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Non-invasive vagus nerve stimulation modulates subthalamic beta activity in Parkinson's disease

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Recently, preliminary studies on patients with Parkinson disease (PD) have suggested a beneficial effect of non-invasive vagus nerve stimulation (VNS) on motor symptoms [1–3], in line with experimental evidence obtained in animal studies [4]. However, the mechanisms of the VNS action have yet to be elucidated. One possibility is that the stimulation acts as a modulator of ascending pathways, such as the serotonergic pathways, previously involved in the pathophysiology of gait dysfunction in PD [4,5]. One of the neurophysiological markers of PD is the exaggerated beta oscillatory activity observed in the sub-thalamic nucleus (STN), which has previously been related to motor symptom severity [6]. Although a link between the ascending vagal systems and the STN has been postulated in animals [7], such a relationship has not yet been investigated in patients with PD.

Here, we directly tested the effect of cervical non-invasive VNS on STN beta band activity by first recording local field potentials (LFP) in a PD patient undergoing awake deep brain stimulation (DBS) surgery, after an overnight withdrawal of PD medication. Unipolar STN-LFPs were acquired during the DBS surgery through Medtronic 3389 macroelectrodes, amplified, sampled at 2048 Hz and common average reference across all recording channels using a TMSi port (TMS International, Netherlands). The stimulation was performed with the GammaCORE device (transcutaneous cervical VNS) placed on his left neck. A conductive water-based gel was applied to maintain an uninterrupted conductive path from the stimulation surfaces to the skin during the full recording session.

After a baseline recording of STN activity, the patient received four blocks of VNS (100 seconds (s) at 25Hz) separated by 60s of interstimulus interval (Fig. 1A). LFPs recordings were prolonged after the last stimulation block to investigate the post-stimulation effects. The recordings lasted about 12 min and the contact between the VNS device and the skin was maintained throughout, to avoid any sensory confound (alternating active and inactive states).

LFPs were analysed offline using custom-written scripts in MATLAB (2019a, Mathworks, Massachusetts, USA). Bipolar montages were created between adjacent contacts to reduce the effect of volume conduction (L01, L12, L23 - left STN and R01, R12, R23 - right STN ventral-to-dorsal order). Continuous LFPs signals were then segmented in three periods as follows: baseline (30s before the first VNS block), inter-stimulation (3 * 60s), and post-stimulation (30s after the last block). For each period, power spectral densities (PSD) were estimated in consecutives 5s time-windows (pwelch method, 50% overlap) normalized to the percentage of total power between 5 and 90 Hz and averaged across all time-windows.

The results revealed a bilateral modulation of PSDs between the 3 periods particularly clear at contact R01 (Fig. 1B and Fig. S1). Cluster-based permutation tests suggest a reduction of low beta power after the last block compared to baseline (15:21Hz, $t = 24.05$, $p = 0.004$) or to the inter-stimulation periods (16:20, $t = 16.7$, $p = 0.035$). An increase of theta power was also observed in the inter-stimulation period compared to baseline (5:9Hz, $t = -14.1$, $p = 0.044$). Similar modulations were observed in other contacts (Figure S1- Table S1) apart from L01, which was located partially below the STN (Fig. S2). Note that beta power was however not significantly reduced during stimulation blocks (Fig. S3), suggesting that a minimal duration of VNS is needed to modulate STN activity.

The dynamics of the VNS effect were further tested at R01, first in the 50s following the last VNS block (post-stimulation period) and then across the inter-stimulation periods (first 30s of each period). To this end, power was averaged in 4 pre-defined frequency bands (theta, 4–8Hz; alpha, 9–12 Hz; low-Beta, 13–20 Hz; high-Beta 20–31 Hz) in short time windows of 2.5 sec expressed as percentage change relative to the baseline. This revealed that low beta power was maximally reduced in the first 20 seconds following VNS offset, before progressively returning to its baseline level (Fig. 1C). In addition, the comparison across consecutive VNS blocks showed a progressive reduction in low beta, which reached its maximum after the last block, suggesting a cumulative effect across blocks (Fig. 1D).

To confirm this first observation in a larger cohort, the experiment was replicated in 6 chronically implanted PD patients (Percept IPG, Sensight leads; Medtronic), recruited from the movement disorders clinic of the Fondazione Policlinico Universitario Campus Bio-Medico (Rome, Italy). All of them had STN-DBS surgery at least 2 months before the recording, to avoid potential artifacts due to the stunning effect (clinical details in Table S2). Non-invasive VNS was applied after overnight withdrawal of parkinsonian treatment and 1 hour after DBS was turned off (med-OFF/stim OFF) following the protocol described in Fig. 1A. The VNS stimulation was well tolerated by all patients and no adverse events were reported. LFPs were recorded with the "indefinite streaming" mode of the Percept and analysed following the same procedure as

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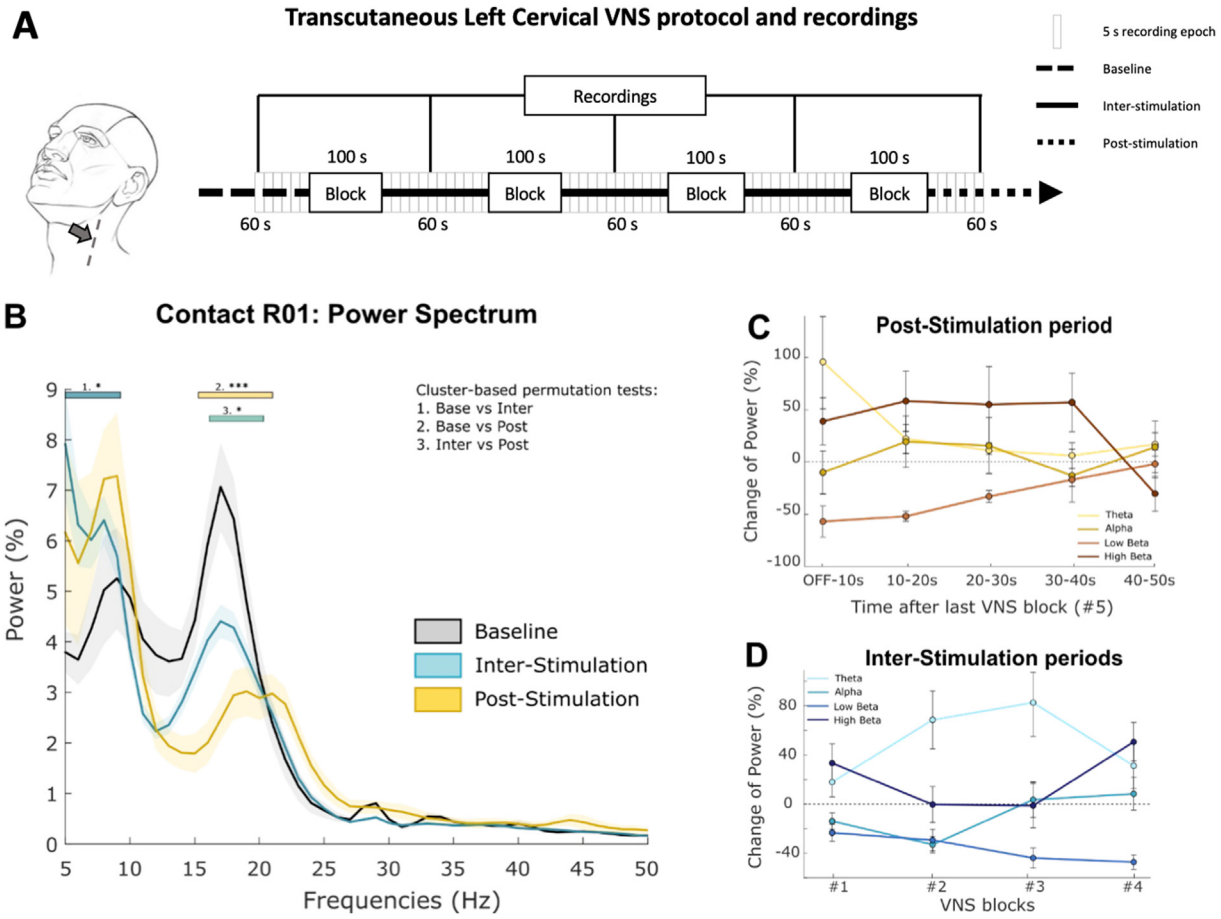

Fig. 1. Protocol and modulation of STN activity during intra-operative LFP recordings. A) Transcutaneous cervical VNS protocol. The patient was stimulated at the left cervical branch of the vagus nerve with 4 stimulation blocks (100 s, 25 Hz). A 60s baseline (dashed line) and post-stimulation (dotted line) period were recorded to obtain a reference and for the investigation of VNS duration, respectively. Inter-stimulation periods (black full line) were analysed to investigate any possible cumulative effect. B) Power Spectral Densities (PSDs) for the 3 main periods (mean±sem across shorter windows of 5 seconds) and one bipolar contact (R01). The horizontal bar indicates the results of the cluster-based permutation tests (see text and Supplementary Table 1 for details). C) Changes in averaged power in the 4 predefined frequency bands (Theta, 4–8Hz; Alpha, 9–12 Hz; Low-Beta, 13–20 Hz; High-Beta 20–35 Hz) during the post-stimulation period and D) during the 30 first seconds of each inter-stimulation period.

patient 1. Data from patient 5 were excluded from further analysis due to the presence of artifacts.

The group analysis showed a significant bilateral reduction of low beta following the VNS protocol (left STN $t = -2.67$, $p = 0.019$; right STN $t = -5.56$, $p < 0.01$; Fig. 2A). In line with the former intraoperative case, this reduction was prominent on the right STN (Fig. S3), was achieved progressively across stimulation blocks, and persisted after the last block for 20–30s before slowly disappearing (Fig. 2BC).

This is the first study analysing the effect of VNS on STN activity in PD. The results suggested that VNS might induce a modulation of power in the low beta range, a frequency band previously shown to be preferentially modulated by levodopa and DBS [8,9], and whose modulation has been associated with improvements of PD motor symptoms (i.e., rigidity, bradykinesia [6,10]). Noteworthy, our results support the clinical benefits previously observed in patients with mild to moderate PD, in whom non-invasive cervical or auricular VNS were able to improve gait features such as step length and variability and stride velocity [1–3,11]. In line with this, low beta power has been previously associated with axial symptoms of PD, including gait [12].

Afferent vagus nerve fibres carry sensory inputs to the nucleus tractus Solitarii, which then mostly projects to the locus coeruleus, the raphe and parabrachial nuclei [13]. While the two first structures play an important role in the noradrenergic and serotonergic pathways, and are probably implicated in the antidepressant effect of VNS [5], the latter connects the vagal afferents to the thalamus and the dopamine system [7]. In line with this, it has recently been shown that VNS can modulate thalamic activity [14]. This raises the possibility that 20Hz-VNS, by modulating the dopamine metabolism in the subcortical network, reduces the pathological STN activity and alleviate motor symptoms in PD. In contrast, direct stimulations of the STN or the primary motor cortex at 20Hz, which are associated with detrimental effects on motor performance, increase synchronization in the beta band [15,16]. This suggests that the known effect of 20 Hz VNS on promoting brain plasticity can happen without a direct entrainment of the motor network.

Future studies using larger cohort and more controlled designs with also larger time series are warranted to confirm these preliminary results and investigate the link between the clinical effects and the neurophysiological changes induced by VNS at different stimulation parameters [17]. This will definitively open new pathways for the VNS as a possible alternative PD therapeutic neuromodulation strategy.

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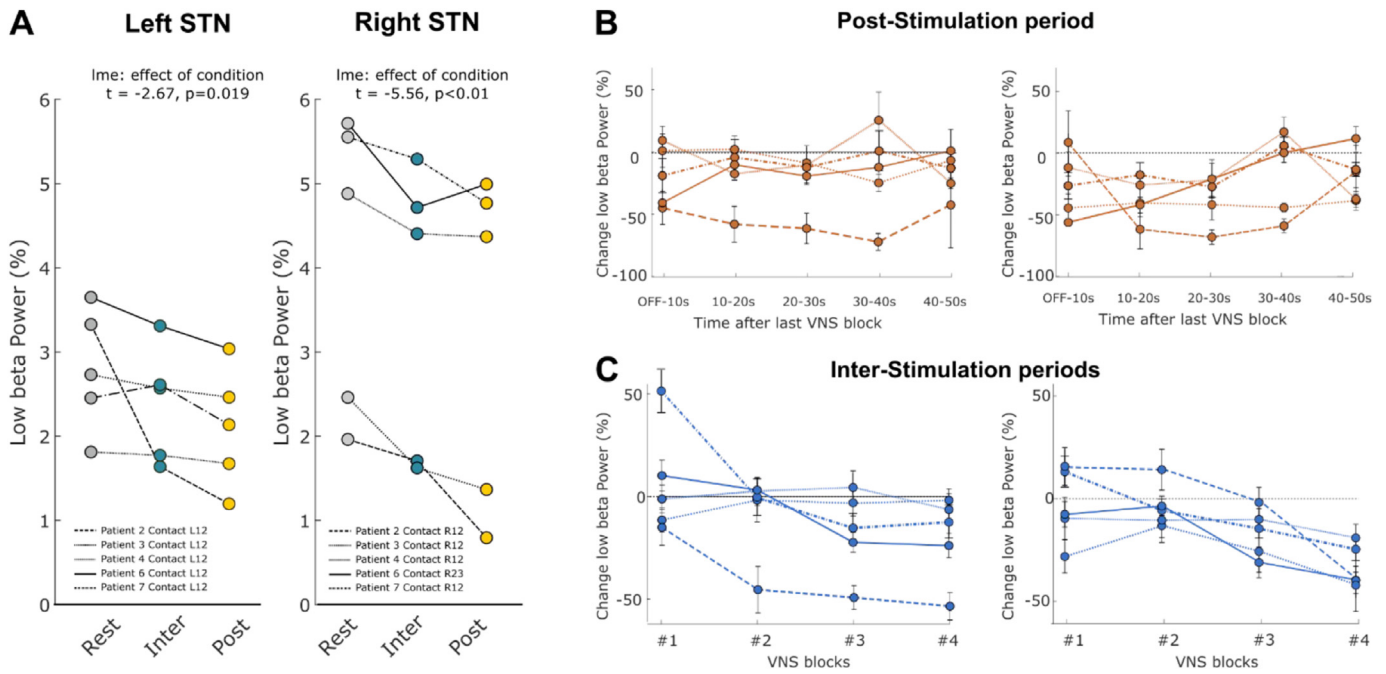

Fig. 2. Modulation of low beta STN activity recorded with Percept during the VNS protocol. A) Group analysis (n = 5) showing the reduction of averaged low beta power between the 3 main periods (baseline, inter-stimulation and post-stimulation) in both hemispheres. B) Changes in averaged low beta power for each patient (patient 2 to 7) during the 50 first seconds of the post-stimulation period and C) during the 30 first seconds of each inter-stimulation period.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.11.006.

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