Brain Stimulation

Subacute Alpha Frequency (10Hz) Subthalamic Stimulation for Emotional Processing in Parkinson's Disease

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Abstract:

Background: Psychiatric comorbidities are common in Parkinson's disease (PD) and may change with high-frequency stimulation targeting the subthalamic nucleus. Numerous accounts indicate subthalamic alpha-frequency oscillation is implicated in emotional processing. While intermittent alpha-frequency (10Hz) stimulation induces positive emotional effects, with more ventromedial contacts inducing larger effects, little is known about the subacute effect of ventral 10Hz subthalamic stimulation on emotional processing.

Objective/Hypothesis: To evaluate the subacute effect of 10Hz stimulation at bilateral ventral subthalamic nucleus on emotional processing in PD patients using an affective task, compared to that of clinical-frequency stimulation and off-stimulation.

Methods: Twenty PD patients with bilateral subthalamic deep brain stimulation for more than six months were tested with the affective task under three stimulation conditions (10Hz, 130Hz, and off-stimulation) in a double-blinded randomized design.

Results: While 130Hz stimulation reduced arousal ratings in all patients, 10Hz stimulation increased arousal selectively in patients with higher depression scores. Furthermore, 10Hz stimulation induced a positive shift in valence rating to negative emotional stimuli in patients with lower apathy scores, and 130Hz stimulation led to more positive valence to emotional stimuli in the patients with higher apathy scores. Notably, we found correlational relationships between stimulation site and affective rating: arousal ratings increase with stimulation from anterior to posterior site, and positive valence ratings increase with stimulation from dorsal to ventral site of the ventral subthalamic nucleus.

Conclusions: Our findings highlight the distinctive role of 10Hz stimulation on subjective emotional experience and unveil the spatial organization of the stimulation effect.

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Highlights

1. The study is the first demonstration of the subacute effects of 10Hz stimulation at the STN on emotional processing in a double-blind, randomized design.

2. We highlight the distinctive role of 10Hz stimulation on subjective emotional experience

3. We unveil the spatial organization of the stimulation effect within the ventral STN.
Subacute Alpha Frequency (10Hz) Subthalamic Stimulation for Emotional Processing in Parkinson’s Disease

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Background:

Psychiatric comorbidities are common in Parkinson’s disease (PD) and may change with high-frequency stimulation targeting the subthalamic nucleus. Numerous accounts indicate subthalamic alpha-frequency oscillation is implicated in emotional processing. While intermittent alpha-frequency (10Hz) stimulation induces positive emotional effects, with more ventromedial contacts inducing larger effects, little is known about the subacute effect of ventral 10Hz subthalamic stimulation on emotional processing.

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Twenty PD patients with bilateral subthalamic deep brain stimulation for more than six months were tested with the affective task under three stimulation conditions (10Hz, 130Hz, and off-stimulation) in a double-blinded randomized design.

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While 130Hz stimulation reduced arousal ratings in all patients, 10Hz stimulation increased arousal selectively in patients with higher depression scores. Furthermore, 10Hz stimulation induced a positive shift in valence rating to negative emotional stimuli in patients with lower apathy scores, and 130Hz stimulation led to more positive valence to emotional stimuli in the patients with higher apathy scores. Notably, we found correlational relationships between stimulation site and affective rating: arousal
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Conclusions:

Our findings highlight the distinctive role of 10Hz stimulation on subjective emotional experience and unveil the spatial organization of the stimulation effect.

**Key Words**

emotional processing, Parkinson’s disease, alpha frequency stimulation, subthalamic nucleus

**Abbreviations**

PD, Parkinson’s disease;

DBS, deep brain stimulation;

STN, subthalamic nucleus;

ERD, event-related desynchronization;

IPG, implanted pulse generator;

LSD, least square differences;

IAPS, International Affective Picture System;

BDI-Ⅱ, Beck Depression Inventory, Second Edition

AES, Apathy Evaluation Scale;

MDS UPDRS-Ⅲ, the part Ⅲ of Movement Disorder Society-Unified Parkinson’s Disease Rating Scale;
MNI, Montreal Neurological Institute;

TEED, total electrical energy delivered;

LEED, levodopa equivalent daily dosage;

VTA, volume of tissue activated.
Introduction

Emotion is critical to most aspects of human behavior. Biases in emotional processing are commonly found in neurological and psychiatric disorders and play key roles in disease pathophysiology. Parkinson’s disease (PD), resulting from the progressive degeneration of the nigrostriatal and mesolimbic dopamine systems, leads not only to predominant motor symptoms but multifarious non-motor features as well, such as mood disturbances [1]. Deep brain stimulation (DBS) is an invasive procedure with established practice in advanced PD, essential tremor (ET), idiopathic dystonia, and emerging applications in psychiatric disorders [2,3]. It delivers electric pulses at specific frequencies via electrodes and modulates oscillatory activity, thus impacting brain function. Whereas high-frequency stimulation targeting the dorsolateral motor subthalamic nucleus (STN) shows efficacy for cardinal motor symptoms of PD [4], little is known about the effects of low-frequency STN stimulation on emotional behaviors in PD patients.

Conceptually, subjective emotional experience is considered a single integral blend of two psychophysiological dimensions: valence, varying from negative to positive, and arousal, varying from low to high [5]. Evidence from anatomical, neuroimaging, and psychological studies has demonstrated the behavioral and functional segregation of affective valence and arousal [6–9], although integrated neural representations may exist within some subcortical regions [10]. PD is associated with a high comorbidity with depression, mood lability, and apathy with elements of decreased emotional reactivity [11]. These comorbidities are variously related to the neurobiology of PD, individual vulnerabilities, and side effects of therapy.

Convergent evidence suggests an important role of the STN in emotion processing [12,13]. A number of studies have reported postoperative changes in mood behaviors with chronic high-frequency STN stimulation [14,15]. The most commonly reported changes include mania and hypomania, impulsivity behaviors, suicidal ideation, apathy, and mood disorders. Chronic high-frequency stimulation to the STN contributes to
negative emotion recognition impairments, either in facial expressions [16–22] or in prosody [23]. Observations in subjective emotional experience also show enhanced valence of positive emotions and reduced intensity of negative feelings induced by film excerpts under tonic high-frequency STN stimulation [24,25].

Oscillatory STN activity at the alpha frequency band is well-documented to be correlated with postoperative mood changes [26–28]. LFP recordings of the STN in PD show a late event-related desynchronization (ERD) in the local alpha frequency band (8–12 Hz) for emotional but not neutral stimuli, which is closely correlated with depression severity following STN DBS [29–31]. These STN alpha findings are predominantly located at the ventral STN, highlighting the functional parcellation of the STN with emotional processing in the limbic territory of STN [28]. Targeting this late alpha ERD using time-locked intermittent stimulation of the right STN, our lab found a dissociable effect of stimulation frequency on the processing of negative emotional stimuli. While stimulating at 10Hz decreases subjective negative bias, and more ventromedial contacts induce larger effects, stimulating at 130Hz appears to selectively decrease arousal ratings [32]. It further raises the possibility of modulating emotional processing using bilateral 10Hz stimulation targeting the ventral STN in the clinical setting. However, the effects of subacute 10Hz stimulation at the ventral STN focused on emotional processing have not been investigated.

Here, we evaluated the subacute effects of bilateral 10Hz stimulation targeting the ventral STN on emotional processing using an affective task in PD patients, and compared it to that of clinical frequency (130Hz) stimulation and off-stimulation. We assumed that subacute 10Hz stimulation and 130Hz stimulation would have a differential influence on subjective valence and arousal, consistent with our previous findings following intermittent time-locked procedure.

**Materials and methods**

*Study design and participants*
This was a prospective double-blinded randomized study designed to compare the subacute effects of bilateral 10Hz stimulation versus 130Hz stimulation versus off stimulation to the ventral STN on emotional processing in PD patients. The study was approved by the ethics committee of Ruijin Hospital, and performed at the Department of Neurosurgery, Center for Functional Neurosurgery, Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Twenty patients with advanced PD who have undergone bilateral STN DBS for more than 6 months were enrolled in the study. These patients met the criteria: (1) age > 18 years old; (2) cognitive intact (mini-mental state examination score more than 24); (3) at least 6 months after DBS surgery; (4) Lead-DBS-based electrode reconstruction confirmed at least one contact located within each STN in both hemispheres. After recruitment, patients were comprehensively evaluated under three stimulation conditions (10Hz stimulation versus 130Hz stimulation versus off stimulation) in the regular on-medication state. Both the assessors and the patients were blinded to the stimulation condition. There was a 15-minute in-between off-stimulation period to avoid the post-STN DBS effect.

**Stimulation paradigm**

We tested three bilateral stimulation conditions: 10Hz stimulation, 130Hz stimulation, and off stimulation. Monopolar configuration was applied with the lead contact as cathode and the implanted pulse generator (IPG) as anode. The lowest contact located within the STN was selected and confirmed by the fused image of preoperative MRI and postoperative CT using Lead-DBS V2 ([https://www.lead-dbs.org](https://www.lead-dbs.org)) toolbox ([Fig. 1](#)) [33]. It should be noted that in this experiment, the contact used is typically positioned more ventrally than the active contact used in clinical conditions. Therefore, the assessments of the motor symptoms under stimulation do not reflect the clinical status of the patients in therapeutic conditions. The same voltage as the clinical setting with a fixed pulse width of 90μs was designated for stimulation. Of note, the total electrical
energy delivered (TEED) by 130 Hz stimulation was 13 times greater compared to 10Hz stimulation [34]. We note that we had previously attempted to control for different stimulation frequencies by keeping TEED constant in an acute study of 130 Hz and 10 Hz but this markedly changed the volume of tissue activated (VTA) which recruits differing brain regions [32]. Hence in this study we have elected not to control for TEED matching. Stimulation frequency order was counterbalanced across all six possible order combinations. Affective task was initiated 10 minutes after each frequency change to allow for acclimatization and stimulation washout. The stimulation was on for the tasks.

*Affective task*

Subjective emotional experience was evaluated in which patients were asked to self-report valence and arousal in response to affective imagery. Patients were shown affective imagery from the validated International Affective Picture System (IAPS) with 3 conditions: positive, neutral, and negative [35]. Each condition consisted of 10 different images, with half rated for valence and half rated for arousal. After each image presentation, valence and arousal were rated successively on sliding visual analog scales ranging from 0 to 100, with 0 indicating very negative (valence) or not exciting at all (arousal) and 100 indicating very positive (valence) or very exciting (arousal). The intertrial interval was 1–1.5 seconds. Ninety images across 3 conditions were randomly allocated to three task versions.

*Clinical evaluation*

Experienced neurologists performed clinical evaluations. Before the experiment, depression and apathy were assessed with the use of the Beck Depression Inventory, Second Edition (BDI-II) [36], and the Apathy Evaluation Scale (AES) [37]. In particular, we calculated the total AES score and the score of the affective AES subscale. The following were assessed repeatedly under three stimulation conditions: self-reported mood (from unpleasant to pleasant), vigor (from no energy to full of energy), and
consciousness (from very sleepy to fully awake) on the visual analog scale within the range of [0, 100] and part □ of Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS UPDRS-□).

**Statistical analysis**

Scores for the three frequency groups were compared using one-way (stimulation frequency: 10Hz, 130Hz, and off) or two-way (category: negative, neutral, and positive, stimulation frequency: 10Hz, 130Hz, and off) repeated-measure ANOVA. Two-way (category: negative, neutral and positive, stimulation frequency: 10Hz, 130Hz, and off) repeated-measure ANOVA of covariance (BDI score or affective apathy score) was used to examine the effect of depression or affective apathy on the stimulation effect, and three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (depressive symptom or affective apathy) was used to clarify the group differences. The relationships between dopaminergic medication and apathy or depression were determined by Spearman or Pearson correlations as appropriate.

Pearson correlations between motor UPDRS score and ratings and an unstructured covariate linear mixed effects model that included fixed effect of stimulation frequency and random effect of individual motor scores were attempted to covary out the motor effects of stimulation frequency. Mauchly’s Test was used to assess sphericity, and Greenhouse-Geisser correction was used for lack of sphericity. Post hoc analysis was performed with protected Fisher’s least square differences (LSD) for multiple comparisons.

To examine the effects of stimulation position on emotional processing, electrode reconstruction was performed, and Montreal Neurological Institute (MNI) coordinates of active contacts were generated using Lead-DBS V2 toolbox [33]. This protocol follows exactly the approach of Horn and colleagues [38]. Exploratory Pearson correlations were conducted between z-scored MNI coordinates and rating scores.
(valence or arousal).

All analyses were performed using SPSS 26.0. $P < 0.05$ was considered significant.

**Results**

Twenty PD patients (4 females and 16 males, mean age $60 \pm 9$, mean disease duration $10 \pm 5$) participated in the study. The mean duration following STN DBS was $12 \pm 9$ months. Detailed demographic information is outlined in Table 1.

Twenty PD patients completed motor evaluation as measured by MDS UPDRS-Ⅲ score in all conditions. One-way repeated-measure ANOVA revealed a significant main effect of stimulation frequency ($F(2, 38) = 15.948, P < 0.001$), with 130Hz stimulation showing notably decreased MDS UPDRS-Ⅲ score when compared to off-stimulation ($P < 0.001$) and to 10Hz ($P < 0.001$) stimulation. Seventeen of the twenty PD patients gave the self-reported mood, vigor, and consciousness scores in all conditions. However, no significant differences among the stimulation frequencies were found in these scores (mood: $F(2, 32) = 0.744, P = 0.483$, vigor: $F(2, 32) = 0.678, P = 0.515$, consciousness: $F(2, 32) = 0.924, P = 0.407$) (Table 2).

**Arousal**

For arousal, there was a significant main effect of stimulation frequency (stimulation frequency: $F(2, 38) = 18.284, P < 0.001$, category: $F(2, 38) = 20.133, P < 0.001$, interaction effects: $F(4, 76) = 0.028, P = 0.998$). Post-hoc testing revealed reduced arousal during 130Hz stimulation compared to off-stimulation (Negative: $P = 0.0035$, Neutral: $P < 0.001$, Positive: $P < 0.001$) and to 10Hz stimulation (Negative: $P = 0.0179$, Neutral: $P < 0.001$, Positive: $P < 0.001$) (Fig. 2A).

To figure out whether the effect of 130Hz stimulation on arousal was related to its motor effects, we performed Pearson correlations between motor UPDRS score and arousal ratings and used a linear mixed effects model with arousal (negative, neutral or positive)
as dependent variable and MDS UPDRS-III score as a covariate. Results showed there was no correlation between motor UPDRS score and arousal ratings in all frequency conditions \( (P > 0.05) \) except for negative arousal at 10Hz stimulation \( (\text{Pearson's } r = 0.485, P = 0.03) \), and the linear mixed effects model analysis confirmed that inclusion of motor scores as a covariate did not affect the statistical significance of the results \( \text{negative: } F(2, 19) = 4.929, P = 0.019, \text{neutral: } F(2, 19) = 9.512, P = 0.001, \text{positive: } F(2, 19) = 11.598, P = 0.001 \).

To explore the effect of affective apathy or depression on the stimulation effect on arousal, two-way repeated-measure ANOVA with a covariate of affective apathy score or BDI score was performed. We found a marginally significant interaction effect between the BDI score and stimulation frequency \( (F(2, 36) = 2.677, P = 0.082) \). This prompted us to subdivide the patients into two groups using the group median as the cut-off value \( (10 \text{ patients, no depression as } \text{BDI} \leq 12; 10 \text{ patients, mild to moderate depressive symptoms as } \text{BDI} > 12) \), and run a three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (depressive symptoms). We saw a significant interaction between depressive symptoms and stimulation frequency \( (F(2, 36) = 6.675, P = 0.003) \). Post hoc Fisher's LSD test showed reduced arousal during 130Hz stimulation compared to off-stimulation \( (P < 0.001) \) and to 10Hz stimulation \( (P < 0.001) \) in the no-depression group. In the depression group, 10Hz stimulation increased the arousal ratings compared to off-stimulation \( (P = 0.028) \) and 130Hz \( (P = 0.007) \) frequency stimulation, while 130Hz stimulation reduced arousal compared to off-stimulation \( (P = 0.032) \) (Fig. 2A).

Valence

For valence, there was no significant effect of stimulation frequency and no significant interaction between stimulation frequency and valence category \( (\text{stimulation frequency: } F(2, 38) = 2.676, P = 0.082, \text{category: } F(2, 38) = 161.838, P < 0.001, \text{interaction effects: } F(4, 76) = 0.749, P = 0.562) \) (Fig. 2B).
To further explore the influence of affective apathy or depression over the stimulation effect on valence, we ran a two-way repeated-measure ANOVA with a covariate of affective apathy score or BDI score. We observed an interaction effect between valence category and stimulation frequency \( F(4, 72) = 3.175, P = 0.018 \) and a three-way interaction between valence category, stimulation frequency, and affective apathy scores \( F(4, 72) = 3.526, P = 0.011 \), only when affective apathy score was taken as a covariate.

To illustrate the observed effects of affective apathy, we also split the patients into two groups using the group median as the cut-off value: no emotional blunting group (8 patients, affective AES score > 7) and mild to moderate emotional blunting group (12 patients, affective AES score ≤ 7). We ran a three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (affective apathy). We found a significant three-way interaction between category, stimulation frequency, and affective apathy \( F(4, 72) = 3.905, P = 0.006 \). Post hoc Fisher’s LSD test revealed a significant positive effect of 10Hz stimulation selectively for negative emotional stimuli compared to off-stimulation \( P = 0.011 \) and 130Hz \( P = 0.011 \) stimulation in the no emotional blunting group, but not for neutral \( P > 0.05 \) or positive \( P > 0.05 \) emotional stimuli. In the emotional blunting group, 130Hz stimulation showed a positive effect for emotional stimuli compared to off (Negative: \( P = 0.072 \), Neutral: \( P = 0.333 \), Positive: \( P = 0.039 \)) and 10Hz (Negative: \( P = 0.034 \), Neutral: \( P = 0.751 \), Positive: \( P = 0.239 \)) stimulation (Fig. 2B).

Furthermore, the correlations between levodopa equivalent daily dosage (LEED) and total AES score, affective AES score or BDI score were not significant \( P > 0.05 \), indicating that the influence of affective apathy or depression was not representing the level of dopaminergic status.

*Spatially separated stimulation effects*

In an exploratory analysis, we examined the electrode position-related effect of ventral
STN stimulation on emotional valence and arousal.

Since no differences were found among arousal categories in stimulation effect, we explored the relationship between global arousal level (averaged across three categories) and electrode position. We observed an electrode position-related effect for arousal predominantly in the anterior-posterior direction. A lower level of global arousal at 130Hz stimulation (Pearson’s $r = -0.456, P = 0.043$) and at 10Hz stimulation (Pearson’s $r = -0.522, P = 0.018$) were associated with more anterior contacts (Fig. 3).

Valence findings were mainly with emotional rather than neutral stimuli. Thus, we took neutral-controlled emotional valence as a major variable and examined its electrode position-related effect. This effect was observed mainly in the dorsal-ventral direction, with more ventral stimulation in the STN leading to greater change in positive rating bias of the neutral-controlled emotional stimuli at 10Hz stimulation (Positive: Pearson’s $r = -0.346, P = 0.136$, Negative: Pearson’s $r = -0.520, P = 0.019$) and 130Hz stimulation (Positive: Pearson’s $r = -0.479, P = 0.033$, Negative: Pearson’s $r = -0.343, P = 0.138$) (Fig. 4).

**Discussion**

This study evaluated the subacute effects of bilateral ventral STN stimulation with different frequencies (10Hz, 130Hz) on subjective emotional experience in PD patients. Collectively, our results highlight the distinctive stimulation effect of 130Hz and 10Hz on emotional processing. The frequency effect on arousal and valence was mediated by depression and affective apathy, respectively. Overall, 130Hz stimulation reduced the global arousal level which was more prominent in patients without depression, whereas 10Hz stimulation increased the global arousal level in patients with more severe depression. In contrast, 10Hz stimulation showed positive effects on valence selectively for negative emotional stimuli, which was observed in patients without affective apathy. 130Hz stimulation also prompted a shift towards more positive ratings for emotional stimuli, but this was observed in patients with more severe affective apathy. On
exploratory analysis of topographic relevance, we noticed a spatially separated stimulation effect on valence and arousal. The electrode position-related effect for the ventral STN showed significant anterior-posterior differences for arousal, with more anterior stimulation inducing a lower level of arousal, and dorsal-ventral differences for valence, with more dorsal stimulation trending towards positive effects and more ventral stimulation towards negative effects. Together, this is the first demonstration of the subacute effects of 10Hz stimulation at the STN on emotional processing in a double-blind, randomized design. It promotes a better understanding of the functional specialization of frequency-based stimulation and their topographic difference within the ventral STN and enables more refined neuromodulation for PD emotional behaviors.

**Distinctive frequency effect on valence and arousal**

Consistent with our findings with intermittent time-locked stimulation [32] and previous observations focused on high-frequency tonic stimulation [24,25], this study shows reduced arousal ratings and increased valence of emotional imagery stimuli with subacute 130Hz stimulation to the ventral STN. One could argue that the satisfactory motor benefit coming from 130Hz stimulation may have a confounding effect on affective processing. Critically, our results revealed the effect of 130Hz stimulation on arousal was unlikely to relate to its considerable motor effects. The exclusive frequency effect on emotional valence and arousal but not on self-reported mood state, also suggests that our observations are independent of subjective mood fluctuation. These findings might have relevance to the neuropsychiatric effects of ventromedial STN stimulation in PD [15] and psychiatric symptoms improved with anteroventral STN stimulation in obsessive-compulsive disorder [39,40].

Note that there have been very few studies into the effect of low frequency stimulation. Some recent pilot studies reported the cognitive effects of theta frequency stimulation, inspiring novel neuromodulation attempts at other cognitive substrates[41–43]. In the present study, we now show that subacute 10Hz stimulation increases arousal rating and selectively reduces subjective negative bias.
A few studies suggest the functional specialization of alpha frequency within the STN on emotion processing, embodied not only at the single-neuron level but also at the local neuronal population level [26–32,44]. Stimulation at 10Hz may have a frequency-specific effect on the alpha ERD with the STN influencing a limbic network. Brain regions that comprise the emotional limbic network located within the orbitofrontal cortex, amygdala, subgenual cingulate and mesolimbic dopamine system, show valence-arousal differences [6–9,45,46]. Alpha frequency-based neuromodulation may create activation or deactivation of arousal-related or valence-related neuronal activity within the ventral STN, tuning an array of emotional processing networks through their downstream connections [47–49].

While still under debate, recent evidence suggests high frequency stimulation may disrupt firing dynamics, resulting in pronounced informational lesion effect, rather than producing an overall neural silencing effect [50–53]. In contrast, low frequency stimulation has been suggested to induce a more prominent neural entrainment effect, thereby facilitating neural network communication at specific frequency [53,54].

Of note, depression and affective apathy severity modulate the extent 10Hz stimulation influences arousal and valence. Given that the features of depression and affective apathy are largely overlapping, a sharing mediating mechanism can be expected [55,56]. Numerous accounts indicate that mood and apathy change with tonic STN stimulation. These changes are associated with preoperative abnormal prefrontal-subthalamic connectivity within limbic circuitry, suggesting a role of interindividual emotional bias and its neural basis [57]. Furthermore, invasive and non-invasive neuromodulation studies have identified several limbic regions and the white matter of their connecting neural fibers, and shown improvement in depressive symptoms by targeting these fibers [58–62]. The current spread to these regions or the surrounding white matter tracts supporting limbic activation might be important for 10Hz stimulation to function.

*Spatially separated stimulation effect*
Evidence supports a role for spatial segregation of emotional processing within the STN. The STN is putatively subdivided into different territories based on anatomical [63,64], electrophysiological [28] and functional findings [65–67]. The limbic region spanning the anterior ventral-medial part of the STN shows great emotional involvement [28,68]. In PD patients, DBS targeting the more anteroventral STN can decrease motor benefits while increasing the incidence of mood side effects [15]. In this study, we observe a spatially separated stimulation effect on valence and arousal in the ventral STN.

Intraoperative micro-recordings along the routine lead trajectory of the STN show an anterior-posterior separation of neuron distribution between arousal and valence, supporting the idea that there’s a neuronal level of specialization within each emotional dimension [44]. Other regions outside of the STN, such as the zona incerta (implicated in fear processing) [69], lateral hypothalamus (implicated in peripheral physiology) [70], substantia nigra (contributed to reward and aversive processing) [71,72], and medial forebrain bundle (a critical role in motivation) [73] are all close to the limbic STN and impact on different aspects of emotional processing [74]. The hyperdirect cortico-subthalamic fibres from the dorsolateral prefrontal and orbitofrontal cortex and cingulate gyrus and the pallidothalamic white matter fiber tracts that are located dorsally and posteriorly to the STN also play a great emotional role[74,75]. The different involvement of the adjacent regions and passing dopaminergic fibers along the dorsolateral-ventromedial direction and anterior-posterior direction of the ventral STN may partly account for our observations.

However, it should be noted that the stimulation sites in this experiment were limited to the posterior half and more ventral region of the STN, unlike the dorsolateral region typically targeted in therapeutic conditions. The contacts were not located within the anterior STN as more commonly observed in OCD targeting hence limiting an influence on the limbic-emotional STN.

There are broad clinical implications for these results. Ventral STN DBS in PD patients can induce psychiatric adverse effects that include mania, depression, suicidal ideation,
apathy, and impulsivity [15]. Most of these behavioral changes are related with altered emotional experience. For example, depression is characterized by diminished experience of positive emotions and increased intensity of negative stimuli [76]. Apathy patients show emotional indifference and lower level of emotional reactivity [77,78]. Former studies posit that impulsivity consists of five separate impulsive personality traits with positive or negative urgency associated with corresponding emotional states [79]. In light of this, more refined contact selection along anterior-posterior STN and ventral-dorsal STN for stimulation may avoid psychiatric side effects or potentially produce antidepressant effects.

Limitations

Several limitations have to be taken into account when interpreting the results. Firstly, since we matched for the current between frequencies, the energy delivered by 10Hz stimulation is much lower than 130Hz stimulation. This could result in an underestimation of the emotional effects of 10Hz stimulation. As it is impossible to control the TEED without expanding the VTA, further investigation is warranted to elucidate the impact of VTA, voltage, and pulse width for 10Hz stimulation. Furthermore, it is not at all clear what is an adequate washout time period and stimulation duration prior to testing, particularly in the context of long-term tonic clinical frequency stimulation. The washout time utilized previously ranges from 5 minutes to 48 hours [80–83]. Notably, three studies focusing on 5Hz stimulation and its cognitive effects use a washout between conditions of up to 15 minutes [41–43], although the timing might be different for 10Hz stimulation and emotional processing.

Conclusion

In conclusion, we highlight the distinctive role of 10Hz stimulation on subjective emotional experience and unveil the spatial organization of the stimulation effect. These findings expand our understanding of the dissociative emotional role of the STN and provide clinical implications for the management of postoperative psychiatric side
effects.

Disclosures

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LW contributed to the conception, design of the study, interpretation of the behavioral data and drafted the manuscript; YP and PH contributed to the conception and acquisition of the data. JL contributed to the interpretation of the data and drafted the manuscript. DL and VV contributed to the conception, design of the study, and interpretation of the data and drafted the manuscript.

The authors declared no financial interests or potential conflicts of interest.

Acknowledgments

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Figures

Fig. 1 Electrodes reconstruction in Montreal Neurological Institute (MNI) space. Coronal (left) and axial (right) views are displayed on a T1-weighted structural MRI template.

Fig. 2 Frequency effect on emotional valence and arousal ratings. A. Changes in valence ratings by stimulation frequency (left) and graphic illustration of interaction effects of stimulation frequency and depression (right) by dividing into no depression group (BDI ≤ 12) and depression group (BDI > 12). B. Changes in valence ratings by stimulation frequency (left) and graphic illustration of the three-way interaction among category, stimulation frequency, and affective apathy (right) by dividing into no emotional blunting group (affective AES > 7) and emotional blunting group (affective AES ≤ 7). * P < 0.05, ** P < 0.01, and *** P < 0.001 indicates significant difference between conditions.

Fig. 3 Electrode position-related effects on arousal. The correlations show the change in global arousal level with 10Hz (left) or 130Hz (right) stimulation relative to z-scored y-axial (anterior-posterior) Montreal Neurological Institute (MNI) coordinates.

Fig. 4 Electrode position-related effects on valence. The correlations show the change in valence with 10Hz or 130Hz stimulation relative to z-scored z-axial (dorsal-ventral) Montreal Neurological Institute (MNI) coordinates. Upper left: change in negative valence with 10Hz stimulation; Upper right: change in positive valence with 10Hz stimulation; Lower left: change in negative valence with 130Hz stimulation; Lower right: change in positive valence with 130Hz stimulation.
Subacute Alpha Frequency (10 Hz) Subthalamic Stimulation for Emotional Processing in Parkinson’s Disease

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Abstract

Background:

Psychiatric comorbidities are common in Parkinson’s disease (PD) and may change with high-frequency stimulation targeting the subthalamic nucleus. Numerous accounts indicate subthalamic alpha-frequency oscillation is implicated in emotional processing. While intermittent alpha-frequency (10Hz) stimulation induces positive emotional effects, with more ventromedial contacts inducing larger effects, little is known about the subacute effect of ventral 10Hz subthalamic alpha-frequency stimulation on emotional processing.

Objective/Hypothesis:

To evaluate the subacute effect of 10Hz subthalamic alpha-frequency stimulation on emotional processing in PD patients using an affective task, compared to that of clinical-frequency stimulation and off-stimulation.

Methods:

Twenty PD patients with bilateral subthalamic deep brain stimulation for more than six months were tested with the affective task under three stimulation conditions (10Hz, 130Hz, and off-stimulation) in a double-blinded randomized design.

Results:

While 130Hz stimulation reduced arousal ratings in all patients, 10Hz stimulation increased arousal selectively in patients with higher depression scores. Furthermore, 10Hz stimulation induced a positive shift in valence rating to negative emotional stimuli in patients with lower apathy scores, and 130Hz stimulation led to more positive valence to emotional stimuli in the patients with higher apathy scores. Notably, we
found correlational relationships between stimulation site and affective rating: arousal ratings increase with stimulation from anterior to posterior site, and positive valence ratings increase with stimulation from dorsal to ventral site of the ventral subthalamic nucleus.

Conclusions:

Our findings highlight the distinctive role of alpha-frequency 10Hz stimulation on subjective emotional experience and unveil the spatial organization of the stimulation effect.

**Key Words**

emotional processing, Parkinson’s disease, alpha frequency stimulation, subthalamic nucleus

**Abbreviations**

PD, Parkinson’s disease;

DBS, deep brain stimulation;

STN, subthalamic nucleus;

ERD, event-related desynchronization;

IPG, implanted pulse generator;

LSD, least square differences;

IAPS, International Affective Picture System;

BDI-Ⅱ, Beck Depression Inventory, Second Edition

AES, Apathy Evaluation Scale;
MDS UPDRS-Ⅲ, the part Ⅲ of Movement Disorder Society-Unified Parkinson’s Disease Rating Scale;

MNI, Montreal Neurological Institute;

**TEED**, total electrical energy delivered;

**LEED**, levodopa equivalent daily dosage;

VTA, volume of tissue activated.
Introduction

Emotion is critical to most aspects of human behavior. Biases in emotional processing are commonly found in neurological and psychiatric disorders and play key roles in disease pathophysiology. Parkinson’s disease (PD), resulting from the progressive degeneration of the nigrostriatal and mesolimbic dopamine systems, leads not only to predominant motor symptoms but multifarious non-motor features as well, such as mood disturbances [1][4]. Deep brain stimulation (DBS) is an invasive procedure with established practice in advanced PD, essential tremor (ET), idiopathic dystonia, and emerging applications in psychiatric disorders [2,3][2,3]. It delivers electric pulses at specific frequencies via electrodes and modulates oscillatory activity, thus impacting brain function. Whereas high-frequency stimulation targeting the dorsolateral motor subthalamic nucleus (STN) shows efficacy for cardinal motor symptoms of PD [4][4], little is known about the effects of low-frequency STN stimulation on emotional behaviors in PD patients.

Conceptually, subjective emotional experience is considered a single integral blend of two psychophysiological dimensions: valence, varying from negative to positive, and arousal, varying from low to high [5][4]. Evidence from anatomical, neuroimaging, and psychological studies has demonstrated the behavioral and functional segregation of affective valence and arousal [6-9][6-9], although integrated neural representations may exist within some subcortical regions [10][10]. PD is associated with a high comorbidity with depression, mood lability, and apathy with elements of decreased emotional reactivity [11][11]. These comorbidities are variously related to the neurobiology of PD, individual vulnerabilities, and side effects of therapy.

Convergent evidence suggests an important role of the STN in emotion processing [12,13][12,13]. A number of studies have reported postoperative changes in mood behaviors with chronic high-frequency STN stimulation [14,15][14,15]. The most commonly reported changes include mania and hypomania, impulsivity behaviors, suicidal ideation, apathy, and mood disorders. Chronic high-frequency stimulation to
the STN contributes to negative emotion recognition impairments, either in facial expressions [16–22] or in prosody [23]. Observations in subjective emotional experience also show enhanced valence of positive emotions and reduced intensity of negative feelings induced by film excerpts under tonic high-frequency STN stimulation [24,25].

Oscillatory STN activity at the alpha frequency band is well-documented to be correlated with postoperative mood changes [26–28]. LFP recordings of the STN in PD show a late event-related desynchronization (ERD) in the local alpha frequency band (8–12 Hz) for emotional but not neutral stimuli, which is closely correlated with depression severity following STN DBS [29–31]. These STN alpha findings are predominantly located at the ventral STN, highlighting the functional parcellation of the STN with emotional processing in the limbic territory of STN [28]. Targeting this late alpha ERD using time-locked intermittent stimulation of the right STN, our lab found a dissociable effect of stimulation frequency on the processing of negative emotional stimuli. While stimulating at 10Hz decreases subjective negative bias, and more ventromedial contacts induce larger effects, stimulating at 130Hz appears to selectively decrease arousal ratings [32]. It further raises the possibility of modulating emotional processing using bilateral alpha-frequency 10 Hz stimulation targeting the ventral STN in the clinical setting. However, the effects of subacute alpha-frequency 10Hz stimulation at the ventral STN focused on emotional processing have not been investigated.

Here, we evaluated the subacute effects of bilateral alpha-frequency 10Hz stimulation targeting the ventral STN on emotional processing using an affective task in PD patients, and compared it to that of clinical frequency (130Hz) stimulation and off-stimulation. We assumed that subacute 10Hz stimulation and 130Hz stimulation would have a differential influence on subjective valence and arousal, consistent with our previous findings following intermittent time-locked procedure.

Materials and methods
Study design and participants

This was a prospective double-blinded randomized study designed to compare the subacute effects of bilateral alpha frequency (10Hz) stimulation versus gamma frequency (130Hz) stimulation versus off stimulation to the ventral STN on emotional processing in PD patients. The study was approved by the ethics committee of Ruijin Hospital, and performed at the Department of Neurosurgery, Center for Functional Neurosurgery, Shanghai Jiao Tong University School of Medicine affilated Ruijin Hospital. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Twenty patients with advanced PD who have undergone bilateral STN DBS for more than 6 months were enrolled in the study. These patients met the criteria: (1) age > 18 years old; (2) cognitive intact (mini-mental state examination score more than 24); (3) at least 6 months after DBS surgery; (4) Lead-DBS-based electrode reconstruction confirmed at least one contact located within each STN in both hemispheres. After recruitment, patients were comprehensively evaluated under three stimulation conditions (10Hz stimulation versus 130Hz stimulation versus off stimulation) in the regular on-medicatin state. Both the assessors and the patients were blinded to the stimulation condition. There was a 15-minute in-between off-stimulation period to avoid the post-STN DBS effect.

Stimulation paradigm

We tested three bilateral stimulation conditions: alpha frequency (10Hz) stimulation, gamma frequency (130Hz) stimulation, and off stimulation. Monopolar configuration was applied with the lead contact as cathode and the implanted pulse generator (IPG) as anode. The lowest contact located within the STN was selected and confirmed by the fused image of preoperative MRI and postoperative CT using Lead-DBS V2 (https://www.lead-dbs.org) toolbox (Fig. 1) [33][36]. It should be noted that in this experiment, the contact used is typically positioned more ventrally than the active
contact used in clinical conditions. Therefore, the assessments of the motor symptoms under stimulation do not reflect the clinical status of the patients in therapeutic conditions. The same voltage as the clinical setting with a fixed pulse width of 90-μs was designated for stimulation. Of note, the total electrical energy delivered (TEED) by 130 Hz stimulation was 13 times greater compared to 10Hz stimulation [34]. We note that we had previously attempted to control for different stimulation frequencies by keeping TEED constant in an acute study of 130 Hz and 10 Hz but this markedly changed the volume of tissue activated (VTA) which recruits differing brain regions [32]. Hence in this study we have elected not to control for TEED matching. Stimulation frequency order was counterbalanced across all six possible order combinations. Affective task was initiated 10 minutes after each frequency change to allow for acclimatization and stimulation washout. The stimulation was on for the tasks. Affective task began 10 minutes after each frequency change to allow for acclimatization and stimulation washout.

Affective task

Subjective emotional experience was evaluated in which patients were asked to self-report valence and arousal in response to affective imagery. Patients were shown affective imagery from the validated International Affective Picture System (IAPS) with 3 conditions: positive, neutral, and negative [35][33]. Each condition consisted of 10 different images, with half rated for valence and half rated for arousal. After each image presentation, valence and arousal were rated successively on sliding visual analog scales ranging from 0 to 100, with 0 indicating very negative (valence) or not exciting at all (arousal) and 100 indicating very positive (valence) or very exciting (arousal). The intertrial interval was 1–1.5 seconds. Ninety images across 3 conditions were randomly allocated to three task versions.

Clinical evaluation

Experienced neurologists performed clinical evaluations. Before the experiment,
depression and apathy were assessed with the use of the Beck Depression Inventory, Second Edition (BDI-II) [36][34], and the Apathy Evaluation Scale (AES) [37][35]. In particular, we calculated the total AES score and the score of the affective AES subscale. The following were assessed repeatedly under three stimulation conditions: self-reported mood (from unpleasant to pleasant), vigor (from no energy to full of energy), and consciousness (from very sleepy to fully awake) on the visual analog scale within the range of [0, 100] and part Ⅲ of Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS UPDRS-Ⅲ).

**Statistical analysis**

Scores for the three frequency groups were compared using one-way (stimulation frequency: 10Hz, 130Hz, and off) or two-way (category: negative, neutral, and positive, stimulation frequency: 10Hz, 130Hz, and off) repeated-measure ANOVA. Two-way (category: negative, neutral and positive, stimulation frequency: 10Hz, 130Hz, and off) repeated-measure ANOVA of covariance (BDI score or affective apathy score) was used to examine the effect of depression or affective apathy on the stimulation effect, and three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (depressive symptom or affective apathy) was used to clarify the group differences. The relationships between dopaminergic medication and apathy or depression were determined by Spearman or Pearson correlations as appropriate.

Pearson correlations between motor UPDRS score and ratings and an unstructured covariate linear mixed effects model that included fixed effect of stimulation frequency and random effect of individual motor scores were attempted to co-vary out the motor effects of stimulation frequency. Mauchly’s Test was used to assess sphericity, and Greenhouse-Geisser correction was used for lack of sphericity. Post hoc analysis was performed with protected Fisher’s least square differences (LSD) for multiple comparisons.
To examine the effects of stimulation position on emotional processing, electrode reconstruction was performed, and Montreal Neurological Institute (MNI) coordinates of active contacts were generated using Lead-DBS V2 toolbox [33][36]. This protocol follows exactly the approach of Horn and colleagues [38][37]. Exploratory Pearson correlations were conducted between z-scored MNI coordinates and rating scores (valence or arousal).

All analyses were performed using SPSS 26.0. $P < 0.05$ was considered significant.

**Results**

Twenty PD patients (4 females and 16 males, mean age $60 \pm 9$, mean disease duration $10 \pm 5$) participated in the study. The mean duration following STN DBS was $12 \pm 9$ months. Detailed demographic information is outlined in Table 1.

Twenty PD patients completed motor evaluation as measured by MDS UPDRS-Ⅲ score in all conditions. One-way repeated-measure ANOVA revealed a significant main effect of stimulation frequency ($F (2, 38) = 15.948, P < 0.001$), with 130Hz stimulation showing notably decreased MDS UPDRS-Ⅲ score when compared to off-stimulation ($P < 0.001$) and to 10Hz ($P < 0.001$) stimulation. Seventeen of the twenty PD patients gave the self-reported mood, vigor, and consciousness scores in all conditions. However, no significant differences among the stimulation frequencies were found in these scores (mood: $F (2, 32) = 0.744, P = 0.483$, vigor: $F (2, 32) = 0.678, P = 0.515$, consciousness: $F (2, 32) = 0.924, P = 0.407$) (Table 2).

**Arousal**

For arousal, there was a significant main effect of stimulation frequency (stimulation frequency: $F (2, 38) = 18.284, P < 0.001$, category: $F (2, 38) = 20.133, P < 0.001$, interaction effects: $F (4, 76) = 0.028, P = 0.998$). Post-hoc testing revealed reduced arousal during 130Hz stimulation compared to off-stimulation (Negative: $P = 0.0035$, Neutral: $P < 0.001$, Positive: $P < 0.001$) and to 10Hz stimulation (Negative: $P = 0.0179$,
Neutral: $P < 0.001$, Positive: $P < 0.001$ (Fig. 2A).

To figure out whether the effect of 130Hz stimulation on arousal related to its motor effects, we performed Pearson correlations between motor UPDRS score and arousal ratings and used a linear mixed effects model with arousal (negative, neutral or positive) as dependent variable and MDS UPDRS-III score as a covariate. Results showed there was no correlation between motor UPDRS score and arousal ratings in all frequency conditions ($P > 0.05$) except for negative arousal at 10Hz stimulation ($Pearson’s \ r = 0.485, P = 0.03$), and the linear mixed effects model analysis confirmed that inclusion of motor scores as a covariate did not affect the statistical significance of the results (negative: $F(2, 19) = 4.929, P = 0.019$, neutral: $F(2, 19) = 9.512, P = 0.001$, positive: $F(2, 19) = 11.598, P = 0.001$).

To explore the effect of affective apathy or depression on the stimulation effect on arousal, two-way repeated-measure ANOVA with a covariate of affective apathy score or BDI score was performed. We found a marginally significant interaction effect between the BDI score and stimulation frequency ($F(2, 36) = 2.677, P = 0.082$). This prompted us to subdivide the patients into two groups using the group median as the cut-off value (10 patients, no depression as BDI $\leq 12$; 10 patients, mild to moderate depressive symptoms as BDI $> 12$), and run a three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (depressive symptoms). We saw a significant interaction between depressive symptoms and stimulation frequency ($F(2, 36) = 6.675, P = 0.003$). Post hoc Fisher’s LSD test showed reduced arousal during 130Hz stimulation compared to off-stimulation ($P < 0.001$) and to 10Hz stimulation ($P < 0.001$) in the no-depression group. In the depression group, 10Hz stimulation increased the arousal ratings compared to off-stimulation ($P = 0.028$) and 130Hz ($P = 0.007$) frequency stimulation, while 130Hz stimulation reduced arousal compared to off-stimulation ($P = 0.032$) (Fig. 2A).

Valence
For valence, there was no significant effect of stimulation frequency and no significant interaction between stimulation frequency and valence category (stimulation frequency: $F(2, 38) = 2.676, P = 0.082$, category: $F(2, 38) = 161.838, P < 0.001$, interaction effects: $F(4, 76) = 0.749, P = 0.562$) (Fig. 2B).

To further explore the influence of affective apathy or depression over the stimulation effect on valence, we ran a two-way repeated-measure ANOVA with a covariate of affective apathy score or BDI score. We observed an interaction effect between valence category and stimulation frequency ($F(4, 72) = 3.175, P = 0.018$) and a three-way interaction between valence category, stimulation frequency, and affective apathy scores ($F(4, 72) = 3.526, P = 0.011$), only when affective apathy score was taken as a covariate.

To illustrate the observed effects of affective apathy, we also split the patients into two groups using the group median as the cut-off value: no emotional blunting group (8 patients, affective AES score > 7) and mild to moderate emotional blunting group (12 patients, affective AES score ≤ 7). We ran a three-way repeated-measure ANOVA with two within-subject factors (stimulation frequency and category) and one between-subject factor (affective apathy). We found a significant three-way interaction between category, stimulation frequency, and affective apathy ($F(4, 72) = 3.905, P = 0.006$). Post hoc Fisher’s LSD test revealed a significant positive effect of 10Hz stimulation selectively for negative emotional stimuli compared to off-stimulation ($P = 0.011$) and 130Hz ($P = 0.011$) stimulation in the no emotional blunting group, but not for neutral ($P > 0.05$) or positive ($P > 0.05$) emotional stimuli. In the emotional blunting group, 130Hz stimulation showed a positive effect for emotional stimuli compared to off (Negative: $P = 0.072$, Neutral: $P = 0.333$, Positive: $P = 0.039$) and 10Hz (Negative: $P = 0.034$, Neutral: $P = 0.751$, Positive: $P = 0.239$) stimulation (Fig. 2B).

Furthermore, the correlations between levodopa equivalent daily dosage (LEED) and
total AES score, affective AES score or BDI score were not significant (P > 0.05), indicating that the influence of affective apathy or depression was not representing the level of dopaminergic status.

Spatially separated stimulation effects

In an exploratory analysis, we examined the electrode position-related effect of ventral STN stimulation on emotional valence and arousal.

Since no differences were found among arousal categories in stimulation effect, we explored the relationship between global arousal level (averaged across three categories) and electrode position. We observed an electrode position-related effect for arousal predominantly in the anterior-posterior direction. A lower level of global arousal at 130Hz stimulation (Pearson’s $r = -0.456$, $P = 0.043$) and at 10Hz stimulation (Pearson’s $r = -0.522$, $P = 0.018$) were associated with more anterior contacts (Fig. 3).

Valence findings were mainly with emotional rather than neutral stimuli. Thus, we took neutral-controlled emotional valence as a major variable and examined its electrode position-related effect. This effect was observed mainly in the dorsal-ventral direction, with more ventral stimulation in the STN leading to greater change in positive rating bias of the neutral-controlled emotional stimuli at 10Hz stimulation (Positive: Pearson’s $r = -0.346$, $P = 0.136$, Negative: Pearson’s $r = -0.520$, $P = 0.019$) and 130Hz stimulation (Positive: Pearson’s $r = -0.479$, $P = 0.033$, Negative: Pearson’s $r = -0.343$, $P = 0.138$) (Fig. 4).

Discussion

This study evaluated the subacute effects of bilateral ventral STN stimulation with different frequencies (alpha-gamma 10Hz, 130Hz) on subjective emotional experience in PD patients.

Collectively, our results highlight the distinctive stimulation effect of...
**gamma frequency**130Hz and alpha frequency**10Hz** on emotional processing. The frequency effect on arousal and valence was mediated by depression and affective apathy, respectively. Overall, 130Hz stimulation reduced the global arousal level which was more prominent in patients without depression, whereas 10Hz stimulation increased the global arousal level in patients with more severe depression. In contrast, 10Hz stimulation showed positive effects on valence selectively for negative emotional stimuli, which was observed in patients without affective apathy. 130Hz stimulation also prompted a shift towards more positive ratings for emotional stimuli, but this was observed in patients with more severe affective apathy. On exploratory analysis of topographic relevance, we noticed a spatially separated stimulation effect on valence and arousal. The electrode position-related effect for the ventral STN showed significant anterior-posterior differences for arousal, with more anterior stimulation inducing a lower level of arousal, and dorsal-ventral differences for valence, with more dorsal stimulation trending towards positive effects and more ventral stimulation towards negative effects. Together, this is the first demonstration of the subacute effects of **alpha frequency**10Hz stimulation at the STN on emotional processing in a double-blind, randomized design. It promotes a better understanding of the functional specialization of frequency-based stimulation and their topographic difference within the ventral STN and enables more refined neuromodulation for PD emotional behaviors.

**Distinctive frequency effect on valence and arousal**

Consistent with our findings with intermittent time-locked stimulation [32][32] and previous observations focused on high-frequency tonic stimulation [24,25][24,25], this study shows reduced arousal ratings and increased valence of emotional imagery stimuli with subacute 130Hz stimulation to the ventral STN. One could argue that the satisfactory motor benefit coming from **gamma frequency**130Hz stimulation may have a confounding effect on affective processing. Critically, our results revealed the effect of 130Hz stimulation on arousal were-**were not** unlikely to relate to its considerable motor effects. The exclusive frequency effect on emotional valence and arousal but not on
self-reported mood state, also suggests that our observations are independent of subjective mood fluctuation. These findings might have relevance to the neuropsychiatric effects of ventromedial STN stimulation in PD [15][16] and psychiatric symptoms improved with anteroventral STN stimulation in obsessive-compulsive disorder [39,40][28,29].

Note that there have been very few studies into the effect of low frequency stimulation. Some recent pilot studies reported the cognitive effects of theta frequency stimulation, inspiring novel neuromodulation attempts at other cognitive substrates[41–43][40–42]. In the present study, we now show that subacute alpha frequency 10Hz stimulation increases arousal rating and selectively reduces subjective negative bias.

A few studies suggest the functional specialization of alpha frequency within the STN on emotion processing, embodied not only at the single-neuron level but also at the local neuronal population level [26–32,44][26–32,43]. Stimulation at alpha frequency 10Hz may have a frequency-specific effect on the alpha ERD with the STN influencing a limbic network. Brain regions that comprise the emotional limbic network located within the orbitofrontal cortex, amygdala, subgenual cingulate and mesolimbic dopamine system, show valence-arousal differences [6–9,45,46][6–9,44,45]. Alpha frequency-based neuromodulation may create activation or deactivation of arousal-related or valence-related neuronal activity within the ventral STN, tuning an array of emotional processing networks through their downstream connections [47–49][46–48].

While still under debate, recent evidence suggests high frequency stimulation may disrupt firing dynamics, resulting in pronounced informational lesion effect, rather than producing an overall neural silencing effect [50–53]. In contrast, low frequency stimulation has been suggested to induce a more prominent neural entrainment effect, thereby facilitating neural network communication at specific frequency [53,54].

Of note, depression and affective apathy severity modulate the extent...
frequency 10Hz stimulation influences arousal and valence. Given that the features of depression and affective apathy are largely overlapping, a sharing mediating mechanism can be expected [55,56][49,50]. Numerous accounts indicate that mood and apathy change with tonic STN stimulation. These changes are associated with preoperative abnormal prefrontal-subthalamic connectivity within limbic circuitry, suggesting a role of interindividual emotional bias and its neural basis [57][44]. Furthermore, invasive and non-invasive neuromodulation studies have identified several limbic regions and the white matter of their connecting neural fibers, and shown improvement in depressive symptoms by targeting these fibers [58–62][52–56]. The current spread to these regions or the surrounding white matter tracts supporting limbic activation might be important for alpha-frequency 10Hz stimulation to function.

Spatially separated stimulation effect

Evidence supports a role for spatial segregation of emotional processing within the STN. The STN is putatively subdivided into different territories based on anatomical [63,64][47,54], electrophysiological [28][48] and functional findings [65–67][59–61]. The limbic region spanning the anterior ventral-medial part of the STN shows great emotional involvement [28,68][28,62]. In PD patients, DBS targeting the more anteroventral STN can decrease motor benefits while increasing the incidence of mood side effects [15][45]. In this study, we observe a spatially separated stimulation effect on valence and arousal in the ventral STN.

Intraoperative micro-recordings along the routine lead trajectory of the STN show an anterior-posterior separation of neuron distribution between arousal and valence, supporting the idea that there’s a neuronal level of specialization within each emotional dimension [44][43]. Other regions outside of the STN, such as the zona incerta (implicated in fear processing) [69][62], lateral hypothalamus (implicated in peripheral physiology) [70][64], substantia nigra (contributed to reward and aversive processing) [71,72][65,66], and medial forebrain bundle (a critical role in motivation) [73][62] are all close to the limbic STN and impact on different aspects of emotional processing.
The hyperdirect cortico-subthalamic fibres from the dorsolateral prefrontal and orbitofrontal cortex and cingulate gyrus and the pallidothalamic white matter fiber tracts that are located dorsally and posteriorly to the STN also play a great emotional role[74,75][68,69]. The different involvement of the adjacent regions and passing dopaminergic fibers along the dorsolateral-ventromedial direction and anterior-posterior direction of the ventral STN may partly account for our observations.

However, it should be noted that the stimulation sites in this experiment were limited to the posterior half and more ventral region of the STN, unlike the dorsolateral region typically targeted in therapeutic conditions. The contacts were not located within the anterior STN as more commonly observed in OCD targeting hence limiting an influence on the limbic-emotional STN.

There are broad clinical implications for these results. Ventral STN DBS in PD patients can induce psychiatric adverse effects that include mania, depression, suicidal ideation, apathy, and impulsivity [15][44]. Most of these behavioral changes are related with altered emotional experience. For example, depression is characterized by diminished experience of positive emotions and increased intensity of negative stimuli [76][74]. Apathy patients show emotional indifference and lower level of emotional reactivity [77,78][72,73]. Former studies posit that impulsivity consists of five separate impulsive personality traits with positive or negative urgency associated with corresponding emotional states [79][74]. In light of this, more refined contact selection along anterior-posterior STN and ventral-dorsal STN for stimulation may avoid psychiatric side effects or potentially produce antidepressant effects.

Limitations

Several limitations have to be taken into account when interpreting the results. Firstly, since we matched for the current between frequencies, the energy delivered by alpha-frequency 10Hz stimulation is much lower than gamma-frequency 30Hz stimulation.
This could result in an underestimation of the emotional effects of alpha-frequency 10Hz stimulation. As it is impossible to control the total electrical energy delivered (TEED) without expanding the volume of tissue activated (VTA), further investigation is warranted to elucidate the impact of VTA, voltage, and pulse width for alpha-frequency 10Hz stimulation. Furthermore, it is not at all clear what is an adequate washout time period and stimulation duration prior to testing, particularly in the context of long-term tonic clinical frequency stimulation. The washout time utilized previously ranges from 5 minutes to 48 hours [80–83][75–78]. Notably, three studies focusing on theta-frequency 5Hz stimulation and its cognitive effects use a washout between conditions of up to 15 minutes [41–43][40–42], although the timing might be different for alpha-frequency 10Hz stimulation and emotional processing.

Conclusion

In conclusion, we highlight the distinctive role of alpha-frequency 10Hz stimulation on subjective emotional experience and unveil the spatial organization of the stimulation effect. These findings expand our understanding of the dissociative emotional role of the STN and provide clinical implications for the management of postoperative psychiatric side effects.

Disclosures

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LW contributed to the conception, design of the study, interpretation of the behavioral data and drafted the manuscript; YP and PH contributed to the conception and acquisition of the data. JL contributed to the interpretation of the data and drafted the manuscript. DL and VV contributed to the conception, design of the study, and
interpretation of the data and drafted the manuscript.

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Figures

Fig. 1 Electrodes reconstruction in Montreal Neurological Institute (MNI) space. Coronal (left) and axial (right) views are displayed on a T1-weighted structural MRI template.

Fig. 2 Frequency effect on emotional valence and arousal ratings. A. Changes in valence ratings by stimulation frequency (left) and graphic illustration of interaction effects of stimulation frequency and depression (right) by dividing into no depression group (BDI ≤ 12) and depression group (BDI > 12). B. Changes in valence ratings by stimulation frequency (left) and graphic illustration of the three-way interaction among category, stimulation frequency, and affective apathy (right) by dividing into no emotional blunting group (affective AES > 7) and emotional blunting group (affective AES ≤ 7). * P < 0.05, ** P < 0.01, and *** P < 0.001 indicates significant difference between conditions.

Fig. 3 Electrode position-related effects on arousal. The correlations show the change in global arousal level with 10Hz (left) or 130Hz (right) stimulation relative to z-scored y-axial (anterior-posterior) Montreal Neurological Institute (MNI) coordinates.

Fig. 4 Electrode position-related effects on valence. The correlations show the change in valence with 10Hz or 130Hz stimulation relative to z-scored z-axial (dorsal-ventral) Montreal Neurological Institute (MNI) coordinates. Upper left: change in negative valence with 10Hz stimulation; Upper right: change in positive valence with 10Hz stimulation; Lower left: change in negative valence with 130Hz stimulation; Lower right: change in positive valence with 130Hz stimulation.
Figure 2 for review

A

B
Figure 3 for review

Pearson's $r = -0.522$, $P = 0.018$

Pearson's $r = -0.456$, $P = 0.043$
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Credit author statement

Linbin Wang contributed to the conception, design of the study, interpretation of the behavioral data and drafted the manuscript; Yixin Pan and Peng Huang contributed to the conception and acquisition of the data; Jun Li contributed to the interpretation of the data and drafted the manuscript; Dianyou Li and Valerie Voon contributed to the conception, design of the study, and interpretation of the data and drafted the manuscript.
### Table 1 Demographic information

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Education (y)</th>
<th>LEED (mg) Total</th>
<th>L-dopa (mg)</th>
<th>DA (mg)</th>
<th>DBS duration (m)</th>
<th>Disease duration (y)</th>
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_Notes._ LEDD, L-dopa equivalent daily dose; DBS, deep brain stimulation.
Table 2  Frequency effects on motor symptoms and subjective emotion, energy and consciousness

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<th>Self-reported VAS (N=17)</th>
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Notes. Values are presented as mean ± SD. VAS, visual analog scale.