

1      **Basal ganglia theta power indexes trait anxiety in people**  
2      **with Parkinson's disease**

3      Bart E. K. S. Swinnen,<sup>1,2</sup> Colin W. Hoy,<sup>1</sup> Elena Pegolo,<sup>1,3,5</sup> Bryony Ishihara,<sup>3</sup> Elena Ubeda  
4      Matzilevich,<sup>1</sup> Julia Sun,<sup>1</sup> Francesca Morgante,<sup>3</sup> Erlick Pereira,<sup>3</sup> Fahd Baig,<sup>3</sup> Michael Hart,<sup>3</sup>  
5      Huiling Tan,<sup>4</sup> Zimi Sawacha,<sup>5</sup> Martijn Beudel,<sup>2</sup> Sarah Wang,<sup>1</sup> Philip Starr,<sup>1</sup> Simon Little<sup>1,†</sup> and  
6      Lucia Ricciardi<sup>1,3,†</sup>

7      **†These authors contributed equally to this work.**

8      **Abstract**

9      Neuropsychiatric symptoms are common and disabling in Parkinson's disease (PD), with  
10     troublesome anxiety occurring in one-third of patients. Management of anxiety in PD is  
11     challenging, hampered by insufficient insight into underlying mechanisms, lack of objective  
12     anxiety measurements, and largely ineffective treatments.

13     In this study, we assessed the intracranial neurophysiological correlates of anxiety in PD patients  
14     treated with deep brain stimulation (DBS) in the laboratory and at home. We hypothesized that  
15     low-frequency (theta-alpha) activity would be associated with anxiety.

16     We recorded local field potentials (LFP) from the subthalamic nucleus (STN) or the globus pallidus  
17     pars interna (GPi) DBS implants in three PD cohorts: 1) patients with recordings (STN) performed  
18     in hospital at rest via perioperatively externalized leads, without active stimulation, both ON or  
19     OFF dopaminergic medication; 2) patients with recordings (STN or GPi) performed at home while  
20     resting, via a chronically implanted commercially available sensing-enabled neurostimulator  
21     (Medtronic Percept<sup>TM</sup> device), ON dopaminergic medication, with stimulation both on or off; 3)  
22     patients with recordings performed at home while engaging in a behavioral task via STN and GPi  
23     leads and electrocorticography paddles over premotor cortex connected to an investigational  
24     sensing-enabled neurostimulator, ON dopaminergic medication, with stimulation both on or off.

1 Trait anxiety was measured with validated clinical scales in all participants, and state anxiety was  
2 measured with momentary assessment scales at multiple time points in the two at-home cohorts.  
3 Power in theta (4-8 Hz) and alpha (8-12 Hz) ranges were extracted from the LFP recordings, and  
4 their relation with anxiety ratings was assessed using linear mixed-effects models.

5 In total, 33 PD patients (59 hemispheres) were included. Across three independent cohorts, with  
6 stimulation off, basal ganglia theta power was positively related to trait anxiety (all  $p < 0.05$ ). Also  
7 in a naturalistic setting, with individuals at home at rest with stimulation and medication ON, basal  
8 ganglia theta power was positively related to trait anxiety ( $p < 0.05$ ). This relationship held  
9 regardless of the hemisphere and DBS target. There was no correlation between trait anxiety and  
10 premotor cortical theta-alpha power. There was no within-patient association between basal  
11 ganglia theta-alpha power and state anxiety.

12 We showed that basal ganglia theta activity indexes trait anxiety in PD. Our data suggest that theta  
13 could be a possible biomarker of neuropsychiatric symptoms and specifically of anxiety in PD,  
14 potentially suitable for guiding advanced DBS treatment tailored to the individual patient's needs,  
15 including non-motor symptoms.

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17 **Author affiliations:**

18 1 Department of Neurology, University of California San Francisco, San Francisco, CA 94158,  
19 USA

20 2 Department of Neurology, Amsterdam University Medical Centers, Amsterdam Neuroscience,  
21 University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

22 3 Neurosciences and Cell Biology Institute, Neuromodulation and Motor Control Section, St  
23 George's University of London, SW17 0RE London, UK

24 4 Medical Research Council Brain Network Dynamics Unit, Nuffield Department of Clinical  
25 Neurosciences, University of Oxford, OX1 3TH, Oxford, UK

26 5 Department of Information Engineering, University of Padova, 35131, Padova, Italy

27

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1 Correspondence to: Dr Lucia Ricciardi  
2 Neurosciences and Cell Biology Institute, Neuromodulation and Motor Control Section, St  
3 George's University of London, SW17 0RE London, UK  
4 E-mail: lricciar@sgul.ac.uk  
5

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9 potential; anxiety  
10

## 11 **Introduction**

12 People with Parkinson's disease (PD) experience a range of non-motor symptoms in addition to  
13 their cardinal motor symptoms, with non-motor symptoms having a significant impact on patients'  
14 and caregivers' quality of life<sup>1,2</sup>. Among non-motor symptoms, neuropsychiatric deficits are  
15 prominent and can be present at any stage of the disease, even preceding motor deficits<sup>3</sup>.  
16 Neuropsychiatric symptoms include, among others, depression, anxiety, apathy, psychosis, and  
17 impulse control disorders and related behaviors (ICB)<sup>4</sup>. The prevalence of neuropsychiatric  
18 symptoms in PD is high, reaching up to 50% for depression and anxiety<sup>5</sup>.

19 Anxiety has been recognized as one of the top three unmet therapeutic needs in PD patients and is  
20 recognized as a high research priority<sup>6</sup>. Despite being so frequent, there are significant challenges  
21 in identifying, measuring, and treating anxiety in PD<sup>7,8,9,10</sup>. The mechanisms underlying anxiety in  
22 PD are unclear and often multifactorial, encompassing multiple disease-specific and individual-  
23 specific factors, which complicates the development of effective treatments. Anxiety in PD can be  
24 persistent, episodic, or a combination of both, and anxiety can fluctuate during the day, influenced  
25 by dopaminergic medication intake<sup>11</sup>. The temporal dimensions of anxiety are often captured using  
26 two constructs: 'trait' anxiety - constituting an individual's general level of anxiety over a  
27 considerable period, as opposed to 'state' anxiety, which reflects a person's momentary and

1 dynamic anxiety level<sup>12,13</sup>. This etiological and temporal variability complicates the assessment of  
2 anxiety presence and severity, which currently relies on clinical interviews, clinician-administered  
3 scales, and self-reported questionnaires. This lack of objective measures of anxiety makes the  
4 management of this common symptom very challenging<sup>14,15</sup>. Moreover, treatment options for  
5 anxiety in PD are currently limited, lack evidence-based support<sup>16</sup>, and are often ineffective<sup>17</sup>.  
6 Altogether, anxiety management would greatly benefit from objective markers capable of indexing  
7 anxiety presence and severity, as well as principled and targeted treatments<sup>7</sup>.

8 Deep brain stimulation (DBS) targeting either the subthalamic nucleus (STN) or globus pallidus  
9 pars interna (GPi) is an effective treatment for motor symptoms in PD<sup>18</sup> and may also improve  
10 non-motor symptoms<sup>19</sup>, but the effect of DBS on neuropsychiatric symptoms and their fluctuations  
11 is still debated<sup>20</sup>. Meta-analytic evidence suggests that, at the group level, anxiety symptoms  
12 improve after DBS<sup>21</sup>. Electrophysiological activity such as local field potentials (LFPs) can be  
13 recorded from the STN or GPi during DBS surgery, immediately postoperatively through  
14 externalized electrodes, and via chronically implanted sensing-enabled neurostimulators<sup>22</sup>. The  
15 latter even allows for exploring physiological markers in the naturalistic environment - the most  
16 relevant setting for PD patients. By providing direct access to subcortical activity, LFP research  
17 has offered valuable insights into disease mechanisms and cognitive functions, including the  
18 identification of physiomarkers of PD motor symptom states that enable precise adjustments of  
19 therapy via adaptive DBS<sup>23-25</sup>. These increasingly available techniques provide a unique  
20 opportunity to identify objective physiomarkers of neuropsychiatric symptoms like anxiety that  
21 will be critical for understanding and treating non-motor symptoms in PD.

22

23 Whereas subcortical beta (13–30 Hz) power has been established as a physiomarker for PD motor  
24 symptoms<sup>26</sup>, the neural correlates of neuropsychiatric manifestations of PD are less well-defined.  
25 Strikingly, although anxiety is such a common and disabling symptom, the neural correlates of  
26 anxiety using basal ganglia electrophysiology have never been assessed. For other  
27 neuropsychiatric symptoms, studies assessing the associations between these symptoms and  
28 subcortical neural signals have only been performed in the hospital setting, by recording intra-  
29 operatively or immediately after surgery from externalized DBS electrodes during periods that can  
30 be confounded by microlesion effects<sup>27,28</sup>. Increased power in the theta-alpha (4-12 Hz) band has

1 been suggested as a biomarker of neuropsychiatric symptoms in PD<sup>29</sup>. Specifically, ICB<sup>30</sup> and  
2 depression<sup>31</sup> have been associated with increased STN theta-alpha and alpha power, respectively,  
3 and the severity of trait impulsivity has been positively related to STN alpha power<sup>32</sup>. Other studies  
4 using behavioral paradigms have also implicated STN theta-alpha activity in emotional and  
5 behavioral processes<sup>29</sup>.

6

7 In the present study, we aimed to investigate the relationship between intracranial theta-alpha  
8 activity and anxiety in three separate cohorts of PD patients with STN and GPi DBS, both in  
9 hospital and at home, using investigational and commercially available sensing-enabled  
10 neurostimulators.

11

## 12 **Material and methods**

13

14 Three independent PD cohorts have been included and assessed in the present study (Fig. 1): (1)  
15 the ‘in-hospital externalized at-rest’ cohort: in-hospital LFP measurements via externalized DBS  
16 electrodes in patients with bilateral STN-DBS (London, UK), (2) the ‘at-home chronic at-rest’  
17 cohort: at-home unsupervised LFP measurements through the chronically implanted Medtronic<sup>©</sup>  
18 Percept<sup>TM</sup> PC neurostimulator in patients with STN-DBS and GPi-DBS (San Francisco, USA),  
19 and (3) the ‘at-home chronic task’ cohort: at-home supervised LFP measurements through the  
20 chronically implanted Medtronic<sup>©</sup> Summit RC+S neurostimulator in patients with STN-DBS and  
21 GPi-DBS performing a reward learning task (San Francisco, USA). Data collection was performed  
22 independently for each of the three cohorts. Data were then collated and analyzed simultaneously  
23 for all three cohorts to test for both 1) statistical reproducibility and 2) generalizability.

24

## 1 **Patients**

### 2 **In-hospital externalized at-rest cohort**

3 Consecutive PD patients (n=12) undergoing bilateral STN-DBS were recruited at St. George's  
4 University Hospital, London, United Kingdom (UK). Inclusion criteria were standard clinical  
5 criteria for DBS<sup>33</sup>. In detail, they were: (1) diagnosis of idiopathic PD, (2) age < 70 years, (3)  
6 bothersome motor fluctuations and/or levodopa-induced dyskinesias despite optimal  
7 pharmacological management, (4) absence of dementia, major depression with suicidal thoughts  
8 or acute psychosis, (5) significant clinical response to levodopa challenge (at least 30%  
9 improvement in Movement Disorders Society-Unified PD Rating Scale III score), and (6) disease  
10 duration >5 years.

11

### 12 **At-home chronic at-rest cohort**

13 Patients (n=13) were recruited at the University of California San Francisco (UCSF), San  
14 Francisco, California, USA. Inclusion criteria: (1) patients with idiopathic PD treated with  
15 unilateral or bilateral DBS of the STN or the GPi, (2) implanted with the Percept<sup>TM</sup> PC  
16 neurostimulator, (3) on relatively stable DBS parameters and PD medication (typically >6 months  
17 after surgery), (4) stimulation parameters in at least one hemisphere compatible with  
18 BrainSense<sup>TM</sup>.

19

### 20 **At-home chronic task cohort**

21 Patients (n=8) were recruited at University of California San Francisco (UCSF), San Francisco,  
22 California, USA. Note that this cohort involves a different sample of patients and different  
23 neurostimulator devices than the patients in the 'at-home chronic at-rest' cohort. Patients were part  
24 of a clinical trial involving PD patients undergoing DBS implantation for motor fluctuations  
25 (NCT03582891). These patients were implanted bilaterally (except for one patient with unilateral  
26 DBS) with subcortical leads (Medtronic<sup>©</sup> models 3389 and 3387) in either the STN or the GPi, as  
27 well as quadripolar electrocorticography paddles (ECoG) (Medtronic<sup>©</sup> model 0913025) over the  
28 sensorimotor cortex. For each hemisphere, these electrodes were connected to an investigational

1 sensing-enabled chronically implanted neurostimulator (Medtronic<sup>©</sup> Summit RC+S model  
2 B35300R<sup>34</sup>). Patients with bilateral DBS were therefore implanted with two neurostimulators.

3

## 4 **Data collection**

### 5 **In-hospital externalized at-rest cohort**

6 Data were acquired 3-5 days after surgical insertion of the DBS leads, before the implantation of  
7 the neurostimulator while patients were admitted to hospital. Recording of STN LFPs (n=24  
8 hemispheres) was performed with a TMSi-Porti amplifier (TMS International, Oldenzaal, The  
9 Netherlands, fs=2048 Hz) while participants were resting with eyes open, comfortably sitting on  
10 a chair for 5 minutes. The LFPs were recorded from the four contacts on the left and right of the  
11 bilateral electrodes. The bipolar signals (i.e., L0-L1, L1- L2, L2-L3, R0-R1, R1-R2, and R2-R3)  
12 were used for LFP analysis. Recordings were performed in two sessions on the same day; (1) in  
13 the morning after overnight withdrawal of antiparkinsonian medication (MedOFF condition) and  
14 (2) in the clinically defined ON medication condition, one hour after the administration of a  
15 participant's regular dose of levodopa (MedON). The presence and severity of anxiety and  
16 depression were assessed using the Hamilton Anxiety Rating Scale (HARS)<sup>35</sup> and Hamilton  
17 Depression Rating Scale (HDRS)<sup>36</sup>, respectively on the day of the recording. Severity of motor  
18 symptoms and dyskinesia were assessed by means of the Unified Parkinson's Disease Rating Scale  
19 (UPDRS) part III and The Unified Dyskinesia Rating Scale (UDRS) part III "Objective  
20 Impairment" on the day of the study.

21

### 22 **At-home chronic at-rest cohort**

23 All participants were assessed in-hospital at baseline. During this visit, demographic and clinical  
24 data were gathered, and the presence and severity of anxiety and depression were rated using the  
25 Beck Anxiety Inventory (BAI)<sup>37</sup> and Beck Depression Inventory (BDI)<sup>38</sup> respectively.  
26 BrainSense<sup>TM</sup> was enabled in the clinically active stimulation group on the Percept<sup>TM</sup> PC  
27 neurostimulator. To this end, sensing was activated in a sandwiched configuration around the  
28 active stimulation contact, located in the STN (n=14 hemispheres) or GPi (n=6 hemispheres).

1 Using the BrainSense™ Event feature, an event called 'Research' was enabled for the patient.  
2 When an event is triggered by the patient using the patient programmer, a 30-second LFP recording  
3 is performed, the power-frequency spectrum of which is stored on the neurostimulator. Patients  
4 were instructed on the study protocol and how to use the patient programmer for the study at home.  
5 Patients performed research activities (see below) at home for a total of 14 days, in a structured  
6 but self-supervised manner. The timing of study activities was consistent within each patient and  
7 in the MedON state (i.e., 1 hour after taking a dose of levodopa). Patients performed two  
8 consecutive rounds of study activities on a research day: once with active stimulation at clinical  
9 amplitude (MedON-StimOn) and once with stimulation at 0.0 mA (MedON-StimOff). The order  
10 of these two activities differed across days, and was pseudorandomized across patients. One round  
11 of research activities involved the following consecutive activities: (1) setting the stimulation at  
12 clinical amplitudes or 0.0 mA using the patient programmer, (2) resting one minute, (3) triggering  
13 a 'Research' event using the patient programmer, (4) resting one minute, (5) rating current anxiety  
14 state on a visual analogue scale (VAS) where 0='not anxious at all', 100='very anxious', and rating  
15 current mood state on a VAS (0='not depressed at all', 100='very depressed'), (6) rating current  
16 motor symptoms severity on a VAS ('How are your Parkinson's disease motor symptoms at the  
17 moment?') where 0='mild', 100='severe', (7) completion of a behavioral paradigm (to be reported  
18 separately). After completing the at-home research activities, data were downloaded (i.e. JSON  
19 file export) from the neurostimulator in the hospital at their next visit.  
20

## 21 **At-home chronic task cohort**

22 Data were collected during a previously conducted but unpublished study investigating neural  
23 correlates of value-based decision making and momentary assessments of mood and anxiety.  
24 Participants performed a modified two-step reward learning task under remote supervision from  
25 the researcher while in their homes<sup>39</sup>. Each participant performed this task between 9-13 times  
26 (n=78 total sessions) across 5-7 days. VAS ratings of anxiety and happiness ('how anxious are you  
27 at the moment?' where 0='not at all anxious' and 100='very anxious', and 'how happy are you at  
28 this moment?' where 0="very unhappy" and 100="very happy"). were collected immediately  
29 before starting the instruction phase of each task run. Experiments were performed in two clinical  
30 conditions: MedON-StimOn and MedON-StimOff, with at least 2 sessions per condition. Two

1 patients could not tolerate the DBS therapy completely off, and were instead recorded at 53/50%  
2 and 92/92% of their clinical amplitude in the left/right hemispheres. LFP data were recorded during  
3 each task session subcortically from the pair of contacts surrounding the clinical stimulation  
4 contact (i.e., sandwich configuration) in the STN (n=8 hemispheres) or GPi (n=7 hemispheres)  
5 and cortically from bipolar pairs of the two most anterior and two most posterior ECoG contacts.  
6 All ECoG contacts contributing to the cortical recording pairs reported here were located anterior  
7 to the central sulcus, ranging from the precentral gyrus to the middle/superior frontal gyrus.  
8 Posterior pairs were not analyzed due to between-subject variability in anatomical localization  
9 relative to the central sulcus. At baseline, the presence and severity of anxiety and depression were  
10 evaluated using the BAI and BDI.

11

## 12 **Data analysis**

### 13 **In-hospital externalized at-rest cohort**

14 All the acquired LFPs originated from a quadripolar electrode. Bipolar arrangement from the  
15 acquired data was obtained offline. In this way, each electrode presented three bipolar signals. Data  
16 were first inspected visually and parts of the signal with marked artefacts (e.g. signal saturation or  
17 movement artefacts) were removed (final signal length (mean±standard deviation): 274.0±77.5 s).  
18 Signals were then detrended and highpass filtered at 1 Hz (Butterworth). Spectral analysis was  
19 performed by computing the power spectrum of the signals using Welch's method (2s Hanning's  
20 windows, 50% overlap) with a frequency resolution of 0.25 Hz. Theta and alpha bands were  
21 computed by averaging the band power between 4-8 Hz and 8-12 Hz, respectively.

22

### 23 **At-home chronic at-rest cohort**

24 The LFP data from the 'Research' events for the 14 days of at-home assessments were retrieved  
25 from the JSON files. Within each 'Research' event, LFP data were proportionally normalized per  
26 frequency band by dividing the sum of powers per canonical frequency band (i.e. theta 4-8 Hz or  
27 alpha 8-12 Hz) over the sum of powers of the frequency range from 0-57.62 Hz. This latter upper  
28 limit was implemented because the powers above a varying frequency are censored by the

1 processing onboard Percept PC, the cut-off of which depends on the stimulation frequencies (e.g.  
2 frequencies >57.62 Hz are censored when stimulating at 180 Hz). For group-level comparisons of  
3 baseline BAI and BDI scores or average VAS anxiety with alpha or theta power, proportionally  
4 normalized powers per frequency band were averaged across events within hemispheres.

5

## 6 **At-home chronic task cohort**

7 LFP data during task sessions were reconstructed using the *processRCS* analysis toolbox<sup>40</sup>. Data  
8 were extracted from 0.9 s epochs when participants were resting during the inter-trial interval.  
9 Trials were excluded for missing behavioral and/or neural data and practice trials (mean+/-SD:  
10 840.6+/-165.0 trials/person). Power spectral density (PSD) estimates were extracted from these  
11 time series using Welch's method (*pwelch* in MATLAB) with 0.4 s windows and 50% overlap for  
12 frequencies ranging from 1-55 Hz in 0.5 Hz steps. To eliminate differences between subjects and  
13 regions, the PSDs were then normalized for each trial by dividing by the sum of all power bands  
14 from 1-55 Hz. Normalized PSDs were then averaged across trials within each session before  
15 computing theta and alpha power as the mean within 4-8 Hz and 8-12 Hz bands, respectively.  
16 Theta and alpha power were then averaged across runs within each participant, yielding one  
17 estimate for each hemisphere within each participant.

18

## 19 **DBS electrodes location**

20 Details on electrodes location reconstruction and contacts position are provided in Supplementary  
21 Material.

22

## 23 **Statistical analyses**

24 Because data were structured with a high level of non-independence, especially concerning  
25 patients with bilateral LFP recordings, linear mixed-effects (LME) models were used to assess the  
26 relation between the power of LFP frequency bands and behavioral measures (i.e. HDRS, HARS,  
27 BAI, BDI, VAS anxiety and VAS motor). LME models predicted neural power averaged within  
28 each hemisphere of each patient using fixed effects of each participant's symptom score,

1 hemisphere (left/right), basal ganglia region (STN/GPi), and random intercepts for each  
2 participant. To control for the effect of motor symptoms including tremor and dyskinesia on theta  
3 and alpha power, in the 'in-hospital externalized at-rest' cohort, a secondary analysis was conducted  
4 with an additional LME model, adding the fixed effect of either tremor or dyskinesia presence  
5 (according to UPDRS III or UDRS part III scores) to the main model. Separate models were used  
6 to predict either theta or alpha power using one of the a priori defined symptom metrics. One-sided  
7 likelihood ratio tests were used to assess the significance of the relationships by using the *compare*  
8 function in Matlab R2023a (Mathworks, Natick, MA), testing whether the model including the  
9 fixed effect of the symptom predictor of interest (e.g. BAI) improved model fit at a *p*-level defined  
10 at 0.05 compared to a null model without that predictor. The same LME model structure was used  
11 to assess state anxiety by using VAS anxiety ratings for individual events in the 'at-home at-rest'  
12 cohort and runs in the 'at-home task' cohort to predict low frequency power, again with separate  
13 models for theta and alpha power.

14

## 15 **Ethical approval**

16 All patients provided written informed consent under the Declaration of the Principles of Helsinki.  
17 For the London cohort, approval was obtained from the Institutional Review Board of the  
18 Integrated Research Application System (IRAS) with the study protocol number 268941 ("Neural  
19 basis of neuropsychiatric symptoms in PD"). For the UCSF cohorts, approval was obtained from  
20 the Institutional Review Board of the University of California, San Francisco (UCSF; study  
21 numbers 10-01350 and 20-31239 respectively).

22

## 23 **Citation diversity statement**

24 Given recent work identifying biases in citation practices such that papers from women and other  
25 minority scholars are under-cited relative to the number of such papers in the field<sup>41-44</sup>, we sought  
26 to proactively consider choosing references that reflect the diversity of the field. To support  
27 equitable practices in science, we report the predicted gender and racial/ethnic category of the first  
28 and last author of each reference using databases that store the probability of a first name being

1 carried by a woman<sup>41</sup> or a person of color<sup>45,46</sup>, alongside the details of these methods and their  
2 limitations (Supplementary Information).

3

## 4 **Results**

5 Thirty-three participants (59 hemispheres) were included: 12 in the ‘in-hospital externalized at-  
6 rest’ cohort, 13 in the ‘at-home chronic at-rest’ cohort, and 8 in the ‘at-home chronic task’ cohort.  
7 Demographics and clinical data are displayed in Table 1 and in Supplementary Results.

8

### 9 **Effect of medication and DBS on low-frequency oscillations**

10 To evaluate the effect of medication (‘in-hospital externalized at-rest cohort’) or stimulation (in  
11 the presence of dopaminergic medication, the two ‘At-home’ chronic cohorts) on the power  
12 frequency spectrum, we evaluated a LME model predicting the power of the band under analysis  
13 (theta, alpha, low-beta, high-beta, and gamma) using fixed effects of each participant’s hemisphere  
14 (left/right), basal ganglia region (STN/GPi, only in San Francisco cohorts with both regions), and  
15 random intercepts for each participant. A separate model adding the fixed effect of medication  
16 (London cohort) or stimulation (San Francisco cohorts) was computed and compared with the null  
17 model using one-sided likelihood ratio tests via the *compare* function in Matlab R2023a  
18 (Mathworks, Natick, MA) with a p-value set at 0.05.

19 In the ‘in-hospital externalized at-rest cohort’, we observed trends towards statistical significant  
20 effect of the medication on theta ( $\beta=0.654$ ;  $p=0.05$ ) and low-beta ( $\beta=-1.004$ ;  $p=0.07$ ) bands, while  
21 no statistically significant effect was found on alpha, high-beta, and gamma bands (all  $p>0.42$ )  
22 (Supplementary Figure 5, panel A).

23 In the ‘At-home chronic at-rest cohort’, results of this analysis show that stimulation has no effect  
24 on the power in the theta ( $p=0.9574$ ) and alpha ( $p=0.7465$ ) frequency ranges, but decreases the  
25 power in the low-beta, high-beta and gamma frequency ranges ( $\beta=-0.4887$ ,  $-0.3689$ , and  $-0.0639$ ;  
26 all  $p<0.0001$ ; Supplementary Figure 5, panel B).

27 In the ‘At-home chronic task cohort’, stimulation had no effect on basal ganglia power in any  
28 frequency band (all  $p>0.147$ ; Supplementary Figure 5, panel C).

## 1    **Effect of DBS on anxiety and mood**

2    We assessed the acute effect of DBS on anxiety and mood in the ‘At-home chronic at-rest’ and ‘at-  
3    home chronic task’ cohorts, as measured with VAS anxiety and VAS mood (“happiness” in the ‘at-  
4    home chronic task’ cohort). We performed LMEs with fixed effects of DBS status and basal ganglia  
5    ROI and random intercepts by subject to predict daily VAS ratings of symptoms. In the ‘At-home  
6    chronic at-rest cohort’, VAS scores of anxiety were lower with MedON-StimOn (mean $\pm$ SD:  
7    23.5 $\pm$ 19.2) compared to MedON-StimOff (28.9 $\pm$ 23.1;  $\beta$ =13.3;  $p$ <0.0001). VAS scores of mood  
8    were also better with MedON-StimOn (18.4 $\pm$ 17.1) compared to MedON-StimOff (20.3 $\pm$ 19.1;  
9     $\beta$ =10.7;  $p$ <0.0001).

10    In the ‘at-home chronic task cohort’, there was no effect of DBS on the VAS anxiety scores ( $\beta$ =-  
11    4.44,  $p$ =0.311; mean $\pm$ SD: 38.9 $\pm$ 21.3 StimOn, 43.4 $\pm$ 24.3 StimOff). VAS happiness ratings  
12    were significantly higher with StimOn (68.2 $\pm$ 16.2) compared to StimOff (63.3 $\pm$ 21.5;  $\beta$ =5.05,  
13     $p$ =0.048).

14

## 15    **Relationship between trait anxiety and neurophysiological measures**

16    First, we aimed to assess whether the low-frequency bands which have been implicated in  
17    neuropsychiatric/cognitive aspects of PD are also associated with anxiety using LFP recordings  
18    obtained shortly after surgery via externalized leads. In the ‘in-hospital externalized at-rest’ cohort,  
19    anxiety (as per HARS score) was positively related with STN theta power with MedOFF-StimOff  
20    ( $p$ =0.039,  $\beta$ =0.044), and this relationship was trending towards significant with MedON-StimOff  
21    ( $p$ =0.370,  $\beta$ =0.058) (Fig. 2, panels A, B, and E). Anxiety was not related to STN alpha power in  
22    either condition (Fig. 2, panels C, D, and E). No significant effect of laterality was found (right/left  
23    hemisphere) either with theta or alpha power (all  $p$ >0.05). The secondary analysis adding tremor  
24    (7 patients with tremor in MedOFF-StimOff, 3 patients with tremor in MedON-StimOff) or  
25    dyskinesia (8 patients with dyskinesia in MedON-StimOff) as fixed effects to the main models,  
26    showed no association between tremor and alpha or theta and between dyskinesia and alpha or  
27    theta (all  $p$ >0.05), and the relationship between theta and anxiety held when controlling for these  
28    motor symptoms in the model ( $p$ =0.04,  $\beta$ =0.041).

29

1 Next, we investigated the relationship between anxiety and low-frequency bands recording LFPs  
2 at-home from patients with chronically implanted neurostimulators equipped with sensing  
3 capabilities. In the ‘at-home chronic at-rest’ cohort with unsupervised LFP recordings (mean=21.9,  
4 SD=5.4 BrainSense™ Event recordings per patients), anxiety (as per BAI score) was positively  
5 related to basal ganglia theta power in both the MedON-StimOff ( $p=0.022$ ,  $\beta=0.0021$ ) and  
6 MedON-StimOn ( $p=0.022$ ,  $\beta=0.0016$ ) conditions (Fig. 3, panels A, B, and E). Moreover, in this  
7 cohort, anxiety was also positively related to basal ganglia alpha power in both conditions  
8 (MedON-StimOff:  $p=0.012$ ,  $\beta=0.0021$ ; MedON-StimOn:  $p=0.020$ ,  $\beta=0.0016$ ; Fig. 3, panels C, D,  
9 and E). In the ‘at-home chronic task’ cohort - with supervised LFP recordings during a reward  
10 learning task, anxiety (as per BAI score) was positively related with basal ganglia theta power in  
11 the MedON-StimOff ( $p=0.034$ ,  $\beta=0.0022$ ) condition, and this relationship was trending towards  
12 significant with MedON-StimOn ( $p=0.079$ ,  $\beta=0.0015$ ) (Fig. 4, panels A, B, and E).  
13 We did not find any association between anxiety and basal ganglia alpha power in either at-home  
14 cohort (Fig. 4, panels C, D, and E).

15  
16 Altogether, a positive relation between anxiety and basal ganglia theta power was consistently  
17 present across three independent cohorts in both subacute clinical and naturalistic environments.  
18

19 We further aimed to assess whether the relation between anxiety and theta is specific to the basal  
20 ganglia structures targeted with DBS (i.e. STN and GPi) compared to anatomically connected  
21 premotor cortical areas. In the ‘at-home chronic task’ cohort, electrocorticography data over the  
22 premotor cortex showed that anxiety was unrelated to cortical theta or alpha power (all  $p>0.560$ ,  
23 Supplementary Fig. 1). Of note, the involvement of other prefrontal-limbic-temporal cortical areas  
24 that have previously been implicated in a non-motor related theta network could not be assessed  
25 in this cohort<sup>47</sup>.  
26

## 1 Assessing contributions of state anxiety and motor symptoms

2 Next, we aimed to investigate whether, beyond indexing ‘trait’ anxiety (e.g. HARS and BAI), basal  
3 ganglia theta power could also be related to within-subject variations in ‘state’ anxiety. This was  
4 assessed in the at-home cohorts. For the ‘at-home chronic rest’ cohort, for a period of  
5 approximately 14 days, patients provided daily reports of ecological momentary assessments of  
6 their anxiety level on a VAS immediately after triggering an LFP recording. At the within-subject  
7 level, VAS anxiety—representing ‘state’ anxiety—was not related to basal ganglia theta or alpha  
8 power, neither in MedON-StimOff ( $p=0.147$  and  $\beta<0.0001$  for theta,  $p=0.832$  and  $\beta<0.0001$  for  
9 alpha) nor MedON-StimOn ( $p=0.960$  and  $\beta<0.0001$  for theta,  $p=0.870$  and  $\beta<0.0001$  for alpha)  
10 conditions (Supplementary Fig. 2, panels A to E). Similarly, VAS anxiety ratings did not predict  
11 low frequency power in the ‘at-home chronic task’ cohort either. Specifically, VAS anxiety ratings  
12 were acquired immediately before starting the task to provide a measure of anxiety fluctuations  
13 across days, and as in the ‘at-home chronic at-rest cohort’, VAS anxiety scores at the run level did  
14 not predict either theta or alpha power in MedON-StimOff or MedON-StimOn (all  $p>0.143$ , all  
15  $\beta<0.0001$ ) conditions (Supplementary Fig. 2, panels F to J). This suggests that within-subject  
16 ‘state’ anxiety fluctuations are not directly related to basal ganglia theta power.

17

18 In contrast, in the ‘at-home chronic rest’ cohort, averaging VAS anxiety scores per patient across  
19 14 days to derive an estimate of ‘trait’ anxiety revealed a positive relationship with basal ganglia  
20 theta power in MedON-StimOff ( $p=0.023$ ,  $\beta=0.0008$ ) and was trending towards significant in  
21 MedON-StimOn ( $p=0.051$ ,  $\beta=0.0007$ ) (Supplementary Fig. 3, panels A, B, and E). Average VAS  
22 anxiety per patient was also positively related with basal ganglia alpha power, with MedON-  
23 StimOff ( $p=0.012$ ,  $\beta=0.0009$ ) and MedON-StimOn ( $p=0.032$ ,  $\beta=0.0007$ ) (Supplementary Fig. 3,  
24 panels C, D, and E). Thus, ‘trait’ measures of anxiety computed by averaging VAS anxiety ratings  
25 across days also predict theta and alpha power, which aligns with our core finding of a relationship  
26 between low frequency power and ‘trait’ anxiety measured by surveys (i.e. HARS and BAI). In  
27 sum, basal ganglia theta and alpha power reflected the average VAS anxiety ratings across days in  
28 the ‘at-home chronic at-rest’ cohort, but did not track day-to-day fluctuations in anxiety in either  
29 at-home cohort, indicating a stronger correspondence with ‘trait’ than ‘state’ anxiety levels.

30

1 Since anxiety fluctuations during the day are often associated with changes in a patient's motor  
2 state, we then explored whether changes in anxiety were influenced by changes in the overall  
3 motor state as perceived by the patient using VAS motor symptoms ratings. We analyzed  
4 concurrent measures of motor symptoms and anxiety from the 'At-home chronic at-rest cohort'  
5 using VAS ratings (as detailed in the methods). We found a positive relation within-subject  
6 between daily VAS anxiety and VAS motor scores in both MedON-StimOff ( $\beta=0.3341$ ;  $p=0.0018$ )  
7 and MedON-StimOn ( $\beta=0.4866$ ,  $p<0.0001$ ) states. These findings validate the previously reported  
8 relationship between anxiety and motor functions in PD<sup>48</sup>.

9 We next examined whether these motor symptoms predicted basal ganglia activity. Using VAS  
10 motor ratings averaged within each patient to predict neural power, we found that average VAS  
11 motor scores were inversely related to basal ganglia theta in the MedON-StimOff condition ( $\beta=-$   
12  $0.0007$ ,  $p=0.0231$ ) but not in the MedON-StimOn condition ( $\beta=0.0003$ ,  $p=0.6340$ ). No significant  
13 relationship was found between average VAS motor scores and basal ganglia alpha activity.

14 Lastly, we tested whether the relationship between anxiety and basal ganglia theta power was  
15 affected by VAS motor symptoms scores by including motor and anxiety VAS scores as fixed  
16 effects in the same LME. We found that average VAS anxiety continued to predict basal ganglia  
17 theta power ( $\beta=0.0012$ ,  $p=0.0004$ ) in the MedON-StimOff state and a trend toward statistical  
18 significance in the MedON-StimOn state ( $\beta=0.0007$ ,  $p=0.0890$ ) in this combined model.

19 In summary, while daily fluctuations in anxiety and motor symptoms are correlated within  
20 subjects, trait anxiety (average VAS anxiety) remains a robust predictor of subcortical theta power,  
21 even when controlling for overall motor symptom severity (average VAS motor).

22

23 Lastly, we explored the relationship between depression and low-frequency oscillations<sup>31</sup>, but  
24 found inconsistent results across the three cohorts (See Supplementary Material).

25

26 In summary, our study revealed a consistent positive association between anxiety and basal ganglia  
27 theta power in PD patients across different cohorts and conditions, indicating a potential neural  
28 correlate of anxiety in PD. Importantly, even when accounting for overall motor symptom severity  
29 - whether assessed in the clinic using clinical scales or at home with VAS ratings - trait anxiety

1 remains a robust predictor of basal ganglia theta power. This underscores that the relationship  
2 between trait anxiety and subcortical theta activity is independent of the severity of motor  
3 symptoms.

4

## 5 **Discussion**

6

7 In the present study, we evaluated the basal ganglia neural correlates of anxiety in PD patients for  
8 the first time, using both in-laboratory and at-home recordings. Across three independent cohorts,  
9 our results demonstrate that subcortical theta power recorded from STN and GPi is positively  
10 related to anxiety in PD, with higher theta power indexing more severe anxiety. This effect was  
11 present regardless of DBS being enabled/disabled and during both rest and waiting periods of a  
12 cognitive task. We did not find any association between anxiety and theta or alpha power recorded  
13 from the electrocorticography over the premotor frontal cortex, suggesting this relationship is  
14 region-specific. Lastly, theta did not track variations in anxiety ratings across days.

15

16 To our knowledge, this is the first study exploring neural biomarkers for non-motor symptoms  
17 using commercially available sensing-enabled DBS devices that allow chronic patient recording  
18 at home. Our approach of parallel lab-based and home-based assessments and recordings supports  
19 both scientific reproducibility and ecological validity.

20

21 Another feature of this study is the observation of the same relation between basal ganglia theta  
22 and anxiety in three independent cohorts, each employing somewhat different methodologies with  
23 regard to clinical setting, assessment of anxiety, and LFP recording. We studied a heterogeneous  
24 DBS population comprising unilateral and bilateral DBS of both the STN and the GPi, with LME  
25 models accounting for heterogeneity across implantation targets and laterality.

26

27 Low frequency oscillations (including alpha and theta bands) in the STN have previously been  
28 evaluated in relation to cognition and emotion in PD patients (for a review see<sup>29</sup>). Current literature

1 implicates low frequencies in cognitive processes such as conflictual judgment<sup>49</sup>, decision  
2 making<sup>50</sup>, reward-related processing<sup>51</sup> and perceptual discrimination<sup>52</sup>. Regarding  
3 neuropsychiatric symptoms, low frequencies have been related with trait impulsivity<sup>32</sup>, ICB<sup>30</sup>, and  
4 depression<sup>53–55</sup>.

5  
6 We extend this knowledge to anxiety, showing a consistent association between theta and anxiety  
7 in each of our three samples. It is however not possible to disentangle whether the relationship  
8 with theta is strictly specific for anxiety or if it is driven by other highly correlated and co-occurring  
9 neuropsychiatric symptoms, especially depression<sup>56</sup>. In our cohort of patients studied subacutely  
10 after surgery, theta was also positively related to depression, but importantly, this was not  
11 replicated in our two at-home cohorts, though these at-home cohorts had lower proportions of  
12 patients meeting clinical criteria for depression. Overall, our data suggest that subcortical theta  
13 may specifically index anxiety and provide some evidence that anxiety and depression may be  
14 neurophysiologically separable. Nevertheless, this remains a challenge for further research since  
15 neuropsychiatric symptoms in PD are highly comorbid<sup>56</sup>. A PD patient with anxiety is very likely  
16 to also present clinical symptoms of depression, ICB or apathy. Moreover, the comorbidity of  
17 anxiety and depression is highly influenced by strong overlap in diagnostic criteria and assessment  
18 scales, which may be responsible for artificially increasing comorbidity rates<sup>57</sup>, and we cannot  
19 exclude that this influences our results and previous reports. From a clinical perspective, although  
20 it has been well demonstrated that anxiety can occur independently from depression in PD<sup>56</sup>, this  
21 conundrum may be less concerning for current therapeutic strategies, as treatments for the different  
22 neuropsychiatric symptoms are often similar. For example, antidepressants and psychotherapy are  
23 validated treatments for anxiety, depression and apathy in PD<sup>17</sup>. However, disentangling different  
24 neuropsychiatric features in PD remains an important although challenging research question for  
25 future studies and a primary aim for developing new, effective therapeutic approaches.  
26

27 Since previous research has also linked theta/alpha power to tremor<sup>58</sup> and dyskinesia<sup>30</sup>, we  
28 controlled for the effects of these motor symptoms with additional analyses in the cohort of patients  
29 assessed in the hospital with externalized leads (referred to as the ‘in-hospital externalized at-rest  
30 cohort’). We found no association between tremor and alpha or theta and between dyskinesia and

1 alpha or theta, and the relationship between theta and anxiety held when controlling for these motor  
2 symptoms in the model.

3

4 Recording LFPs via sensing-enabled DBS at home in the Percept and RC+S cohorts also enabled  
5 a comparison with daily VAS anxiety severity ratings, but we found no evidence that theta tracked  
6 these day-to-day variations in anxiety. The psychobiological substrates of fluctuations in anxiety  
7 captured by VAS ratings may differ substantially from standardized clinical questionnaires (e.g.  
8 BAI and HARS), which measure an average level of anxiety over the previous few weeks. The  
9 former is often referred to as 'state' anxiety, while the latter is conceptualized as 'trait' anxiety<sup>13,59</sup>.  
10 It's therefore conceivable that 'trait' and 'state' anxiety may have different biomarker profiles.  
11 The lack of correspondence between theta and day-to-day anxiety VAS ratings, as well as the  
12 persistence of the relationship to clinical anxiety scores even during quiet attentive periods in the  
13 reward task and during both stimulation on and off conditions, suggest that basal ganglia theta may  
14 be more closely related to 'trait' anxiety.

15

16 The dissociation between state and trait anxiety in terms of biomarkers might also reflect the  
17 heterogeneous phenomenology of anxiety in PD, which encompasses persistent and episodic  
18 anxiety or a combination of both. Also, factors such as non-motor fluctuations and situation-  
19 specific anxiety (e.g. fear of falling) are not really explored with the currently available  
20 questionnaires or ecological momentary assessment tools. This measurement gap reflects a need  
21 in future studies for more disease-specific measures to disentangle 'state' and 'trait' anxiety in PD,  
22 possibly including objective measures such as peripheral physiology (e.g. heart rate variability,  
23 skin conductance, etc.).

24

25 A limitation of this study is the relatively small sample size, which has limited our analysis. The  
26 sample sizes of the cohorts did not allow a full, data-driven exploration of potential biomarkers.  
27 Instead, we relied on a priori testing of hypotheses concerning canonical theta and alpha frequency  
28 bands, which were informed by prior literature implicating these signals in cognitive and emotional  
29 processing<sup>29</sup>. However, it is worth noting that despite smaller sample sizes per cohort, this was

1 independently replicated across three different cohorts and significant within each cohort. Our  
2 LME modelling approach included fixed effects for hemisphere and basal ganglia region to control  
3 for these potential confounds, as well as random intercepts to account for the hierarchical nature  
4 of our repeated-measures data. However, these theoretically motivated decisions reduced statistical  
5 power to detect effects with our sample sizes, which may explain some inconsistencies across the  
6 three cohorts with regard to presence/absence of a relation in the different stimulation-medication  
7 conditions. For example, with MedON-StimOff, there is a significant relation between basal  
8 ganglia theta and anxiety in two out of three cohorts, with a trend ( $\beta=0.061$ ) in the same direction  
9 in the remaining cohort. Similarly, restricted statistical power due to sample sizes creates  
10 challenges for reliably disentangling the different contributions of hemisphere (left versus right)  
11 and target (STN versus GPi). Also, we showed an association between theta and anxiety, however  
12 we cannot ascertain whether this reflects a primarily pathological or a secondary/compensatory  
13 process. For example, top-down communication in theta frequencies from medial prefrontal cortex  
14 to STN reflects cognitive control adjustments during uncertainty and punishment<sup>60-62</sup>, and this  
15 medial frontal theta signal is stronger in individuals with higher trait anxiety<sup>63,64</sup>. These data  
16 support the proposal that chronically increased anxiety may be related to excessive theta signaling  
17 of uncertainty and punishment<sup>65</sup>, but the observational nature of our study precludes any inferences  
18 about brain-symptom causality and constrains our ability to assess theta's role in the above  
19 mentioned dynamics of state anxiety.

20

21 Despite these limitations, the current study strongly suggests that basal ganglia theta could serve  
22 as an objective biomarker of the general anxiety level in PD patients treated with DBS. Our  
23 work could potentially also provide insights into the mechanism of similar neuropsychiatric  
24 symptoms in people who do not have PD. Indeed, alpha and theta frequencies power have been  
25 linked to major depression<sup>66</sup>, drug addiction<sup>67</sup>, obsessive-compulsive disorder<sup>68</sup> and Tourette  
26 syndrome<sup>69</sup>, thus suggesting possible transdiagnostic networks.

27

28 More studies should confirm and extend our findings to clarify the causality of the relation between  
29 anxiety and theta in PD. More research is also required to assess whether, within a patient, theta  
30 changes along with long-term (weeks-months) changes in general anxiety level ('trait' anxiety).

1 Similar to beta-based adaptive DBS for motor symptoms<sup>23,25</sup>, basal ganglia theta could  
2 theoretically drive closed-loop paradigms aimed at providing targeted neuromodulation for  
3 anxiety. However, our current findings do not yet support the implementation of such responsive  
4 neuromodulation strategies. Unlike beta-based motor adaptive DBS, which operates on shorter  
5 timescales, potential closed-loop systems for anxiety may require adjustments for longer  
6 timescales due to the nature of trait versus state biomarkers. Indeed, response to DBS for  
7 depression and obsessive-compulsive disorder can require months or even years<sup>70–72</sup>. To develop  
8 effective closed-loop paradigms that address short-term fluctuations in anxiety, we will need a  
9 biomarker specifically associated with ‘state’ anxiety. Finally, the field would greatly benefit  
10 from the discovery of other objective markers of anxiety, residing in the subcortical/cortical LFP  
11 signal, autonomic system (e.g. heart rate variability<sup>73</sup>, temperature, or respiration changes) or  
12 elsewhere.

13

14 In conclusion, we demonstrate that basal ganglia theta is related to anxiety in PD patients treated  
15 with DBS. This objective marker of anxiety could have diagnostic and therapeutic implications in  
16 clinical care .

17

## 18 **Data availability**

19 Individual patient data fall under the health data category of the General Data Privacy Regulation  
20 and require the lawful definition of data sharing agreements from all data controllers. Data sharing  
21 agreements can be set in place upon reasonable request to the senior authors (SL, LR).

22

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27

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6

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16

17 **Supplementary material**

18 Supplementary material is available at *Brain* online.

19

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14

## 1 **Figure legends**

2 **Figure 1 Three independent investigational cohorts for neurophysiological analysis.** This  
3 study included three cohorts of PD patients treated with DBS. In the ‘in-hospital externalized at-  
4 rest’ cohort, basal ganglia LFP recordings were obtained from the STN a few days after surgery  
5 via externalized electrodes with the patient at rest. Patients were either OFF or ON medication, but  
6 stimulation was not enabled yet. Anxiety was rated with the Hamilton anxiety rating scale (HARS).  
7 In the ‘at-home chronic at-rest’ cohort, basal ganglia (STN or GPi) LFPs were obtained at home  
8 in an unsupervised but semi-structured setting using the Percept PC’s BrainSense technology  
9 (BrainSense ‘Event’ triggered by the patient) with the patient at rest. Stimulation was either off or  
10 on, but patients were always in a Medication ON state. Anxiety was rated with the Beck anxiety  
11 inventory (BAI). Whereas in the other two cohorts offline LFP processing was required to obtain  
12 frequency domain data, raw LFPs were not available in the ‘at-home chronic at-rest’ cohort. In the  
13 ‘at-home chronic task’ cohort, basal ganglia (STN or GPi) and cortical (premotor cortex) LFPs  
14 were obtained via remotely supervised streaming via the Summit RC+S system with the patient at  
15 rest between trials of a behavioral task. Experimental conditions involved Medication ON  
16 Stimulation on, and Medication ON Stimulation off. Anxiety was rated with the Beck anxiety  
17 inventory (BAI). In all three cohorts, analyses were focused on the relation between anxiety  
18 measures and power in the theta and alpha frequency bands. Infographics in the first row have  
19 been generated with the help of the generative AI platform Stable Diffusion Online  
20 (<https://stablediffusionweb.com/>). Abbreviations: LFP, local field potential; GPi, globus pallidus  
21 pars interna; PSD, power spectral density; STN, subthalamic nucleus.

22  
23 **Figure 2 Anxiety is related to basal ganglia theta in in-hospital externalized recordings.** This  
24 figure displays the relation between anxiety measured by the Hamilton anxiety rating scale and  
25 basal ganglia (STN) theta and alpha band power in the ‘in-hospital externalized at-rest’ cohort.  
26 Each color represents a patient (n = 12 patients), empty/filled markers indicate right/left  
27 hemisphere recordings (n = 24 hemispheres). With Medication OFF Stimulation off, a positive  
28 relation is present between anxiety and basal ganglia theta (panel A). Panel E illustrates the  
29 coefficients of anxiety in LME models. \*, p < 0.05. Abbreviations: CI, confidence interval; HARS,  
30 Hamilton anxiety rating scale; LME, linear mixed-effects model; STN, subthalamic nucleus.

1 **Figure 3 Anxiety is related to basal ganglia theta and alpha in at-home at-rest recordings.**  
2 Relation between anxiety and subcortical LFP in the ‘at-home chronic at-rest’ cohort. Scatter plot  
3 colors indicate participant (n = 13 patients), with circles indicating STN and squares indicating  
4 GPi implants. Empty/filled markers indicate right/left hemisphere recordings (n = 19  
5 hemispheres). Theta and alpha band power were extracted from at-home at-rest BrainSense Event  
6 LFP recordings, and correlation was assessed with baseline anxiety measured with Beck anxiety  
7 inventory (BAI). With Medication ON Stimulation off (panels A and C) and Medication ON  
8 Stimulation on (panels B and D), anxiety is positively related with subcortical theta (panels A and  
9 B) and alpha (panels C and D) band power. Panel E illustrates the coefficients of BAI in LME  
10 models. \*, p < 0.05. Abbreviations: BAI, Beck anxiety inventory; CI, confidence interval; GPi,  
11 globus pallidus pars interna; LFP, local field potential; LME, linear mixed-effects model; STN,  
12 subthalamic nucleus.

13

14 **Figure 4 Anxiety is related to basal ganglia theta in at-home recordings during a cognitive**  
15 **task.** Relation between anxiety and subcortical LFP during a reward task in the ‘At-home chronic  
16 task’ cohort. Theta and alpha power were extracted from the inter-trial interval in a reward task,  
17 and correlation was assessed with baseline anxiety (BAI). Scatter plot colors indicate participant  
18 (n = 8 patients), with circles indicating STN and squares indicating GPi implants. Empty/filled  
19 markers indicate right/left hemisphere recordings (n = 15 hemispheres). With Medication ON  
20 Stimulation off (panel A), there is a positive relation between anxiety and subcortical theta band  
21 power. Panel E illustrates the coefficients of BAI in LME models. \*, p < 0.05. Abbreviations: BAI,  
22 Beck anxiety inventory; CI, confidence interval; GPi, globus pallidus pars interna; LFP, local field  
23 potential; LME, linear mixed-effects model; STN, subthalamic nucleus.

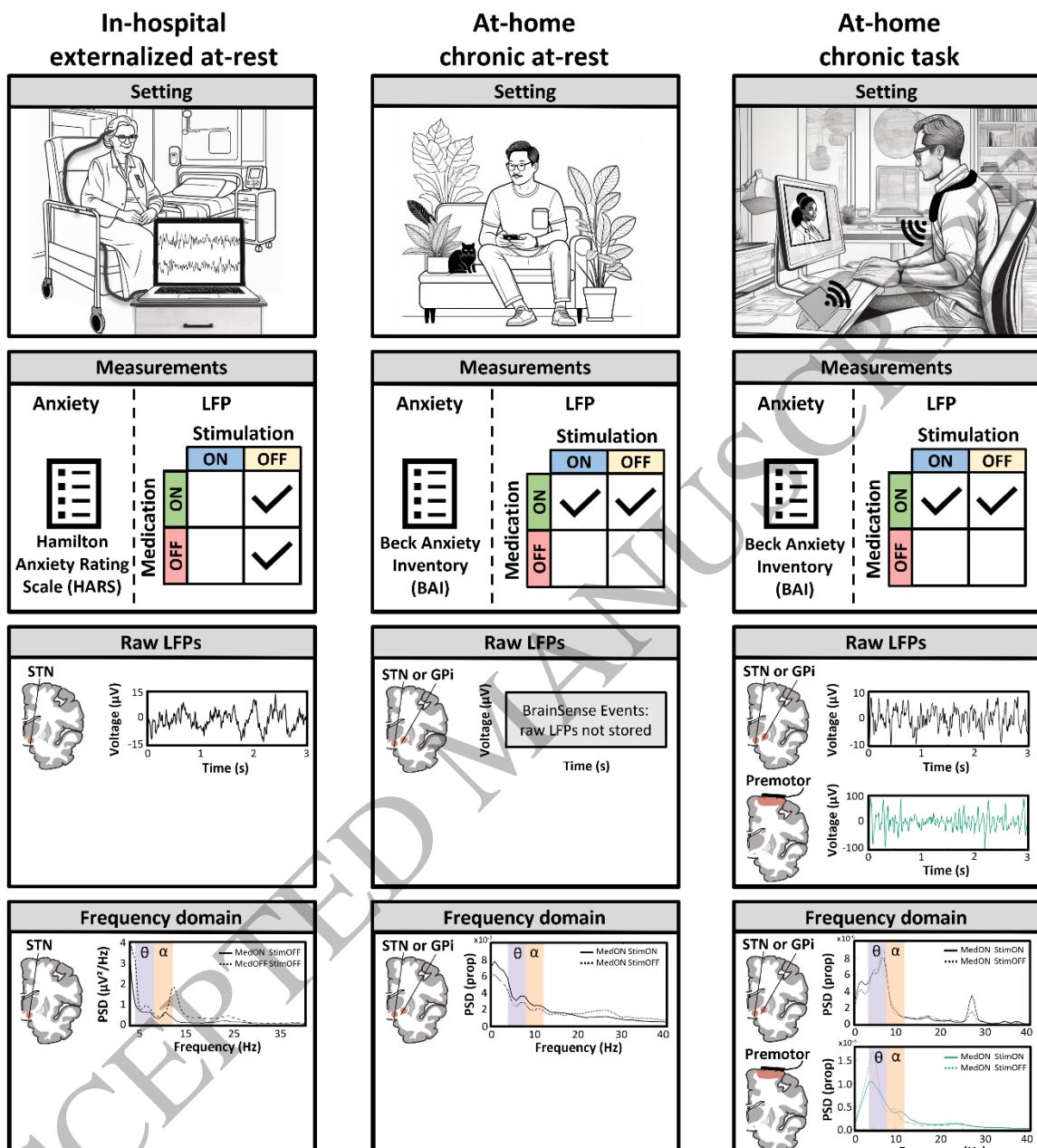
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**Table 1** Patient characteristics across the three cohorts

Characteristics	In-hospital externalized at-rest	At-home chronic at-rest	At-home chronic task
Patients (n)	12	13	8
Hemispheres (n)	24	20	15*
Target (n hemispheres) - STN   GPi	24   0	14   6	8   7
Sex (n patients) - F   M	8   4	2   11	1   7
Age (y) - mean (SD)	62.5 (3.9)	64.9 (9.8)	61.9 (9.6)
Use of anxiolytics and antidepressants	1/12; 0/12	0/13; 8/13	1/8; 6/8
Disease duration (y) - mean (SD)	11.2 (5.6)	11.3 (4.2)	11.4 (5.7)
DBS duration (y) - mean (SD)	N/A	1.5 (1.8)	2.5 (1.1)
Anxiety			
BAI - mean (SD)	N/A	9.9 (9.3)	10.5 (3.5)
HARS - mean (SD)	9.2 (7.6)	N/A	N/A
Depression			
BDI - mean (SD)	N/A	6.2 (3.7)	9.8 (8.0)
HDRS - mean (SD)	8.4 (5.4)	N/A	N/A

BAI, Beck anxiety inventory; BDI, Beck depression inventory; GPi, globus pallidus pars interna; HARS, Hamilton anxiety rating scale; HDRS, Hamilton depression rating scale; N/A, not applicable; SD, standard deviation; STN, subthalamic nucleus.

\*Each with a quadripolar electrocorticography paddle over the sensorimotor cortex.



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Figure 1  
159x176 mm (x DPI)

### In-hospital externalized at-rest – anxiety and basal ganglia LFP

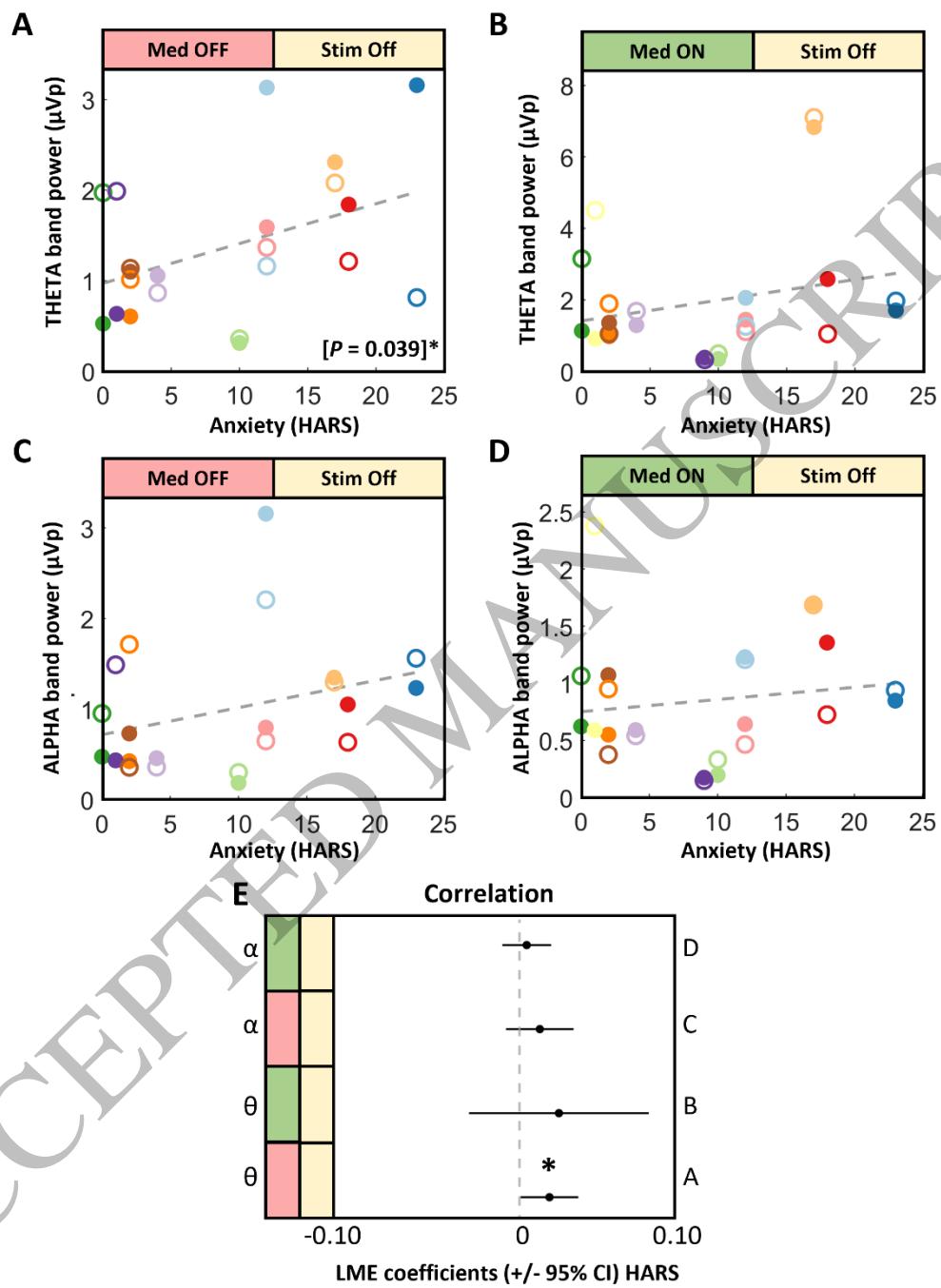


Figure 2  
159x221 mm (x DPI)

### At-home chronic at-rest – anxiety and basal ganglia LFP

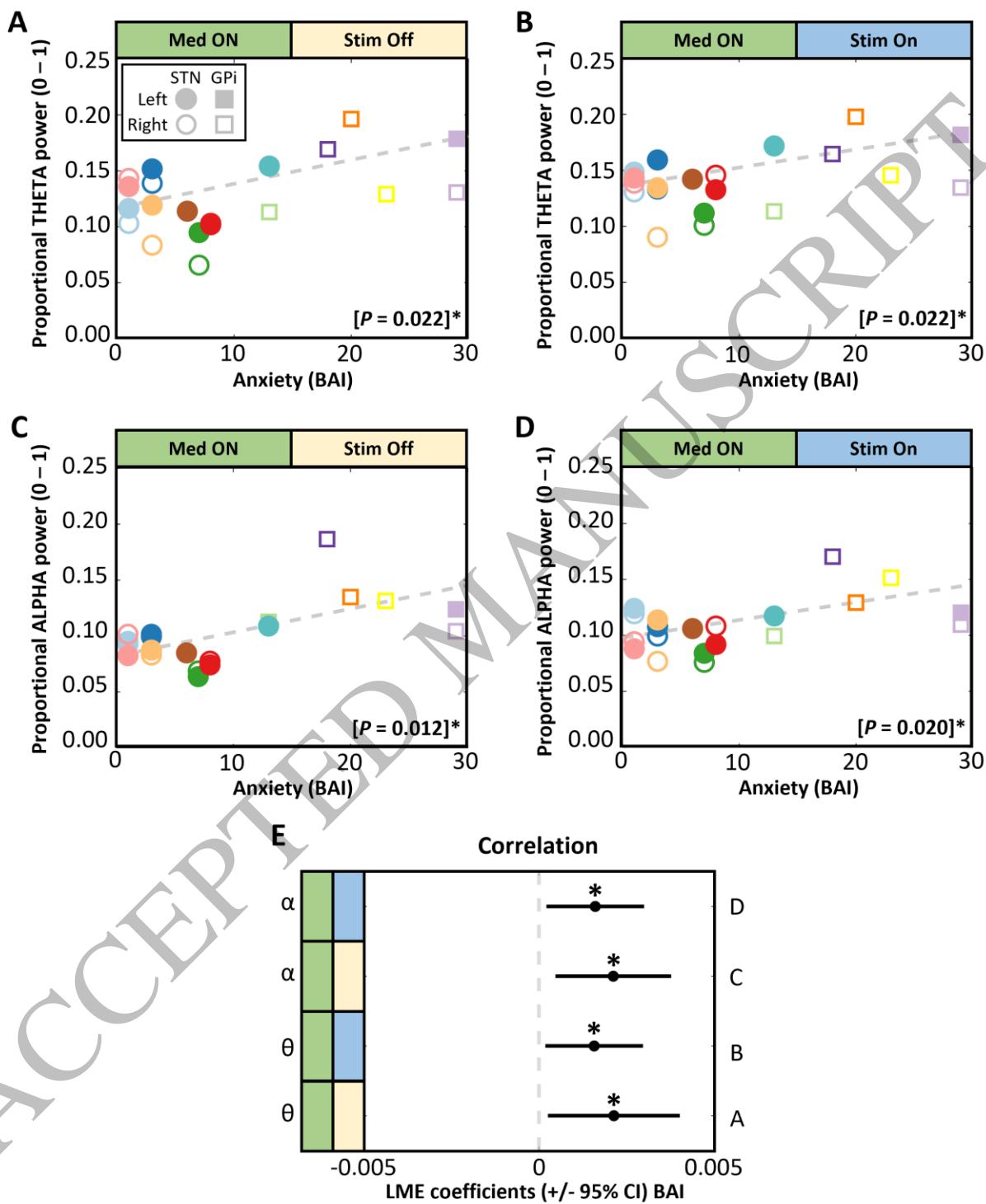


Figure 3  
159x198 mm (x DPI)

### At-home chronic task – anxiety and basal ganglia LFP

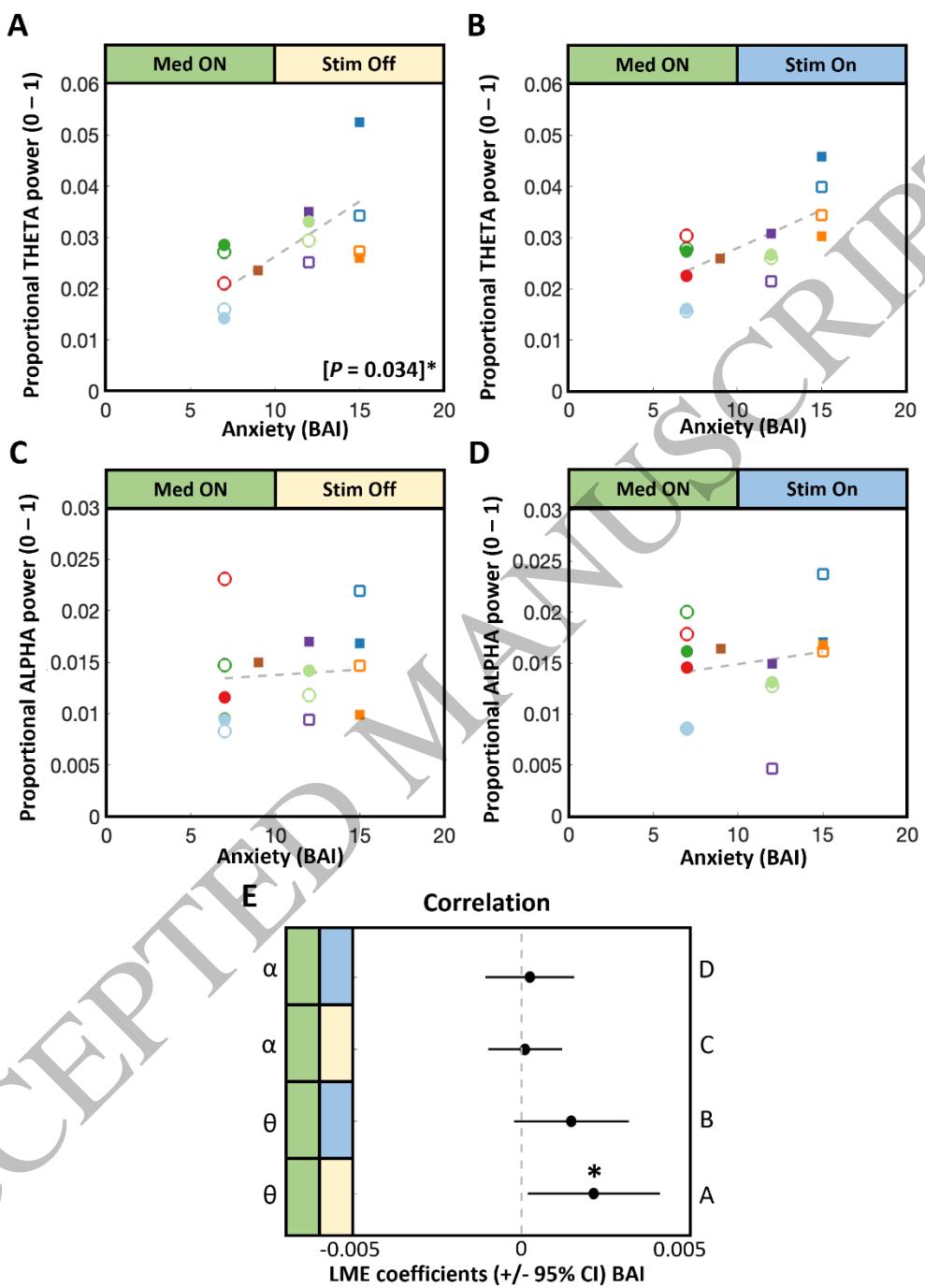


Figure 4  
159x226 mm (x DPI)