speed. The stepping pace of several patients (P03-P08) was considerably faster during  
274 the recording than in the brief initial assessment, hence in those, the fast alternating DBS  
275 condition matched their performed stepping rhythm more closely.

276 Pairwise comparisons of the step intervals between the two alternating DBS conditions and of  
277 the change in variability between speed-matched alternating DBS and continuous DBS were

278 performed using two-tailed t-tests or Wilcoxon signed-rank tests (with an alpha-level of  
279 0.05) if the normality assumption (assessed by Lilliefors tests) was violated. To get a robust  
280 estimate for each patient and condition, first the median of all step intervals within each 20s  
281 stepping sequence was computed, and then again the median over all sequences was computed.

282 To investigate the step timing variability, we computed the coefficient of variation of the step  
283 intervals (STD / mean \* 100) as well as the standard deviation of the difference between two  
284 consecutive step intervals for each sequence. The median over all sequences was again  
285 computed to get a robust estimate.

286 To test in each patient individually if the step timing variability was significantly modulated  
287 by alternating DBS, we computed two-samples t-tests or rank-sum tests (if the normality or  
288 variance homogeneity assumption was violated) between the step timing variability estimates  
289 of the stepping sequences that were recorded in each DBS condition.

290

## 291 **Localization of the active electrode contacts**

292 Each DBS lead has four contacts of which only one or two are activated during stimulation.  
293 The location of the active contacts was assessed in Brainlab (Brainlab AG, Germany) by a  
294 neurosurgeon and a neurologist who manually drew the lead on the post-operative T1 MR  
295 images centered on the DBS electrode artefact. The position of the contacts within the STN  
296 was then assessed visually in the patients' pre-operative artefact-free T2 images. We did not  
297 have access to imaging data for P7 who received the surgery in Israel, and the quality of the  
298 imaging data was insufficient in two patients, so in these cases no accurate estimate of the  
299 contact position could be obtained.

300 **Data availability**

301 The data that support the findings of this study and custom code used for analyses are available  
302 from the corresponding author upon request.

303

304 **Results**

305 **Entrainment to DBS which alternates with a frequency matching that of stepping**

306 Ten patients with Parkinson's disease started sequences of 20s stepping in place while  
307 alternating DBS was already ongoing. Testing for significant entrainment of their steps to the  
308 stimulation pattern thus quantified to which extent patients aligned their stepping rhythm in  
309 each sequence to the ongoing stimulation pattern despite not being consciously aware of the  
310 precise pattern. An example of the recorded force plate measurements is shown in **Fig. 2**. **Fig.**  
311 **3A** shows significant entrainment of the stepping movement to altDBS at the group level  
312 compared to surrogate data ( $p=0.002$ ). The fact that all long vectors point into the same corner  
313 highlights that the preferred phase was remarkably consistent across patients. We also  
314 confirmed this finding using a simple Rayleigh test, comparing the preferred phases across  
315 patients irrespective of the strength of their entrainment, as this cannot be taken into account  
316 by a conventional Rayleigh-test. This demonstrated again significant clustering of three of the  
317 four stepping events (left heel strike  $p = 0.109$ , right heel strike:  $p = 0.033$ , left leg raised:  $p =$   
318  $0.020$ ; right leg raised:  $p = 0.015$ ).

319 On an individual level, half of the ten recorded patients showed significant entrainment in the  
320 speed-matched stimulation condition (**Table 2**). **Fig. 4A** shows two examples of patients that  
321 were significantly entrained and **Fig. 4B** shows one example of a patient that was not entrained.  
322 The two plots to the left show the stimulation phases coinciding with the left and right heel  
323 strikes. The plots to the right with fewer arrows show the preferred phase and strength of

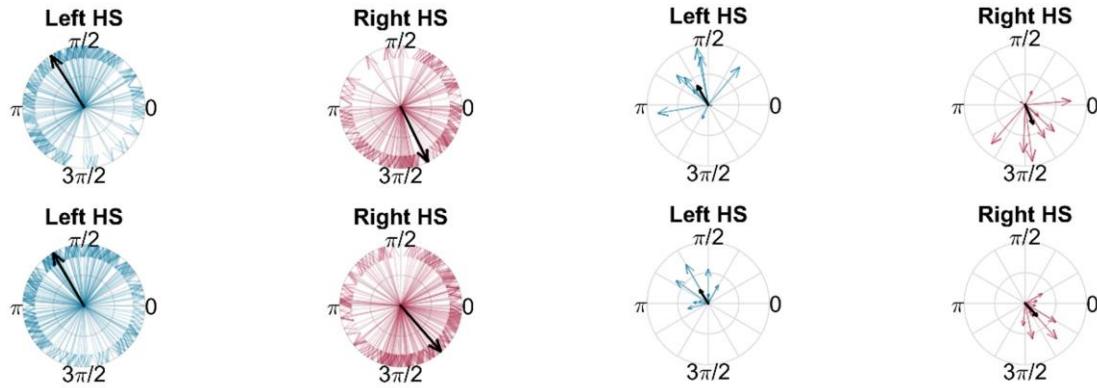
324 entrainment for each of the separate sequences of 20s stepping that patients performed. The  
325 arrows are clustered again around the preferred phase in the patients that were entrained to the  
326 stimulation pattern, which was not the case in **Fig. 4B**. **Table 1** shows the stimulation  
327 parameters and location of the electrode contact used for stimulation. The location of the active  
328 contacts varied across patients such that some were located in the ventral, some in the dorsal  
329 STN, but no criteria emerged that would distinguish between the groups of responders. The  
330

**Table 2 | Stimulation speed, stepping speed and p-values testing for significant entrainment in the two alternating DBS conditions.** The p-values in bold highlight the patients that were significantly entrained to the alternating DBS pattern (assessed with Rayleigh-tests). Significant entrainment always occurred in the condition in which the stepping speed was closer to the stimulation speed (sometimes this was in the altDBS fast condition as some patients performed the task faster than in the initial speed recording). Only P02 was also entrained to alternating DBS in the other condition. P05 and P07 reported that when stimulation was switched off outside of this study, they did not notice an immediate deterioration of symptoms, suggesting that DBS only had weak positive effects. These two patients were not entrained to alternating

	alt DBS slow			alt DBS fast			p- value
	stimSpeed	stepSpeed	p-value	stimSpeed	stepSpeed		
P01	1.2	1.12	0.317	0.96	1.07	0.079	
P02	<b>1.8</b>	<b>1.69</b>	<b>&lt;0.001</b>	<b>1.44</b>	<b>1.62</b>	<b>0.039</b>	
P03	1.2	0.87	0.893	<b>0.96</b>	<b>0.87</b>	<b>&lt;0.001</b>	
P04	1.2	0.91	0.845	0.96	0.81	0.744	
P05	1.1	0.89	0.124	0.88	0.92	0.976	
P06	1.2	1	0.762	<b>0.96</b>	<b>0.98</b>	<b>0.007</b>	
P07	1.1	1.01	0.875	0.88	1.11	0.738	
P08	1.2	0.87	0.878	<b>0.96</b>	<b>0.86</b>	<b>0.008</b>	
P09	1.5	1.39	0.841	1.2	1.47	0.728	
P10	<b>1.2</b>	<b>1.21</b>	<b>&lt;0.001</b>	0.96	1.31	0.994	

331

**A Example of two responders: Rayleigh test  $p < 0.001$**



**B Example of a non-responder: Rayleigh test:  $p = 0.926$**

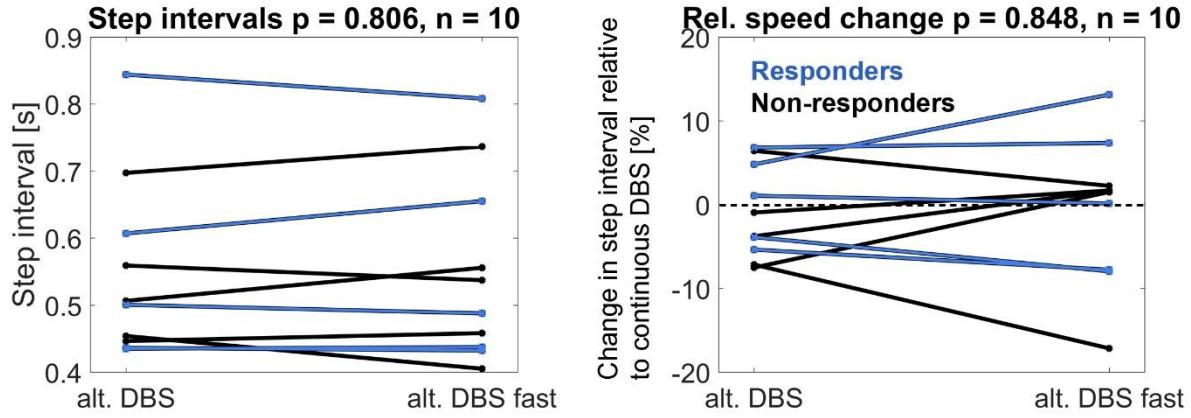


332

**Fig. 4 | A Example data of two responders (P02 and P03).** Blue and red vectors show the phases of the alternating stimulation pattern at the time of the left and right heel strikes, respectively. The heel strikes were clustered around one point of the stimulation cycle (between  $\Pi/2$  and  $\Pi$  for the left heel strike). The black vectors show the average preferred phase (scaled to unit length on the left two plots to enable a better visual comparison of the similarity between the two patients). The two plots to the right show the preferred phase and strength of entrainment (indicated by the length of the black vector) for each of the separate sequences of 20s stepping. Here the vectors also point relatively consistently to the same quarter. **B** No consistent clustering was present in non-responders (P04).

333

334 only parameter that may be associated with entrainment may be the stimulation frequency, as  
335 in the group of responders it was either 80 Hz or 100 Hz, but never 130 Hz, which is the  
336 conventional frequency for STN DBS (Moro et al., 2002). However, two non-responders also  
337 had a stimulation frequency of 80 and 100 Hz.



338

**Fig 5 | Difference in step intervals between the alternating DBS and the fast alternating DBS condition.** When the alternating DBS rhythm was 20% faster, the stepping intervals were not systematically accelerated.

339

340 **Faster alternating DBS did not systematically accelerate patients' stepping**

341 **rhythm**

342 We also tested if patients' stepping rhythms were faster in the fast altDBS condition compared  
343 to the slower altDBS condition. We performed this comparison across all patients to test if  
344 speeding up the stimulation pattern would generally accelerate the stepping rhythm,  
345 irrespective of which condition matched their speed more closely. **Fig. 5** shows that the  
346 stepping intervals were not systematically shortened (left plot, altDBS =  $0.55 \pm 0.13$ s, fast  
347 altDBS =  $0.55 \pm 0.14$ s,  $t(9) = -0.3$ ,  $p = 0.806$ ). We also compared the change in interval duration  
348 relative to the baseline condition of continuous DBS, which again showed that the fast DBS  
349 condition resulted in speed changes in either direction (**Fig. 5**, right plot).

350 We also looked for order effects and found no evidence of these on stepping speed or the  
351 strength of entrainment in the speed-matched and fast-alternating conditions. In three  
352 responders (P06, P08 and P10) the two alternating DBS conditions were separated by the

353 continuous DBS condition, showing that the strength of entrainment was not dependent on  
354 potentiation effects of prolonged alternating stimulation.

355

### 356 **Step timing variability during alternating DBS**

357 First, we compared if the step timing variability changed in the alternating speed-matched DBS  
358 condition compared to continuous DBS. The variability metrics were computed within stepping  
359 sequences that included on average  $40 \pm 5$  steps. No significant differences were found across  
360 the ten patients in the coefficient of variation (CV) of the step intervals (contDBS =  $8.3 \pm 3.4\%$ ,  
361 speed-matched altDBS =  $9.3 \pm 3.2\%$ ,  $t(9) = -0.8$ ,  $p = 0.450$ ) or in the STD of the differences  
362 between consecutive step intervals (contDBS =  $0.07 \pm 0.03$ , speed-matched altDBS =  $0.07$   
363  $\pm 0.03$ ,  $t(9) = -0.4$ ,  $p = 0.674$ ).

364 Next we restricted the analysis to the group of responders, and found that the CV of the step  
365 intervals in the speed-matched alternating DBS condition was increased compared to  
366 continuous DBS (contDBS =  $8.2 \pm 3.0\%$ , speed-matched altDBS =  $10.9 \pm 3.9\%$ ,  $t(4) = -2.9$ ,  $p =$   
367 0.045). This is consistent with a failure of the step cycle to continuously entrain to the  
368 alternating stimulation rhythm, leading to increased phase slips as stepping falls in and out of  
369 register with the stimulation rhythm. When testing individually in each patient how the step  
370 timing variability changed between the stepping sequences recorded in the contDBS and speed-  
371 matched altDBS conditions, two of the five patients showed significantly increased variability  
372 during alternating DBS (rank-sum test between the respective stepping sequences: P03  $p =$   
373 0.040, P08:  $p = 0.004$ ).

374 In the group of the five responders, we also compared if their step timing variability differed  
375 between the speed-matched and mismatched altDBS condition. We found no significant  
376 difference across the group (speed-matched altDBS =  $10.9 \pm 3.9\%$ , mismatched altDBS =  $9.9$

377  $\pm 2.9\%$ ,  $t(4) = 2.1$ ,  $p = 0.101$ ), but in the within-patients tests, one of the responders (P10) had  
378 a significantly higher step timing variability when stimulated with mismatched altDBS  
379 compared to speed-matched altDBS (two-samples t-test:  $t(21) = -2.8$ ,  $p = 0.010$ ).

380

### 381 **Clinical assessments**

382 The blinded UPDRS-III assessment showed no significant differences between continuous  
383 DBS ( $25.1 \pm (\text{STD}) 5.7$ ) and alternating DBS at the preferred walking speed ( $26.5 \pm 6.45$ ,  
384 Wilcoxon signed-rank test ( $n=10$ ),  $p = 0.254$ ). The UPDRS items 27-31 reflecting balance and  
385 gait also were very similar (in seven of the ten recorded patients the scores were identical  
386 between conditions, and p-values of the signed-rank tests were 1.0; item 27 mean: contDBS =  
387  $0.8 \pm 0.6$ , altDBS =  $0.9 \pm 0.9$ ; item 28: contDBS =  $0.8 \pm 0.6$ , altDBS =  $0.9 \pm 0.9$ ; item 29:  
388 contDBS =  $1.2 \pm 0.4$ , altDBS =  $1.2 \pm 0.4$ ; item 30: contDBS =  $1.0 \pm 0.7$ , altDBS =  $1.1 \pm 0.9$ ; item  
389 31: contDBS =  $1.4 \pm 0.5$ , altDBS =  $1.5 \pm 0.7$ ). In the six patients that performed a timed 20m  
390 walking assessment (walk 10m straight, turn and return back to the starting point) the time  
391 needed and numbers of steps did not differ significantly between stimulation conditions  
392 (continuous DBS:  $19.8s \pm 5.2s$  and  $35 \pm 8$  steps, alternating DBS:  $19.8s \pm 4.5s$  and  $35 \pm 6$  steps).

393 **Discussion**

394 We found that alternating DBS – intermittently lowering and increasing stimulation intensity  
395 with an offset between the right and left STN to produce an alternating stimulation pattern –  
396 can significantly manipulate the step timing of Parkinson's patients. The preferred timing of  
397 the steps relative to the stimulation pattern was highly consistent across the patients that  
398 significantly entrained to alternating DBS, providing evidence that the STN is mechanistically  
399 involved in organising stepping. This is consistent with the alternating pattern of beta activity  
400 previously reported in the STN during stepping movements (Fischer et al., 2018), although, by  
401 themselves, correlational observations so far could not distinguish between the mechanistic or  
402 secondary (afferent) involvement of STN activity (Fischer et al., 2018; Georgiades et al., 2019;  
403 Singh et al., 2013).

404 Our findings also suggest that entrainment only occurs when the stimulation speed closely  
405 matches the participants' stepping speed. The faster alternating DBS condition, which was  
406 accelerated by 20%, failed to accelerate patients' stepping speed. Amongst responders,  
407 alternating DBS could increase patients' step timing variability. Step timing variability would  
408 not change if the stepping and stimulation rhythms were aligned only by coincidence. The  
409 increase in variability suggests that entrainment was relatively weak and that stimulation can  
410 act like an attractor, pulling the intrinsic rhythm in to register, but only intermittently,  
411 punctuated by phase slips. How frequently phase slips occur likely depends on how well the  
412 alternating stimulation rhythm matches that of natural stepping.

413 We would like to acknowledge that stepping in place performance does not necessarily reflect  
414 how alternating DBS would affect gait variability during free walking. Despite the instruction  
415 to maintain a comfortable stepping movement as consistently as possible, some patients  
416 showed considerable variability in how high they lifted their feet across the recording session  
417 and even within individual stepping sequences, which may have affected their step intervals.

418 As we had no recordings of leg kinematics, this could not be quantified or analysed further.  
419 We decided to use stepping in place on force plates for the entrainment assessment because it  
420 is safer than free walking, could be performed in a relatively small space and provided a simple  
421 measure of step timing, which was our main focus in this study. Moreover, the speed of  
422 stepping in place appears to match the speed of real walking reasonably well, at least in healthy  
423 participants (Garcia, Nelson, Ling, & Van Olden, 2001).

424 Our study was not optimized for testing potential therapeutic benefits of alternating DBS, but  
425 we have now attained a first template for the preferred alignment between alternating DBS and  
426 the stepping cycle based on the five responders. This template can be used to inform future  
427 studies, in which the stimulation pattern could be aligned to the stepping rhythm as the patient  
428 starts walking with the help of external cues or by tracking the stepping rhythm (Tan et al.,  
429 2018).

430 We chose to stimulate at a high intensity for two thirds of the gait cycle and reduce stimulation  
431 for one third of the gait cycle, partially because the device used to communicate with the  
432 implanted impulse generator did not allow a 50-50% stimulation pattern. Based on our findings,  
433 we cannot infer the preferred alignment for other stimulation patterns or if the strength of  
434 entrainment would differ.

435 The consistent entrainment patterns among the responders cannot be explained by an awareness  
436 of the stimulation condition because none of the patients reported any rhythmic stimulation-  
437 induced sensations when asked if anything felt different. Five of our ten patients did not get  
438 entrained to alternating DBS. Two of these patients reported that switching DBS off outside of  
439 this study did not result in immediately noticeable deterioration of symptoms, and are thus  
440 atypical in their response to DBS, but were still included in the analyses. For the remaining  
441 three patients it is less clear why their stepping was not entrained. As we did not assess how

442 quickly motor symptoms deteriorated OFF DBS and recovered after switching it back on, we  
443 could not investigate if rapid responses to changes in DBS were linked to responsiveness to  
444 alternating DBS. The stimulation speed for the non-responders was matched similarly well to  
445 their stepping speed as in the group of responders, and the severity of gait impairments was  
446 similarly variable. The presence of freezing also did not seem to play a role in this  
447 comparatively small sample. Also the location of the active DBS contacts did not appear to be  
448 critical, considering that in some responders the active contacts were located in the dorsal while  
449 in others they were in the ventral part of the STN. The only criterion that stood out was that the  
450 patients in the responding group had a stimulation frequency of either 80 or 100 Hz, slightly  
451 lower than the conventional stimulation frequency of 130 Hz for STN DBS (Moro et al., 2002).  
452 This is interesting considering that several studies suggest that lowering the frequency can be  
453 beneficial for improving gait problems in some patients (di Biase & Fasano, 2016; Di Giulio  
454 et al., 2019; Xie et al., 2018). The question whether the stimulation frequency plays a critical  
455 role in enabling entrainment to alternating DBS should be tested in future studies.

456 At present we can only speculate about the mechanisms underlying the observed entrainment.  
457 Patients tended to perform the most effortful part of the gait cycle – lifting a foot off the ground  
458 – after the contralateral STN had been stimulated at the clinically effective threshold for several  
459 hundred milliseconds, which is in line with the known movement-facilitatory effects of DBS.  
460 High-intensity stimulation also coincided with the time of the beta rebound, which peaks after  
461 the contralateral heel strike according to our previous study (Fischer et al., 2018). Because STN  
462 DBS can counteract excessive beta synchrony (Eusebio & Brown, 2009; Tinkhauser et al.,  
463 2017), stimulating with a high intensity after the contralateral heel strike could potentially  
464 prevent beta synchronization going overboard in the stance period. Excessive beta synchrony  
465 has recently been related to freezing episodes (Georgiades et al., 2019; Storzer et al., 2017) and  
466 to the vulnerability to such episodes (Chen et al., 2019), hence stimulating more strongly at

467 points where beta synchronization is more likely may be a more effective stimulation strategy  
468 for preventing freezing than continuous DBS.

469 A recent study also found that non-invasive transcranial alternating current stimulation (tACS)  
470 over the cerebellum can entrain the walking rhythm of healthy participants (Koganemaru et al.,  
471 2019). The STN projects to the cerebellum via the pontine nuclei, thus alternating STN DBS  
472 could potentially entrain the gait rhythm via this route (Bostan, Dum, & Strick, 2010). The  
473 pedunculopontine nucleus (PPN), part of the mesencephalic locomotor region, also is  
474 reciprocally connected with the STN, and might provide another pathway by which STN DBS  
475 modulates stepping (Jenkinson et al., 2009; Morita et al., 2014; Thevathasan et al., 2018).  
476 Finally, the STN also communicates with the mesencephalic locomotor region through the  
477 substantia nigra pars reticulata (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004). The latter  
478 structure may be preferentially sensitive to lower stimulation frequencies (Weiss, Milosevic,  
479 & Gharabaghi, 2019), and it is interesting to highlight again that lower stimulation frequencies  
480 tended to be associated with successful entrainment to alternating stimulation in the present  
481 study.

482 In summary, this study provides evidence that the STN is causally important in the dynamic  
483 control of the stepping cycle and provides a novel means of modulating this control through  
484 alternating STN DBS in patients with Parkinson's disease. This stimulation mode can entrain  
485 stepping and parallels the alternating pattern of beta activity recorded in the STN during gait.  
486 It remains to be seen whether such a potentially biomimetic stimulation pattern can provide the  
487 basis for a novel treatment strategy for patients with debilitating gait disturbances. Our results  
488 suggest that it will be key to match the stimulation pattern closely to the patients' preferred  
489 walking speed if this is to be reinforced through entrainment.

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500

501 **Competing interests**

502 PB has received consultancy fees from Medtronic. TF has received honoraria for speaking at  
503 meetings sponsored by Boston Scientific, Bial, Profile Pharma.

504

505 **Figure legends**

506 **Fig. 1 | A Alternating DBS pattern.** DBS was set to the clinically effective voltage for 2/3 of  
507 the stimulation cycle and reduced for 1/3 of the cycle. For the reduced period, stimulation  
508 intensity was set to 0V in eight patients and it was reduced by -1V and -1.2V relative to the  
509 clinically effective threshold in the remaining two patients. The pattern was offset between the  
510 left and right STN such that the pauses occurred at exactly opposite points of the stimulation  
511 cycle. Grey dashed lines show the start and end of one full stimulation cycle (compare with

512 Fig. 3B). **B** Recording setup. Patients performed stepping while standing on force plates and  
513 were allowed to hold on to parallel bars positioned next to them if they felt unstable or if they  
514 felt more comfortable resting their arms on the bars.

515

516 **Fig. 2 | Force measurements and step cycle events.** x = heel strikes. The force increased  
517 during heel strikes.  $\Delta$  = when the foot was raised from the force plate the force decreased.

518

519 **Fig. 3 | Entrainment at the group level.** **A** Blue vectors show the average phase of alternating  
520 DBS at all left heel strikes and the strength of entrainment for individual patients (n=10). Long  
521 arrows show strong entrainment. The group average vector (black arrow) shows the average of  
522 the blue vectors. The length of this vector was significantly larger than in the surrogate data,  
523 demonstrating consistent alignment of stepping to the alternating DBS pattern across the group.

524 **B** Group-averaged timing of key events of the gait cycle (x and  $\Delta$ ) relative to the stimulation  
525 pattern. The blue and red horizontal lines indicate high-intensity stimulation of the left and  
526 right STN, respectively. The left heel strike (blue x) was made just before contralateral  
527 stimulation (right STN DBS shown in red) increased. Grey horizontal bars indicate the standard  
528 error of the mean phases across the patients.

529

530 **Fig. 4 | A Example data of two responders (P02 and P03).** Blue and red vectors show the  
531 phases of the alternating stimulation pattern at the time of the left and right heel strikes,  
532 respectively. The heel strikes were clustered around one point of the stimulation cycle (between  
533  $\Pi/2$  and  $\Pi$  for the left heel strike). The black vectors show the average preferred phase (scaled  
534 to unit length on the left two plots to enable a better visual comparison of the similarity between

535 the two patients). The two plots to the right show the preferred phase and strength of  
536 entrainment (indicated by the length of the black vector) for each of the separate sequences of  
537 20s stepping. Here the vectors also point relatively consistently to the same quarter. **B** No  
538 consistent clustering was present in non-responders (P04).

539

540 **Fig. 5 | Difference in step intervals between the alternating DBS and the fast alternating**  
541 **DBS condition.** When the alternating DBS rhythm was 20% faster, the stepping intervals were  
542 not systematically accelerated. Three of the five responders (in blue) had slightly faster step  
543 intervals, however, the differences of -4.2%, -2.5% and -0.9% (right plot) were much smaller  
544 than the 20% change in the stimulation rhythm.

545

546

547

548 **Table legends**

549 **Table 1 | Clinical details and stimulation parameters for all patients.** Patients who were  
550 significantly entrained to alternating DBS are highlighted in bold. No distinct differences  
551 between the group of responders and non-responders were apparent with respect to the  
552 stimulation intensity boundaries, location of the active contact, severity of motor symptoms  
553 or gait problems. The only criterion that stood out was the stimulation frequency, which was  
554 either 80 or 100 Hz in the group of responders. The four contacts on each electrode are  
555 labelled as 0-3 (ventral-dorsal) on the left electrode and 8-11 on the right electrode. The  
556 clinically effective stimulation intensity during standard continuous stimulation was set as  
557 *Upper threshold* (rounded to the first decimal place). *Stim threshold diff* was the difference  
558 between the upper threshold and the intensity during the periods of lower or absent  
559 stimulation during the alternating mode. This difference was the same in the two sides. All  
560 patients received stimulation with a pulse width of 60 $\mu$ s. GFQ = Gait and falls questionnaire  
561 (Giladi, 2000). LED = Levodopa equivalent dose.

562

563 **Table 2 | Stimulation speed, stepping speed and p-values testing for significant**  
564 **entrainment in the two alternating DBS conditions.** The p-values in bold highlight the  
565 patients that were significantly entrained to the alternating DBS pattern (assessed with  
566 Rayleigh-tests). Significant entrainment always occurred in the condition where the stepping  
567 speed was closer to the stimulation speed. Only P02 was also entrained to alternating DBS in  
568 the other condition. P05 and P07 reported that when stimulation was switched off outside of  
569 this study, they did not notice an immediate deterioration of symptoms, suggesting that DBS  
570 only had weak positive effects. These two patients were not entrained to alternating DBS.

571

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