國立臺灣大學醫學院物理治療學系暨研究所

碩士論文

School and Graduate Institute of Physical Therapy

College of Medicine

National Taiwan University

Master's Thesis

經皮迷走神經電刺激對有、無焦慮症狀巴金森患者重心轉移控制的影響：於不同轉移速度下討論

The Impact of Transcutaneous Vagus Nerve Stimulation on Weight-Shifting Control in People with Parkinson's Disease with and without Anxiety: under Different Shifting Speeds

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中華民國 113 年 7 月

July 2024

doi:10.6342/NTU202403646

摘要

背景與研究目的：良好的重心轉移為巴金森患者姿勢控制的重要因素之一，尤其在快速移動下，正確的重心轉移可降低跌倒發生率。除動作症狀，焦慮問題亦會惡化巴金森患者姿勢平衡控制能力。經皮迷走神經刺激為一種降低焦慮的神經電刺激介入法，然而目前尚無研究探討巴金森患者在不同姿勢動作速度下，經皮迷走神經電刺激對焦慮與姿勢控制的影響。本研究目的為探討經皮迷走神經電刺激是否有助於巴金森患者焦慮程度降低與提升不同速度下重心轉移控制表現，並探討其相對應之大腦皮質活動變化。

方法：本研究共招募 15 名患具焦慮症狀的巴金森患者與 15 名不具焦慮症狀的巴金森患者。每位受試者分別於接受主動經皮迷走神經電刺與假性經皮迷走神經電刺下，站立於力板進行不同節律重心轉移動作，分別為：慢速(0.25 Hz)、中速(0.33 Hz)、快速(0.50 H)，於重心轉移動作過程中，同時量測皮膚電導訊號與腦電圖訊號。主要參數為：重心轉移軌跡誤差量、重心轉移軌跡急動值、重心轉移幅度、、各頻帶大腦活動強度、動作時主觀與客觀焦慮程度。除主觀焦慮程度採無母數分析，其餘參數以 2×2 混合變異數分析(2×2 mixed ANOVA)與邦佛洛尼校正(Bonferroni correction)進行事後檢定，分析主動、假性迷走神經電刺激對有焦慮組、無焦慮組於各重心轉移速度下，各行為表現參數及腦電圖頻譜強度的影響。

結果：於行為表現上，僅有焦慮組在接受迷走神經刺激時，於各種速度情境下皆可顯著降低重心轉移軌跡誤差量與增加重心轉移軌跡急動值，非焦慮組的行為表現

doi:10.6342/NTU202403646

則在中速(0.33 Hz)情境下，給予迷走神經刺激反而降低重心轉移幅度。於慢速與中速情境下，焦慮組比起非焦慮組有更高的主觀焦慮強度。無論重心轉移運動的速度如何，焦慮組在前額葉、額葉、感覺運動、頂葉-枕葉皮質區的 theta 波和 alpha 波功率都較非焦慮組高；相反的，非焦慮組在感覺動作區有較高的的 high gamma 頻帶功率。而經皮迷走神經電刺激對腦電圖相對功率的調節主要影響在較慢的速度情境(0.25 Hz 與 0.33 Hz)。經皮迷走神經刺激會增加非焦慮患者前額葉區 delta 與降低 high gamma 頻帶強度，並降低焦慮患者額葉區 low gamma 頻帶強度。

結論：短時間的經皮迷走神經電刺激可改善具有焦慮症狀的巴金森患者的重心轉移控制表現，並在較慢的重心轉移速度上呈現大腦活動調節。於臨床上可利用經皮迷走神經促進巴金森患者重心轉移表現。本研究並無發現經皮迷走神經電刺激對焦慮程度的效果，未來可探討經皮迷走神經刺激的長時間介入效果，以更完整探討經皮迷走神經刺激對巴金森患者平衡控制、焦慮調節與大腦活動之效益。

關鍵詞：巴金森、焦慮、姿勢控制、迷走神經電刺激、腦電圖

doi:10.6342/NTU202403646

Abstract

Background and purpose: Effective weight-shifting is a crucial factor in posture control for people with Parkinson's disease (PD), especially during rapid movements, as proper weight-shifting could reduce fall incidence. In addition to motor symptoms, anxiety would deteriorate posture control in people with PD. Transcutaneous vagus nerve stimulation (tVNS) is a neuroelectric intervention which has been used to reduce anxiety. However, no studies have explored the impact of tVNS on anxiety and posture control in at different movement speeds in PD. Therefore, the aim of this study was to investigate tVNS effects on weight-shifting performance, anxiety, and related cortical activities at different shifting speeds in people with PD.

Methods: The study recruited 15 PD patients with anxiety and 15 PD patients without anxiety. Each participant performed weight-shifting tasks on a force plate at different speed (slow: 0.25 Hz, medium: 0.33 Hz, fast: 0.50 Hz) with receiving active tVNS or sham tVNS. During the weight-shifting tasks, skin conductance signals and electroencephalogram (EEG) signals were also recorded. The primary outcomes included weight-shifting tracking error, weight-shifting trajectory jerk, weight-shifting amplitude, relative power of EEG, and subjective and objective anxiety levels. Statistical analyses were conducted by 2×2 mixed ANOVA with Bonferroni correction for post-hoc tests, to examine the effects of tVNS and group in each parameter except subjective anxiety level.

doi:10.6342/NTU202403646

The subjective anxiety level was examined by nonparametric analysis.

Results: In terms of behavioral performance, the anxiety group showed reduced weight-shifting tracking error and increased weight-shifting trajectory jerk in active tVNS session, regardless of weight-shifting speed. On the other hand, the weight-shifting amplitude decreased under the 0.33 Hz condition in the non-anxiety group. The anxiety group reported higher subjective anxiety levels than the non-anxiety group under both 0.25 Hz and 0.33 Hz conditions. Regardless of the speed of weight-shifting, the anxiety group exhibited greater theta and alpha power at prefrontal, frontal, sensorimotor, and parietal-occipital cortices compared to the non-anxiety group. In contrast, the non-anxiety group exhibited greater high gamma power at sensorimotor area than the anxiety group. tVNS related EEG modulation was observed in slower speeds (0.25 Hz and 0.33 Hz) conditions. tVNS led to increased delta power and decreased high gamma power at prefrontal cortex in the non-anxiety group. In addition, tVNS resulted in decreased low gamma power at frontal cortex in the anxiety group.

Conclusion: Brief tVNS could improve weight-shifting performance in anxiety PD group, and modulated brain activity particularly in the conditions with slower shifting speed. tVNS could be used as an adjunct intervention for improving weight-shifting performance for people with PD in the clinic. However, the tVNS effect on anxiety reduction was not observed in the present study. Further studies are needed with long-term tVNS

doi:10.6342/NTU202403646

intervention to confirm the benefits of tVNS to balance control, anxiety regulation, and brain activity in people with PD.

Key words: Parkinson, anxiety, postural control, vagus nerve stimulation, electroencephalogram

doi:10.6342/NTU202403646

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Chapter 1

INTRODUCTION

1.1. Overview of posture control in Parkinson's disease with anxiety

Weight shifting is essential for dynamic postural control in activities of daily life such as walking, turning, or transitioning from sitting to standing.[1,2,3,4,5] Incorrect weight shifting contributes to approximately 60% of falls risk in people with PD, and they have high falling risk when quickly shifting body weight, such as encountering with an unpredictable postural perturbation.[6] People with PD tend to shift their body weight inaccurately and decrease weight-shifting amplitudes under the condition with high movement speed.[2,8] Moreover, the compromised amplitude of weight shift during high-speed movements may contribute to freezing of gait (FOG).[8]

In addition to postural control deficits of motor symptoms, people with PD often suffer from some non-motor symptoms which may also impair postural control. The prevalence of anxiety in people with PD is disparate among studies with a range from 5% to 69%.[9] For instance, a survey conducted in French reported that 51% of PD has possible/probable anxious signs from 450 PD patients.[10] In terms of anxiety prevalence in Taiwan, a recent study reported that there was 13.2% of PD has fear/anxiety symptom from 370 PD patients.[11] Anxiety would adversely impact motor control and deteriorate motor fluctuation, dyskinesia, and gait disturbances.[12,13,14] Studies have shown that PD

doi:10.6342/NTU202403646

with anxiety exhibit poorer balance control than those with low anxiety either in quiet standing or walking.[15,16] The association between anxiety and balance control may attribute to the overlapping circuits involving the fear circuit and the limbic cortico-striato-thalamocortical circuits.[17] The malfunction of neural circuits not only lead to motor symptoms like postural and gait deficits, but also increases the likelihood of anxiety in people with PD.

Recently, intervention for anxiety symptom in PD including both pharmacological and non-pharmacological managements. However, there is lack of consistent treatment effect for these interventions and some of them may entail side effects. For instance, although antianxiety medications can lower anxiety levels in patients, the medication may increase the falling risk and decline cognitive function.[18] Non-pharmacological management can be further categorized into non-neurostimulation and neurostimulation methods. Exercise and mindfulness yoga belong to non-neurostimulation managements which were used for anxiety reduction in people with PD.[19,20] However, the efficacy of these approaches for reducing anxiety in PD is still inconclusive. Neurostimulation interventions, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), may have benefit to reduce anxiety.[21] However, both rTMS and tDCS might be not accessible in clinical practice due to high price of the instruments.

doi:10.6342/NTU202403646

Vagus nerve stimulation (VNS) is a neurostimulation interventions that has been used to treat epilepsy, depression and anxiety in both animal and human studies.[22,23,24,25] It can be divided into invasive VNS and non-invasive VNS. The non-invasive VNS is also named as transcutaneous vagus nerve stimulation (tVNS), which could be applied to human body through the instrument of transcutaneous electrical nerve stimulation, which is one kind of common electrical stimulation instruments in the clinic.[26] It has been reported that tVNS could reduce stress-related thoughts or threat-related physiological response in healthy young adults or high-worry people.[28,29] However, the tVNS has not been applied to PD patients with anxiety and investigated its effect on postural control under anxious postural conditions.

1.2. Literature review

1.2.1. Effects of speed on motor control in PD

The relationship between the motor performance and speed (i.e. speed-accuracy tradeoff) was first proposed by Woodworth in 1899.[30] Participants were instructed to match a target line with a pencil according to the rhythm produced by a metronome. The rhythm of the metronome started at a speed of 20 beats per minute (bpm) and increased by 20 bpm increments up to 200 bpm. The task error was measured by the difference between the distance between the lines drawn by the participants and the target line. With

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the increase in metronome's rhythm, the error gradually increased from 1 mm to 6 mm. Furthermore, Fitts proposed the association among movement speed, movement amplitude and movement accuracy with the formula: $T=a+b\log_2(2D/W)$.[31] In the formula, a and b are constants, T is the movement time, D is the required movement amplitude, and W is the error from the target. The equation indicates the movement time is affected by the required task accuracy and movement amplitude. In other words, if the participants are asked to perform a motor task faster (i.e. shorter movement time), it is challenging for participants in maintaining movement amplitude and accuracy. It has been reported that people with PD have more difficulty in performing high-speed movement. In Mazzoni et al.'s study, PD and age-matched healthy participants were asked to perform a speed-accuracy task.[32] Participants had to move a cursor to the target within a specific speed range by manipulating their hand's position. The task goal was to achieve 20 successful aiming movements within the required movement speed range. The result showed that the PD group required more movement trials for achieving 20 successful aiming movements than the healthy control group, especially under fast speed condition.

Most previous studies investigating the relationship between the motor performance and speed targeted for upper limb movements, such as arm pointing,[33] arm reaching[34] and index finger force tracking task,[35] in healthy adults. For example, in Huang et al.'s study (2014), young adult subjects were asked to track a sinusoidal target by exerting isometric

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force with the right index finger.[33] The target speed was set at 0.5 Hz, 1.0 Hz, or 2.0 Hz within a range between 12.5% and 37.5% of maximal voluntary contraction. The result showed that the tracking error in the fastest speed (2.0 Hz) condition was significantly larger than that the slower (0.5 Hz and 1.0 Hz) conditions. Similar to the healthy adults, Almeida and colleagues found that the accuracy of movement decreased during high-speed movements in people with PD; however, the movement decline was greater in PD population than the healthy adults.[34] In Almeida et al.'s study, PD and healthy participants executed a bimanual movement using two linear sliding devices. The participants had to control displacements of left and right arms toward and away from the midline of their body within a plane. The task goal was to replicate a designated line on the computer screen. Participants were instructed to perform the movements based on metronome beats at three different speeds, including 0.75 Hz, 1.25 Hz, and 1.75 Hz. The results showed that there was no significant difference in actual movement frequency between the PD group and the control group in the slow-speed (0.75 Hz) condition. However, a significant difference in actual movement frequency was observed in the medium-speed (1.25 Hz) condition. The PD group was unable to keep up their movements with the corresponding rhythm. Furthermore, in high-speed (1.75 Hz) condition, PD participants were unable to coordinate their limb movements with larger movement delay compared to healthy participants.

doi:10.6342/NTU202403646

In addition to upper limb movement, the performance of continuous postural movement (e.g., weight-shifting movement) could be affected by the movement speed. In Kasahara and Saito's study (2015), young healthy adults stood in step stance with the dominant leg in front of the non-dominant leg.[1] Then, the participants were instructed to track a moving target on a computer monitor by controlling the body weight on a force platform. The target frequencies were set at 0.1 Hz, 0.25 Hz, 0.5 Hz, 0.8 Hz, or 1.0 Hz. The target weight was set between the 20% and 80% of total body weight. The results showed that greater tracking error (worse tracking accuracy) were observed at higher target frequency (0.8 Hz and 1.0 Hz) conditions than at lower target frequency (0.1 Hz, 0.25 Hz, and 0.5 Hz) conditions. In the aspect weight-shifting amplitude, Beckley et al. instructed healthy and PD participants to perform paced left-right and forward-backward continuous weight-shifting tasks at slow (3 second per transition), medium (2 second per transition), and fast (1 second per transition) speeds.[37] Their results showed that the weight shift amplitude was smaller in PD participants than that the healthy participants in all testing conditions. Furthermore, weight shift amplitude in PD was particularly reduced at the fast condition. However, in healthy participants, the amplitudes of weight shifting did not different significantly among the three testing conditions.

People with PD is characterized by impaired dynamic postural control, leading to an increased falling risk.[37] The ability of weight shifting is essential for postural control,

doi:10.6342/NTU202403646

crucial in performing functional tasks and daily activities like walking, turning, and transitioning from sitting to standing, especially in aging or PD populations.[5,38,39,40,41] People with PD were 1.3 times as likely as people without PD to fall because of incorrect weight-shifting and the falls of PD patients are occurred during activities that requires precise weight-shifting control, such as turning around, standing up, and bending forward.[6] In particular, people with PD are more likely to experiencing greater instability under faster perturbations, thereby increasing the risk of falls.[43] The compromised weight shift amplitude during high-speed movements may also contribute to the FOG in PD patients. In Dijkstra et al.' study (2021), populations of PD with FOG (freezers) and PD without FOG (non-freezers) were instructed to control the moving of center of mass by shifting their body weight mediolaterally at increasing frequencies while tracking a sinusoidal target.[8] The amplitude of the target was set as 50% of each subject's stance width. The results demonstrated that freezers had a smaller weight shift amplitude than non-freezers. Additionally, as the frequency increased, freezers had difficulty in keeping up with the target speed. The freezers failed to match the target at the frequency of 0.72 Hz, which was significantly lower than the cut-off frequency (0.8 Hz) of the non-freezers.

1.2.2. Effect of anxiety on posture control in PD

Previous studies have shown that the emotion of anxiety induced by posture threat

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could attenuate balance performance in young adults.[44,45 ,46] For example, in Johnson et al.'s study, the participants of young healthy adults were asked to keep upright stance for 1 minute with or without posture threat.[46] During each threat trial, the participants would receive a perturbation, and the perturbation was given at the 5th, 15th, 30th, 45th, or 60th second during a testing trial. Electrodermal activity was recorded to represent the physiological arousal. Greater electrodermal activity (i.e., high physiological arousal) and larger self-report state anxiety were observed under threat condition relative to no-threat condition. Additionally, the participants showed higher mean power frequency of center of pressure (COP) movement under threat condition than no-threat condition. Higher mean power frequency of postural sway indicated that participants devoted more conscious control to keep postural balance.[47,48,] In addition, some studies also proposed that the high anxiety state would lead to postural instability.[49,50,51] Anxiety intensity was positively correlated to amplitude or frequency of postural sway.[50,51]

Besides a common neuropsychiatric symptom in people with PD, anxiety also deteriorate motor control in PD, such as motor fluctuation, dyskinesia, and gait disturbance.[12,13,14] It has been reported that PD individuals with high anxiety had worse balance control than PD individuals with low anxiety under quiet standing, weight-shift task or walking.[15,16,56,57,58] For example, Jazaeri et al. (2018) divided the PD participants into low anxiety PD and high anxiety PD groups based on the anxiety subscale of the

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hospital anxiety and depression scale. The PD participants who had an anxiety subscore less than 11 were assigned to low anxiety group; the PD participants who had an anxiety subscore equal or greater than 11 were assigned to high anxiety group. The results showed that high anxiety PD group had greater velocity of postural sway than low anxiety PD group no matter when the participants stood on a rigid surface or on a foam surface.[15] Moreover, only high anxiety PD group showed greater velocity of postural sway than healthy control group, whereas the velocities of postural sway were not significantly different between low anxiety PD group and healthy control group. Similar findings were also observed in the Ehgoetz Martens et al.'s study of quiet standing under virtual reality condition in PD individuals with high and low anxiety.[16] In this study, high anxiety PD was defined as the PD patients had a State Trait Anxiety Inventory score equal or greater than 34; low anxiety PD was defined as the PD patients had a State Trait Anxiety Inventory score less than 34. The participants (PD and healthy adults) were asked to stand quietly on a force platform for 30 seconds in low-threat and high-threat conditions presented virtual environments. In the low-threat condition, participants stood in the middle of a virtual plank on the floor. In the high-threat condition, participants stood in the middle of a virtual plank elevated 8 meters above a deep pit. The results of center of gravity displacement showed that PD individuals with high anxiety significantly reduced anterior-posterior lean distance in the high-threat condition compared to the low-threat

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condition, whereas the PD individuals with low anxiety and healthy controls did not significantly adjust the center of gravity displacement to postural threat. This finding implies that in PD with high anxiety, who exhibit poorer postural control, would reduce postural flexibility and make their posture more rigid under high-challenge condition. In addition, PD with high anxiety had significantly higher standard deviation value of center of gravity displacement than PD with low anxiety and healthy control participants under both low-threat and high-threat conditions. Besides center of gravity displacement, all the participants were asked to report anxiety levels after each testing trial. The self-reported anxiety rating was larger in high-anxiety PD participants than low-anxiety PD participants and healthy control participants under both low-threat and high-threat conditions. Specifically, the self-reported anxiety rating of high-anxiety PD was increasing as the trials progressed under high-threat condition, but the phenomenon was not observed in low-anxiety PD participants and healthy control participants.

Akin to quiet standing, PD individuals with high anxiety exhibited slower walking velocity, smaller step length, and greater variability (coefficients of variation) of step length and step time compared to those with low anxiety during both single-task walking and dual-task walking (e.g., performing multiplication while walking).[56] Similar findings were also observed in a walking experiment under virtual reality condition with low-threat condition and high-threat condition for PD individuals with high anxiety (the score

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of State Trait Anxiety Inventory ≥ 34) and low anxiety (the score of State Trait Anxiety Inventory < 34).[57] In the low-threat condition, participant were asked to walk across a plank which was placed on the ground. In the high-threat condition, participants were asked to walk across the plank, which appeared to be approximately 8 m above the deep pit. The result showed that PD individuals with high anxiety had greater step time variability under high-threat condition compared to PD individuals with low anxiety and healthy controls. However, PD individuals with low anxiety and healthy controls showed similar step time variability under both low-threat and high-threat conditions. Furthermore, healthy participants slightly increased their step width under high-threat condition compared to low-threat condition. PD with low anxiety did not adjust their step width. In contrast, PD with high anxiety slightly reduced their step width under high-threat condition compared to low-threat condition.

Besides the tasks of quiet standing and walking, recent study showed that with greater anxiety level (anxiety subscore of the Hospital Anxiety and Depression Scale), PD individuals had worse weight-shifting control (e.g., large weight-shifting error and less weight-shifting correction) when they were asked to make rhythmic weight shifts at a speed of 0.25 Hz within a range of 10% to 90% of body weight.[58] In addition, anxiety level positively correlated to cortical theta activity at prefrontal area, which indicates anxious PD individuals have to devote larger amount of attention or conscious control for

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weight-shifting movement. However, the larger devotion of attention did not lead to greater weight-shifting performance even in such slow-speed weigh-shifting movement.

The present results about the association about anxiety and postural control suggest that (i) the compromised postural control in PD with high anxiety becomes more pronounced in high-threat (or high-challenging) conditions, and (ii) neural economy might be impaired in PD with anxiety since they consume more attention resource for controlling dynamic balance but without getting better postural accuracy.

1.2.3. Current assessments and interventions of anxiety in PD

Assessment of anxiety level

The Beck Anxiety Inventory, anxiety subscale of Hospital Anxiety and Depression Scale, Hamilton Anxiety Rating Scale, and State Trait Anxiety Inventory are common clinical questionnaires for anxiety assessment.[59] The Beck Anxiety Inventory is a 21-item self-report questionnaire, which was designed to measure the severity of affective somatic, and cognitive symptoms associated with anxiety in psychiatric populations.[60] The optimal cut-off point in PD population is 12/13 for discriminating anxiety disorder (≥ 13) from no anxiety disorder (≤ 12).[61] The Hospital Anxiety and Depression Scale is used to assessed anxiety and depression symptoms with 7 items for each symptom. The 7 items of the anxiety subscale in Hospital Anxiety and Depression

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Scale aim to assess symptoms of panic disorder and generalized anxiety disorder.[62] The optimal cut-off point in PD population is 6/7 for discriminating anxiety disorder (≥ 7) from no anxiety disorder (≤ 6).[61] The Hamilton Anxiety Rating Scale is a 14-item clinician-rated scale, which is used to assess and quantify severity of anxiety symptom.[63] The optimal cut-off point of the Hamilton Anxiety Rating Scale in PD population is 12/13 for distinguishing between with anxiety disorder (≥ 13) and without anxiety disorder (≤ 12).[61] The State Trait Anxiety Inventory is a self-report questionnaire, which is comprised of two components, one for indicating how participants feel right now (at this moment) and one for indicating how the participants generally feel. Each component includes 20 items to measure feelings of apprehension, tension, nervousness, and worry.[64] The optimal cutoff pint for geriatric patients is 54/55 for distinguishing between with psychiatric disorder (≥ 55) and without any psychiatric disorder (≤ 54).[65]

However, there are some limitations of these anxiety rating scales.[59,65,67] For example, many items of the Beck Anxiety Inventory relate to physical manifestations of panic symptoms.[59] Patients have physical symptoms such as PD may show a high score on these items due to overlapping with motor symptoms. Hospital Anxiety and Depression Scale is not recommended to be use as a diagnostic tool due to its low value of area under ROC curve (0.63).[61] The State Trait Anxiety Inventory is limited in lack of evaluating some symptoms of anxiety such as panic disorder.[59] In addition, the positive

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predictive value of these anxiety questionnaires was poor in PD population.[61] The positive predictive value is the ratio of patients truly diagnosed as anxiety disorder to all those who had positive test results. According to the previous study, in people with PD, the positive predict value is 0.63 in the Hamilton Anxiety Rating Scale, is 0.47 in the anxiety subscale of the Hospital Anxiety and Depression Scale, and is 0.59 in the Beck Anxiety Inventory.[61] In order to assess anxiety intensity for people with PD specifically, the Parkinson Anxiety Scale was developed for PD population in 2014.[67] The Parkinson Anxiety Scale is a 12-item questionnaire with three components, including persistent anxiety, episodic anxiety, and avoidance behavior. The anxiety score could be rated by patients or by health professionals. Presently, the Parkinson Anxiety Scale is considered as a more reliable and valid anxiety measure for patients with PD.[3] The total score of the Parkinson Anxiety Scale is 48. The intra-class correlation coefficient (ICC) values of inter-rater and intra-rater reliability of Parkinson Anxiety Scale is 0.92 and 0.89, respectively.[67] In the diagnostic properties, the sensitivity and specificity is 71% and 91%, and the value of area under curve is 0.85.[67] The optimal cut-off point of the Parkinson Anxiety Scale is 13/14 to distinguish between anxiety disorder (≥ 14) and no anxiety (≤ 13).[67]

In addition to subjective scale assessments, anxiety can also be evaluated through physiological data. Skin conductance is an electrophysiological measure which is used to

doi:10.6342/NTU202403646

represent objective anxiety intensity.[69,70] With two disposable tab electrodes affixed on the second knuckles of the index finger and middle finger of the left hand, the skin conductance is assessed by the transient change in skin electrical potential resulting from momentary voltage fluctuations across the cell membrane of eccrine sweat glands.[71,72] Skin conductance could reflect the function of the autonomic nervous system, which has been used to represent the level of autonomic arousal or physiological anxiety.[73,74,75,76] A larger skin conductance value represents larger excitability of the sympathetic nervous system, indicating higher level of arousal or anxiety. The measurement of skin conductance has often been used in studying assess attention processing, decision making, and emotional responses.[77,78,79] For example, skin conductance was used to evaluate anxiety level in patients with PD under various standing and walking conditions.[57,16] Larger skin conductance value was observed during the high-threat standing condition compared with the low-threat standing condition.[57] Moreover, both healthy subjects and PD patients had larger skin conductance values during walking than during standing.[16]

Interventions for reducing anxiety

The intervention for anxiety symptoms can be categorized into pharmacological and non-pharmacological approaches.[82] Pharmacological treatments for anxiety in PD include the use of medications such as Selective Serotonin Reuptake Inhibitors (SSRIs), benzodiazepines, and antidepressants.[82] SSRIs are commonly prescribed for managing

doi:10.6342/NTU202403646

anxiety disorders, which could inhibit serotonin reuptake, leading to increased serotonin levels in the synapse. SSRIs could also enhance serotonin neurotransmission through the progressive desensitization of serotonin auto-receptors and down-regulation of postsynaptic 5-HT2 receptors.[83,84] However, a meta-analysis research reported that the SSRLs effects on PD anxiety did not achieve significantly benefits.[85] Additionally, SSRIs may induce some side effects, such as hyponatremia, sexual dysfunction, agitation, diarrhea, insomnia, nausea, and sedation.[86] By binding to a specific receptor site on the gamma-aminobutyric acid-A receptor (GABA-A) complex, benzodiazepines could enhance GABA's inhibitory effects through the activation of a chloride ion channel.[87] Bromazepam is one kind of a long-acting benzodiazepine and it could alleviate psychic and somatic symptoms of anxiety by exerting potent short-term effects.[88] Although excessive use of benzodiazepines can rapidly diminish anxiety, patients would show some adverse effects, such as severe avoidance behaviors and prolonged dependence on the drug.[89] This drug dependence may relate to less treatment effect of cognitive-behavioral therapy in people who take benzodiazepines for long time. [87,89] Chronic benzodiazepine use is also linked to physiological dependence, short-term cognitive and psychomotor impairment, and rebound anxiety upon discontinuation.[90] Moreover, studies also reported that the use of antianxiety medications would result in greater postural instability, higher falling risk and cognitive decline in PD individuals and older adults.[91,92,93]

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Due to obvious adverse effect of antianxiety medications, non-pharmacological treatment, such as exercise therapy and neurostimulation, are proposed for anxiety reduction in clinical practice. Besides the improvements in muscle strength, balance, and walking ability.[94,95,96] Ferreira et al. (2018) reported that resistance training could reduce anxiety intensity and improve quality of life in people with PD.[19] Although this study did not specifically target for PD with anxiety, the mean score of Beck Anxiety Inventory in resistance training group and control group was 18.0 and 21.3, respectively before resistance training, indicating the PD participants would have a moderate level of anxiety symptom. The exercise of resistance training included bench press, deadlift, unilateral rowing, standing calf raise, and lower abdominal exercises, under the guidance of an exercise specialist. The resistance training program was 30-40 minutes per training session with two sessions per week for 6 months. After training, a decreased score in Beck Anxiety Inventory and an increased score quality of life measured by Parkinson's Disease Questionnaire-39 were observed. However, the resistance exercise effects on reducing anxiety are not consistent among different studies. For example, in Kwok et al.'s study, PD participants were assigned into the mindfulness yoga group or the exercise group (stretching and resistance exercises). The training program was 60 minutes per session, one session per week for 8 weeks.[20] After 8-week training, the mindfulness yoga group significantly reduced the score of anxiety subscale of the Hospital Anxiety and

doi:10.6342/NTU202403646

Depression Scale. In contrast, the group undergoing stretching and resistance exercises did not show a significant decrease in anxiety intensity after training. Besides resistance exercise, Beck and colleagues proposed that exercising with internal-focus strategy could reduce anxiety intensity in PD patients, whereas exercising with external-focus strategy did not show this training benefit.[97] In this study, participants engaged in an 11-week goal-based exercise program (1 hour per sessions; 3 sessions per week), including stretching, coordination, balance, and gait training. For the internal focus group, participants were instructed to concentrate on the sensory feedback from their limbs in the physical space during performing the exercises. For the external focus group, participants were instructed to focus on the movement of colored labels attached to their limbs. After 11-week training, although both groups decreased the score of Unified Parkinson's Disease Rating Scale part III (i.e. motor impairment intensity), only the internal-focus group exhibited a significant decrease the score of Parkinson Anxiety Scale.

Recently, some researchers propose that neurostimulation such as tDCS and rTMS may have treatment benefits to anxiety in PD.[98,99,100] Feng and colleagues investigated the effects of tDCS on Parkinsonism rats in frontal lobe.[98] The rat anxiety-related behaviors, such as increased grooming, reduced exploration, altered locomotor activity, were recorded before and after 4-week tDCS intervention (20 minutes per day). After tDCS intervention, the Parkinsonism rats reduced anxiety-related behaviors. However,

doi:10.6342/NTU202403646

the tDCS benefits to anxiety reduction may not observed in people with PD. For example, in Doruk et al.'s study, PD individuals underwent 10-session tDCS intervention targeting the dorsolateral prefrontal cortex (DLPFC).[99] Although the participants improved their executive function and reduced depression intensity after 2-week tDCS intervention, the anxiety intensity, which was measured by the Hamilton Anxiety Scale, did not decrease. Besides the well-known treatment benefit to depression reduction, recently, rTMS is also investigated about its treatment benefit to anxiety reduction in people with PD. In Epstein et al.' study, people with PD underwent a 10-day rTMS treatment with a stimulation frequency of 10 Hz, comprising a total of 19 sessions with 1000 pulses for each session.[100] The stimulation site was the left dorsolateral prefrontal cortex. The levels of depression and anxiety were assessed using the Beck Depression Inventory and Hamilton Anxiety Scale, respectively. The assessments were conducted at baseline, 3 days post-intervention, 3 weeks post-intervention, and 6 weeks post-intervention. Significant decreases in both depression intensity and anxiety intensity were observed at 3 days, 3 weeks, and 6 weeks after the last rTMS session. However, a study of meta-analysis in PD reported that non-invasive brain stimulation (including tTMS and tDCS) only has significant effects on depression reduction, but not on anxiety reduction when comparing to sham-stimulation or placebo intervention.[21] In addition, combining non-invasive brain stimulation and antidepressant therapy is required for decreasing anxiety intensity in PD.

doi:10.6342/NTU202403646

1.2.4. Effects of transcutaneous vagus nerve stimulation on anxiety

Despite some evidence showing that rTMS and tDCS may have benefit to reduce anxiety, rTMS and tDCS might be not accessible in clinical practice due to high price of the instruments. Like rTMS and tDCS, VNS is one kind of neurostimulation. VNS has been approved by Food and Drug Administration (FDA) for treating refractory depression and epilepsy. It demonstrates clinically significant antidepressant and antiseizure effects.[27,101] VNS could be invasive or non-invasive. For invasive VNS, the wire is attached to the left vagus nerve between carotid artery and internal jugular vein in cervical region, and the battery is implanted in the upper left chest. For implanting the stimulus wire, a dissection of the vagus nerve from the carotid artery is required.[26] Although the surgery of VNS implantation is minimally invasive, it still has some inherent risk. Possible complications resulting from the surgical procedure include bradyarrhythmia during device placement, peritracheal hematoma (due to surgical trauma), and additional respiratory issues such as vocal cord dysfunction and dyspnea (attributed to nerve trauma).[26] In order to reduce the risk of surgery, the tVNS was developed, which is usually applied on auricular branch of vagus nerve.[102] According to the anatomy of vagus nerve, the auricular branch of vagus nerve distributes over tragus, cavum conchae, and cymba conchae.[102] Stimulating the auricular branch of vagus nerve is thought to induce therapeutic effects comparable to invasive VNS.[104,105,106] Particularly, the cymba concha of external ear is innervated solely by the auricular branch of the vagus nerve, whereas

doi:10.6342/NTU202403646

the tragus and cavum conchae also receive afferent innervation by other nerve.[102,107] Therefore, the cymba conchae is the most common site for tVNS. Although the mechanisms of tVNS are not yet fully understood, functional magnetic resonance imaging (fMRI) studies showed that tVNS could impact on various brain regions through neural pathways linked to the nucleus tractus solitarius and locus coeruleus, including the thalamus, cerebellum, hypothalamus, amygdala, insula, cingulate, and frontal cortex.[108,109,110,111] In terms of stimulation parameters of tVNS, most studies adopted an intensity of blow pain threshold;[110,111,112] however, the pulse width and duration were varied across studies. For example, in Frangos et al.'s study (2015), after receiving tVNS with pulse width of 250 μs and frequency of 25 Hz for 7 minutes, brain activation changes in ipsilateral Solitary nucleus (NTS) and amygdala were observed in young healthy adults.[110] However, other studies showed brain activation change would be observed with shorter stimulus duration of tVNS. Badran et al. (2018) reported after receiving tVNS with pulse width of 500 μs, and frequency of 25 Hz for 60 seconds, increasing activities in bilateral anterior cingulate cortex and frontal lobe were shown in young healthy adults.[112]

As tVNS largely affects brain regions involved in emotional regulation, numerous experiments have investigated its effects on psychological disorders such as depression, anxiety, and other related issues.[113,114,115] For example, in Bretherton et al.'s study (2019),

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older adults (> 55 years old) underwent tVNS by a transcutaneous electrical nerve stimulation (TENS) machine for 15 minutes daily over two weeks, with a pulse width of 200 μs, a pulse frequency of 30 Hz, and an intensity slightly below the sensory level.[113] The stimulation clips of tVNS were attached on the inner and outer surface of the tragus of the ear. In this study, the electrode leads were disconnected from the TENS machine without the participant's awareness (i.e., no stimulation) for the sham tVNS. Baroreflex sensitivity (BRS) was used to assess automatic control of the cardiovascular system. Higher BRS indicates greater autonomic control in the cardiovascular system. After two weeks, the increase of BRS was greater in the active tVNS group than the sham tVNS group, whereas no increase of BRS was observed in the sham tVNS group. Furthermore, there was a significant improvement in health-related quality of life, as measured by the 36-Item Short Form Survey (SF-36), and mood, as assessed by the Profile of Mood States questionnaire in the active tVNS group. The Profile of Mood States questionnaire includes the dimensions of anxiety, depression, anger, vigor, fatigue, and confusion. Liu and colleagues (2016) investigated the effect of tVNS on patients with major depressive disorder.[114] Participants received tVNS intervention with stimulus frequency of 20 Hz, pulse width of 100 μs and intensity of patients' tolerance (4-6 mA). There were 30 minutes for each tVNS intervention session (active tVNS vs. sham tVNS) and there were two sessions per day with one session in the morning and one session in the evening. There

doi:10.6342/NTU202403646

were 5 days of tVNS intervention per week for 4 consecutive weeks. Active tVNS was applied on the cymba concha, and sham tVNS was applied at the superior scapha. The result showed that after 4-week intervention, only the active tVNS group reduced the scores of Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Self-Rating Anxiety Scale, indicating decreases in depression and anxiety intensities. Besides clinical questionnaires, resting brain activities by fMRI was assessed before and after tVNS intervention. The active tVNS group exhibited increased resting-state functional connectivity between the right amygdala and left dorsolateral prefrontal cortex after intervention compared to baseline evaluation. Moreover, the increase in right amygdala-DLPFC resting-state functional connectivity was negatively correlated to the reduction score of anxiety across all participants.

In addition to long-term intervention effect, some studies investigated immediate effect of tVNS by stimulating vagus nerve while people performed an anxious task.[28,29] For example, Burger and colleagues (2019) recruited individuals who had a Penn State Worry Questionnaire (PSWQ) score ≥ 45. People with a PSWQ score ≥ 45 could be considered having clinical generalized anxiety disorder.[28] The participants were dividing into active tVNS group (left cymba conchae) or sham tVNS group (left earlobe). The parameters of tVNS were 0.5 mA of intensity, 25 Hz of frequency, and 250 μs of pulse width with 30 seconds of on time and off time. Participants conducted a breathing focus

doi:10.6342/NTU202403646

task for 5 minutes with tVNS concurrently. During the breathing focus task, participants closed eyes and directed their attention to their breath. In addition, auditory cues were provided with a time interval of 20–30 seconds. When hearing the cues, participants opened their eyes promptly, and answered a question of "whether your focus was on their breathing or if you were worry about something else". Worries are the main component of generalized anxiety disorder. People who have generalized anxiety disorder or have high levels of worry tend to be occupied with stress-related thoughts. The study finding showed that the participants who underwent active tVNS had less worries than the participants who underwent sham tVNS, indicating that tVNS could have immediate effect on reducing worry or stress-related thoughts. In addition, tVNS could also reduce the physiological arousal responses under high-challenge conditions. Sanchez-Perez and colleagues (2023) applied auricular tVNS (on left cymba concha), cervical tVNS (on left carotid sheath) and sham tVNS (on left sternocleidomastoid muscle) to young healthy adults when they performed three high-challenge tests, which were mental arithmetic test, n-back test, and the cold pressor test.[29] The parameters of tVNS were 40 ms of train duration, 500 μs of pulse width, and intensity was set below pain threshold. For the mental arithmetic test, participants were instructed to sum the three digits of a three-digit number. For the n-back test, a series of digits (0–9) was sequentially displayed on a screen, and participants had to press the space key on the keyboard while the number was the same

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as the number of two digits back. For the cold pressor test, participants had to immerse their left feet in an ice bucket. Electrocardiogram, electrodermal activity, blood pressure, seismocardiogram, and photoplethysmogram were measured during the tasks. Left ventricular ejection time and pre-ejection period were analyzed from seismocardiogram. Compared to the sham tVNS, active tVNS on cymba conchae led to shorter left ventricular ejection time, lower blood pressure and larger ratio of pre-ejection period to left ventricular ejection time responses during all 3 tasks. These cardiac timing changes (i.e., shorter left ventricular ejection time and pre-ejection period) suggest stroke volume reduction. The results implied tVNS on cymba conchae could counteract stress-induced increases in stroke volume while people performed high-challenge tests. Similarly, the group of tVNS on cymba conchae also showed a lower electrodermal activity than the sham tVNS group. However, there was no significant difference in any physiological variable between cervical tVNS and sham tVNS, suggesting that the beneficial effects of anxiety reduction may only occur when tVNS stimulates on the cymba conchae. Moreover, a fMRI study further showed a relationship between the changes in brain activation and the reduction in anxiety intensity induced by tVNS.[25] Garcia and colleagues (2021) recruited premenopausal women with recurrent major depressive disorder and stimulated their vagus nerve for 30 minutes when they exhaled or when they inhaled.[25] Stimulus electrodes were placed in the left cymba concha with monophasic

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rectangular pulse trains (pulse width: 300 μs; train duration: 0.8 s; frequency: 30 Hz; intensity: below subjects' pain threshold). Brain activities were recorded by fMRI before and after tVNS intervention, when the participants conducted a visual stress task which consisted high arousal pictures such as being pointed with a gun. In addition, the anxiety level was evaluated by State Trait Anxiety Inventory. Contrary to applying tVNS during inhalation, applying tVNS during exhalation significantly reduced anxiety level and increased activation in bilateral anterior cingulate cortex, orbitofrontal and ventromedial prefrontal cortices and increased connectivity between hypothalamus and dorsolateral prefrontal cortex, and from nucleus tractus solitarius to locus coeruleus and ventromedial prefrontal cortex. Notably, the increase in connectivity strength between nucleus tractus solitarius and locus coeruleus and the increase in connectivity strength between nucleus tractus solitarius and ventromedial prefrontal cortex positively correlated to the reduction score of State Trait Anxiety Inventory. The people who had greater increase in this brain connectivity strength showed a more reduction in anxiety intensity.

1.3. Limitation of previous studies about posture control under different speeds in PD with anxiety

Based on the previous studies about postural control in PD with anxiety, there are three critical issues needed to be further concerned.

doi:10.6342/NTU202403646

First, although the ability of weight shifting is fundamental for dynamic postural control,[1,2,5] only few studies investigated the weight-shifting control under different speeds in PD. Previous studies have explored the association among movement amplitude, accuracy, and speed.[33,35,116] They found with movement speed increased, movement accuracy or movement amplitude would decrease. However, the difference in weight-shifting control between PD with anxiety and PD without anxiety has not been investigated. People with anxiety may devote their major attention to threat-related information rather than to the goal-directed task itself, resulting in worse movement performance, particularly in high-challenge conditions.[117,118]

Secondly, although tVNS has been applied to anxiety reduction in some studies,[28,29,25] its benefit to dynamic postural control is still unknown in PD with anxiety. tVNS is an accessible instrument to reduce stress-related thoughts or threat-related physiological response in healthy young adults or high-worry people.[28] Studies reported tVNS intervention could decrease subjective and objective anxiety level,[28,29] and modulate brain connectivity in patients with major depressive disorder.[25] However, there is no study investigate the effects of tVNS on anxiety intensity and dynamic postural control (e.g., weight-shifting control) in PD, especially under different speed-demand conditions.

The third, the neural-related mechanism of weight-shifting control has not been

doi:10.6342/NTU202403646

comprehensively investigated in PD, particularly in PD who also have anxiety. A systematic review article discussed neuroimage findings in PD with anxiety by integrating the studies of MRI, fMRI, positron emission tomography (PET), and single-photon emission computed tomography (SPECT).[17] This article proposed that the high prevalence of anxiety in PD patients may due to the overlap circuits between the fear circuit and the limbic cortico-striato-thalamocortical circuits.[17] Not only inducing motor symptoms, such as postural and gait deficits, the malfunctioning limbic cortico-striato-thalamocortical circuits would also increase the risk of anxiety in people with PD. In addition, Dan and colleagues analyzed brain functional connectivity from resting state fMRI in PD with anxiety.[119] There were three distinct brain activities in PD with anxiety: (i) increased connectivity strength between the limbic and orbitofrontal cortex; (ii) decreased connectivity strength between the limbic-dorsolateral prefrontal cortex and orbitofrontal-dorsolateral prefrontal cortices; and (iii) decreased connectivity strength between the sensorimotor cortex and orbitofrontal cortex. The first two findings of functional connectivity change suggest a less voluntary and more automatic emotion regulation. The third pattern reflects an impaired ability of the orbitofrontal cortex to guide goal-directed movements in PD with anxiety. This finding might explain why anxious PD patients have worsen motor control than those without anxiety. Although the fMRI could provide greater spatial resolution of brain activity, the

doi:10.6342/NTU202403646

electroencephalography (EEG) data could be recorded during performing dynamic balance tasks with greater temporal resolution.[120] Although Hung et al.'s study proved that anxious PD would consume more attentional resource than non-anxious PD in very slow weight-shifting movement (0.25 Hz), the required speed of weight-shifting could be faster in daily life. Therefore, it is worth to investigate how the brain activity modulation for weight-shifting control between PD with anxiety and without anxiety under different shifting speeds.

1.4. Purposes and significance

Purposes of the study

1. Investigate the impact of tVNS (active tVNS vs. sham tVNS) on weight-shifting performance and anxiety level in PD with and without anxiety under different shifting speeds (0.25 Hz, 0.33 Hz, and 0.50 Hz) respectively.
2. Investigate the relationships among daily anxiety level and the changes in weight-shifting performance and anxiety level due to tVNS in people with PD when they performed weight-shifting movements.
3. Investigate the impact of tVNS (active tVNS vs. sham tVNS) on cortical activity in PD with and without anxiety when they perform weight-shifting movement with different shifting speeds.

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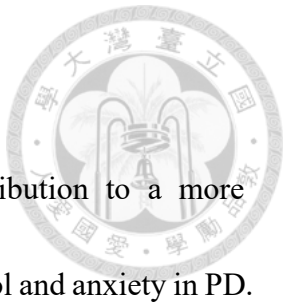

Significance of the study

The academic significance of this research lies in its contribution to a more comprehensive understanding of the interplay between postural control and anxiety in PD. In the clinical aspects, balance problem and anxiety were rated as the first and the second priority for the PD management from all motor and non-motor symptoms by people with PD, their caregivers and professionals of healthcare and social care.[121] This study combined the top 2 issues of PD, balance dysfunction and anxiety, to investigate whether tVNS intervention could lead to anxiety reduction associated with an improvement of weight-shifting control or not.

1.5. Hypotheses

1. The impact of tVNS on weight-shifting performance and anxiety level would be greater in PD with anxiety than PD without anxiety, especially under the condition of fast shifting speed.
2. The daily anxiety level would be positively correlated to the changes in weight-shifting performance and anxiety level due to tVNS.
3. Cortical activation would be modulated due to tVNS when people with PD performed weight-shifting movements, particularly in PD with anxiety under the condition with fast shifting speed.

doi:10.6342/NTU202403646

Chapter 2

METHODS

2.1. Participants

Thirty people with PD were recruited in the present study with 15 participants had anxiety and 15 participants did not had anxiety. Table 1 presents participant demographics and clinical characteristics. The inclusion criteria were as follows: (i) the participant had a confirmed diagnosis of idiopathic PD in line with the clinical diagnostic criteria outlined by the United Kingdom PD Society Brain Bank, (ii) the participant had the ability to stand independently without the need for assistive devices ≥ 60 seconds, (iii) the PD onset age > 40 years old to exclude cases of young onset PD, (iv) since the task involves tracking target waves on a screen, the participant should have normal vision or vision corrected to normal, and (v) the participant did not have any other neurological or orthopedic conditions that may affect their balance capabilities. Additionally, to ensure the factors of cognition, neuropsychiatric features (other than anxiety), and postural alignment would not induce adversely impact on the control of weight-shifting, individuals were ineligible for participation if they had any of the following conditions: (i) a history of brain surgery, (ii) a score of < 26 on the Mini-Mental State Examination (MMSE),[122] (iii) a score > 2 on item 3.13 (posture) of the MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). A score > 2 on item 3.13 signifies the presence of moderate

doi:10.6342/NTU202403646

to severe stooped posture or scoliosis, or (iv) taking any antidepression medication or had a score > 1 on item 1.3 (depression) of the MDS-UPDRS. Participants were assigned to either the anxiety group or the non-anxiety group depending on the score of the Parkinson Anxiety Scale (PAS).[123] Participants with PAS scores > 13 were assigned to the anxiety group, while those with PAS scores ≤ 13 were assigned to the non-anxiety group.[67] All procedures in the experiment were approved by the National Taiwan University Hospital Research Ethics Committee (202301082RIND).

The sample size estimation was calculated by G*power software. Based on data from a previous study,[8] 30 participants (15 participants in each group) would be sufficient to detect the influence of anxiety on weight-shifting performance (Cohen's d = 0.543, power = 0.90, $\alpha = 0.05$).

2.2. Study procedures and data recording

All participants were on their antiparkinsonian medications during the study procedures. Each participant underwent two experimental sessions with a minimum 48-hour interval between the two sessions, but within one week. One session was for active tVNS, and the other session was for sham tVNS. The order of active tVNS and sham tVNS was randomized across all participants. For each participant, both sessions were scheduled at the same period in the daytime. After the participant enrolling the study, the

doi:10.6342/NTU202403646

symptom severity of the PD disease and the disease stage were assessed with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the modified Hoehn and Yahr stages, respectively.

Participants stood with their feet in shoulder-width apart on a level surface to perform a weight-shifting task. with the affected leg standing on a force plate (9260AA6, Kistler, Switzerland)(Figure 1). The affected leg was defined as the side of lower extremity with greater sum of scores for items 3.3 (rigidity), 3.7 (toe tapping), 3.8 (leg agility), and 3.17 (rest tremor amplitude) from the MDS-UPDRS.[124] Participants were instructed to perform rhythmical weight-shifting movement and track a target signal by adjusting their body weight distribution on the force plate. The target signal moved horizontally on a 22-inch screen in a sinusoidal waveform, with the maximum and minimum values at 90% and 10% of the participant's body weight, respectively. The monitor was positioned at eye-level, 1.0 meter from participants. the speed of target signal of this experiment was set as 0.25 Hz, 0.33 Hz, and 0.5 Hz, respectively. Based on Hung et al.'s study, PD patients with anxiety had worse weight-shifting control than PD patients without anxiety when they performed weight-shifting movement with a speed of 0.25 Hz.[58] The weight-shifting frequencies of 0.33 Hz and 0.5 Hz represent very slow and slow walking speeds.[2] In addition, 0.5 Hz is suggested as a critical frequency at which the difficulty level increases while young healthy adults perform rhythmic weight-shifting

doi:10.6342/NTU202403646

task. the frequency.[1] Therefore, the speed of target signal of this experiment was set as 0.25 Hz, 0.33 Hz, and 0.5 Hz, respectively. The three weight shifting tracking conditions of different target speed were randomized for each participant. Each condition contained six 60-s tracking trials with a 30-s resting period between the tracking trials.

During the execution of the weight-shifting tasks, participants concurrently were subjected to either active tVNS or sham tVNS by a TENS (GM3A50TE, Gemore Technology, Taiwan). In the active tVNS session, the stimulation electrode was applied to the left cymba conchae. For the sham tVNS session, the stimulation electrode was situated on the left earlobe because the area has been proposed that lacks branches of the vagus nerve.[110] The pulse width and frequency of electrical stimulation were 250 μs and 25 Hz, respectively. The intensity was adjusted to slightly below the pain threshold.[125]

The brain activity was recorded when the participants perform rhythmical weight-shifting movement. A RT 64–channel EEG amplifier (SymAmps RT, NeuroScan Inc., USA) was used to record cortical activities. The EEG electrodes were placed based on 10-20 electrode system of the International Federation. The electrodes placed above the left eyebrow, below the left eye, and horizontally on the outer canthi of both eyes will be used to monitor vertical and horizontal eye movements and blinks. The impedances of all electrodes are below 5 kΩ and referenced to linked mastoids on both sides. The EEG data

doi:10.6342/NTU202403646

was band-pass filtered at 0.1-00 Hz. The data from the force plate and EEG were synchronized and digitized at a sampling rate of 1 kHz.

Besides the data of vertical force from the force plate and cortical activities, skin conductance level (SCL) was recorded to stand for the level of arousal or physiological anxiety during each trial.[70,79] The data of skin conductance was obtained using a skin conductance sensor (Q-S222 GSR sensor, Qubit System Inc., Canada). Two disposable tab electrodes were affixed on the second knuckles of the index finger and middle finger of the left hand.[70] Skin conductance level has been previously employed to evaluate anxiety levels in patients with PD under various standing and walking conditions.[79,80] Skin conductance levels reflect sympathetic arousal specifically, which is implicated in anxiety.[70] The higher the skin conductance level, the higher the level of anxiety. Additionally, at the end of each testing trial, participants will be asked to assess their subjective anxiety levels using the 9-point Self-Assessment Manikin.[126] The 9-point Self-Assessment Manikin is divided into three rating categories: pleasure, arousal, and dominance. We utilized arousal as the primary rating category of subjective anxiety level in this experiment, with scores ranging from 1 to 9. A higher score indicates a higher level of anxiety experienced by the participants during the weight-shifting task.

2.3. Data analyses

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For the rhythmical weight-shifting movement, the data from the force plate was conducted with a zero-phase low-pass filter (cut-off frequency: 6 Hz). For weight-shifting trajectory, tracking error and smoothness were calculated. The amount of tracking error in weight-shifting was quantified using the root mean square value of the discrepancy between the target body weight and the actual weight-bearing. Tracking correction was calculated by the jerk square mean (JSM) value of tracking trajectory by the following formula.

$$\text{JSM} = \int_0^{MT} \frac{J^2}{2} dt$$

Jerk (J) is the time derivative of acceleration, and JSM has been used as an index of movement smoothness during movement time (MT).[127] Larger JSM value represents less movement smoothness. Moreover, for movement control, less smoothness of movement trajectory indicates more frequent movement correction.[128,129] In addition, the amplitude of weight-shifting movement toward the more-affected side was calculated.

The EEG data was processed by Curry 8 software (CURRY 8, NeuroScan Inc., USA). After removing eye movements and blinks, the data was conditioned with 1 Hz to 100 Hz band-pass filter and processed using a 60 Hz notch filter. The conditioned EEG data was categorized into prefrontal (Fp1, Fpz, Fp2, AF3, AF4), frontal (F1, F3, F5, F7, F11, Fz, F2, F4, F6, F8, F12, FC1, FC3, FC5, FCz, FC2, FC4, FC6), sensorimotor (C1, C3, C5, Cz, C2, C4, C6, CP1, CP3, CPz, CP2, CP4, CP6), parietal-occipital (P1, P3, P5, P7, Pz,

doi:10.6342/NTU202403646

P2, P4, P6, P8, PO3, PO7, POz, PO4, PO8, O1, Oz, O2). Then, principal component analysis (PCA) was used to transform data into a set of principal components (PCs) at each area. For each cortical area, the relative significance of the PCs was ranked with respect to their eigenvalues (λ1, λ2…, λn), which explained the variance of the whole set of EEG data. The eigenvector (U1, U2…, Un), acting as weighting coefficients, was used to calculate the relative contribution of each PC from EEG for all electrodes. The factor loading (W1, W2…, Wn) of PCs in each electrode as following:[130]

$$\mathrm{Wi} = \frac{\mathrm{Ui}^2}{\sum_{i=1}^{n} \mathrm{Ui}^2} \times 100\%$$

In the formula, n indicates the number of channels in the specific areas. The EEG data PC1 was analyzed further as it accounted for more than 70% of the total variance properties of the EEG data at each cortical area.[130] Table 2 shows the percentage of the total variance in the EEG data for each cortical area. The relative powers of each frequency band (delta: 1-4 Hz; theta: 4-8 Hz; alpha: 8-12 Hz; beta: 12-30 Hz; low gamma: 30-50 Hz; high gamma: 50-80) were determined by dividing the absolute power in each spectral band with the total power of all spectral bands (1-100 Hz).

For skin conductance analysis, we recorded SCL for 5 minutes while the participant is seated with their eyes closed (in a resting state) before conducting the three rhythmical weight-shifting testing conditions. In addition, the changes of SCL between the averaging SCL value (from the 11th second to the 60th seconds of each weight-shifting trial) and

doi:10.6342/NTU202403646

resting state SCL value was used to reflect anxiety level when participants performed the weight-shifting moevemts.[79]

2.4. Statistical analyses

The effects of tVNS (active tVNS vs. sham tVNS) and group (anxiety vs. nonanxiety) on the variables of weight-shifting tracking error, weight-shifting amplitude, weight-shifting JSM, SCL and relative power of EEG were examined with two-way mix analysis of variance (ANOVA) under different the three shifting speeds, respectively. When necessary, post hoc Bonferroni test comparisons were conducted. For subjective anxiety level (the score of arousal from the 9-point Self-Assessment Manikin), Mann-Whitney U test was used to compare the effect of group and Wilcoxon signed-rank test was used to compare the effect of tVNS. In addition, the Pearson correlation coefficients was conducted to investigate the relationship between the scores on the PAS and the changed values in behavioral data and anxiety level between the active tVNS and sham tVNS conditions (active tVNS – sham tVNS; △). The significance level was set at $p < 0.05$. Signal processing and statistical analyses were completed using MATLAB v. R2022b (MathWorks, MA, USA) and SPSS v. 21 (SPSS Inc., USA). All data was presented as the mean ± standard error.

doi:10.6342/NTU202403646

Chapter 3

RESULTS

3.1. Behavioral performance

In the aspect of the error of weight-shifting trajectory (Figure 3, upper plot), in the 0.25 Hz condition, the ANOVA results revealed that the tracking error of weight-shifting was affected by group-by-tVNS interaction effect ($F_{(1,28)} = 4.483$, $p = 0.043$), although there was no tVNS ($F_{(1,28)} = 0.667$, $p = 0.421$) or group ($F_{(1,28)} = 0.663$, $p = 0.422$) effect. Post hoc analysis showed that anxiety group with active tVNS had smaller tracking errors when they received active tVNS than when they received sham tVNS ($p = 0.041$). However, the tracking error was not affected by tVNS in the non-anxiety group ($p = 0.381$). In the 0.33 Hz condition, both tVNS effect ($F_{(1,28)} = 3.659$, $p = 0.056$) and group-by-tVNS interaction effect ($F_{(1,28)} = 4.055$, $p = 0.054$) showed marginal significant effects on tracking error, without a significant group effect ($F_{(1,28)} = 6.70$, $p = 0.402$). Due to marginally significant tVNS and group-by-tVNS interaction effects, we further conducted the post hoc analysis, and the results showed that the anxiety group had smaller tracking error when they received active tVNS than when they received sham tVNS ($p = 0.008$). In the 0.50 Hz condition, the tracking error was affected by interaction effect ($F_{(1,28)} = 12.962$, $p = 0.001$), although there was no group ($F_{(1,28)} = 1.757$, $p = 0.196$) or tVNS effect ($F_{(1,28)} = 2.782$, $p = 0.106$). Post hoc analysis showed that anxiety group with active tVNS

doi:10.6342/NTU202403646

had smaller tracking errors when they received active tVNS than when they received sham tVNS ($p = 0.001$). Furthermore, with active tVNS, tracking error was smaller in the anxiety group than that in the non-anxiety group ($p = 0.024$).

In the aspect of JSM of weight-shifting trajectory (Figure 3, lower plot), the ANOVA results revealed that the JSM was affected by group-by-tVNS interaction effect in each speed condition (0.25 Hz: $F_{(1,28)} = 6.308$, $p = 0.018$; 0.33 Hz: $F_{(1,28)} = 5.129$, $p = 0.031$; 0.5 Hz: $F_{(1,28)} = 5.751$, $p = 0.023$), although there was no significant tVNS effect (0.25 Hz: $F_{(1,28)} = 1.825$, $p = 0.188$; 0.33 Hz: $F_{(1,28)} = 1.024$, $p = 0.320$; 0.5 Hz: $F_{(1,28)} = 0.471$, $p = 0.498$) or group effect (0.25 Hz: $F_{(1,28)} = 3.515$, $p = 0.071$; 0.33 Hz: $F_{(1,28)} = 3.402$, $p = 0.079$; 0.5 Hz: $F_{(1,28)} = 3.727$, $p = 0.064$). Post hoc analysis indicated that with active tVNS, the anxiety group exhibited significantly higher JSM when they received active tVNS than when they received sham tVNS (0.25 Hz: $p = 0.009$; 0.33 Hz: $p = 0.023$; 0.5 Hz: $p = 0.023$). Furthermore, with active tVNS, anxiety PD had larger JSM value compared to the non-anxiety group (0.25 Hz: $p = 0.029$; 0.33 Hz: $p = 0.032$; 0.5 Hz: $p = 0.022$).

For the weight-shifting amplitude (Figure 4), the ANOVA results did not reveal any significant main effect of tVNS ($F_{(1,28)} = 0.127$, $p = 0.724$), anxiety ($F_{(1,28)} = 2.839$, $p = 0.203$) or interaction effect ($F_{(1,28)} = 2.369$, $p = 0.135$) under the 0.25 Hz condition. In contrast, under the 0.33 Hz condition, the ANOVA results revealed that the weight-shift

doi:10.6342/NTU202403646

amplitude was affected by the main effects of group ($F_{(1,28)} = 8.416$, $p = 0.007$) and group-by-tVNS interaction effect ($F_{(1,28)} = 5.807$, $p = 0.023$), although there was no significant tVNS effect ($F_{(1,28)} = 1.507$, $p = 0.230$). Post hoc analysis showed that non-anxiety PD had smaller weight-shift amplitude when they received active tVNS than when they received sham tVNS ($p = 0.019$), whereas weight-shifting amplitude was not different between active tVNS and sham tVNS in the anxiety group ($p = 0.394$). Additionally, regardless of tVNS mode, the non-anxiety group showed a smaller weight-shifting amplitude than the anxiety group (active tVNS: $p = 0.002$; sham tVNS: $p = 0.035$). Under the 0.5 Hz condition, the weight-shift amplitude was affected by main effects of group ($F_{(1,28)} = 4.494$, $p = 0.043$) and group-by-tVNS interaction effect ($F_{(1,28)} = 4.329$, $p = 0.047$), although there was no significant tVNS effect ($F_{(1,28)} = 0.009$, $p = 0.925$). Post hoc analysis showed that the anxiety group had larger weight-shifting amplitude than the non-anxiety group in active tVNS session ($p = 0.006$), but the group difference was not observed in sham tVNS session ($p = 0.294$).

3.2. Anxiety level

In terms of subjective anxiety level (Figure 5, upper plot), Mann-whitney U test revealed that the anxiety group had higher score of the 9-point Self-Assessment Manikin than the non-anxiety group in both active tVNS ($p = 0.002$) and sham tVNS ($p < 0.001$)

doi:10.6342/NTU202403646

session under the 0.25 Hz condition. However, Wilcoxon signed-rank test revealed that subjective anxiety level was not affected by tVNS mode in both anxiety group (p = 0.755) and non-anxiety group (p = 0.141) under the 0.25 Hz condition. Under the 0.33 Hz condition, the anxiety group showed a higher subjective anxiety level than the non-anxiety group only in sham tVNS session (p = 0.025), but not in active tVNS session (p = 0.193). In addition, there was no significant difference in subjective anxiety level between active tVNS session and sham tVNS session in both anxiety group (p = 0.230) and non-anxiety group (p = 0.080). Under the 0.50 Hz condition, there was no significant group difference in subjective anxiety level in sham tVNS (p = 0.334) or active tVNS (p = 0.131) session. Also, there was no significant difference in subjective anxiety level between active tVNS and sham tVNS sessions in both anxiety group (p = 0.834) and non-anxiety group (p = 0.176).

For the physiological anxiety level (Figure 5, lower plot), the ANOVA results revealed that there was no significant group effect (0.25 Hz: $F_{(1,28)} = 1.020$, $p = 0.322$, 0.33 Hz: $F_{(1,28)} = 1.051$, $p = 0.315$, 0.5 Hz: $F_{(1,28)} = 0.997$, $p = 0.327$), tVNS effect (0.25 Hz: $F_{(1,28)} = 0.076$, $p = 0.785$, 0.33 Hz: $F_{(1,28)} = 0.188$, $p = 0.669$, 0.5 Hz: $F_{(1,28)} = 1.700$, $p = 0.204$), or their interaction effect (0.25 Hz: $F_{(1,28)} = 0.105$, $p = 0.749$, 0.33 Hz: $F_{(1,28)} = 0.195$, $p = 0.662$, 0.5 Hz: $F_{(1,28)} = 0.105$, $p = 0.749$) in the values of SCL under each speed condition.

doi:10.6342/NTU202403646

3.3. Correlation between PAS and changes behavior/anxiety parameters (Table 3)

Under the 0.25 Hz condition, PAS score positively correlated to the tVNS changes (active tVNS – sham tVNS, △) in weight-shifting JSM ($r = 0.469$, $p = 0.006$). In addition, △subjective anxiety level negatively correlated to the △weight-shifting amplitude ($r = -0.323$, $p = 0.047$).

Under the 0.33 Hz condition, PAS score positively correlated to the △weight-shifting JSM ($r = 0.407$, $p = 0.016$), △weight-shifting amplitudes ($r = 0.380$, $p = 0.023$), and negatively correlated to the △weight-shifting tracking error ($r = -0.373$, $p = 0.025$) and △subjective anxiety level ($r = -0.340$, $p = 0.038$). In addition, △subjective anxiety level negatively correlated to △weight-shifting amplitude ($r = -0.464$, $p = 0.006$).

Under the 0.50 Hz condition, PAS score positively correlated to the normalized difference of weight-shifting JSM ($r = 0.447$, $p = 0.009$), but negatively correlated to the normalized difference of weight-shifting tracking error ($r = -0.476$, $p = 0.005$).

3.4. Relative power of EEG

Prefrontal cortex

For the relative power of EEG in delta band (Figure 6), the ANOVA results revealed that there was a tVNS effect ($F_{(1,28)} = 10.933$, $p = 0.003$) and group-by-tVNS interaction effect ($F_{(1,28)} = 11.764$, $p = 0.002$) but no significant group effect ($F_{(1,28)} = 0.114$, $p = 0.738$)

doi:10.6342/NTU202403646

under the 0.25 Hz condition. Post hoc analysis showed that non-anxiety PD group had higher power when they received active tVNS than when they received sham tVNS ($p <$ 0.001). In addition, under the 0.33 Hz condition, there was a tVNS effect ($F_{(1,28)} = 8.909$, $p = 0.006$) and marginally significant group-by-tVNS interaction effect ($F_{(1,28)} = 4.122$, $p = 0.052$) but no group effect ($F_{(1,28)} = 0.059$, $p = 0.810$). Due to marginally significant interaction effect, we further conducted the post hoc analysis. Post hoc analysis showed that non-anxiety PD group had also higher power when they received active tVNS than when they received sham tVNS ($p = 0.002$). In contrast, under the 0.50 Hz condition, delta band was not affected by tVNS effect ($F_{(1,28)} = 1.665$, $p = 0.207$), group effect ($F_{(1,28)} = 0.466$, $p = 0.501$) or interaction effect ($F_{(1,28)} = 0.001$, $p = 1.000$).

For theta power (Figure 7), there was a significant group effect (0.25 Hz: $F_{(1,28)} = 13.046$, $p = 0.001$; 0.33 Hz: $F_{(1,28)} = 14.453$, $p = 0.001$, 0.50 Hz: $F_{(1,28)} = 11.939$, $p = 0.002$) but no tVNS effect (0.25 Hz: $F_{(1,28)} = 1.617$, $p = 0.214$; 0.33 Hz: $F_{(1,28)} = 0.144$, $p = 0.707$, 0.50 Hz: $F_{(1,28)} < 0.000$, $p = 0.984$) or interaction effect (0.25 Hz: $F_{(1,28)} = 0.225$, $p = 0.639$; 0.33 Hz: $F_{(1,28)} = 0.282$, $p = 0.600$, 0.50 Hz: $F_{(1,28)} = 0.759$, $p = 0.391$) under each speed condition.

For alpha power (Figure 8), there was also a significant group effect (0.25 Hz: $F_{(1,28)} = 14.397$, $p = 0.001$; 0.33 Hz: $F_{(1,28)} = 14.453$, $p = 0.001$, 0.50 Hz: $F_{(1,28)} = 11.958$, $p = 0.002$) but no tVNS effect (0.25 Hz: $F_{(1,28)} = 0.930$, $p = 0.343$; 0.33 Hz: $F_{(1,28)} = 0.047$, p

doi:10.6342/NTU202403646

= 0.830, 0.50 Hz: $F_{(1,28)} < 0.000$, $p = 0.984$) or interaction effect (0.25 Hz: $F_{(1,28)} = 0.252$, $p = 0.619$; 0.33 Hz: $F_{(1,28)} = 0.282$, $p = 0.600$, 0.50 Hz: $F_{(1,28)} = 0.361$, $p = 0.553$) under each speed condition.

For beta band (Figure 9), there was no significant tVNS effect (0.25 Hz: $F_{(1,28)} = 1.068$, $p = 0.301$; 0.33 Hz: $F_{(1,28)} = 4.372$, $p = 0.066$, 0.50 Hz: $F_{(1,28)} = 0.001$, $p = 0.984$), group effect (0.25 Hz: $F_{(1,28)} = 1.153$, $p = 0.292$; 0.33 Hz: $F_{(1,28)} = 0.782$, $p = 0.384$, 0.50 Hz: $F_{(1,28)} = 1.784$, $p = 0.192$) or interaction effect (0.25 Hz: $F_{(1,28)} = 0.514$, $p = 0.479$; 0.33 Hz: $F_{(1,28)} = 0.464$, $p = 0.501$, 0.50 Hz: $F_{(1,28)} = 0.759$, $p = 0.391$) under each speed condition.

For the EEG power in low gamma band (Figure 10), there was no significant tVNS effect (0.25 Hz: $F_{(1,28)} = 0.544$, $p = 0.467$; 0.33 Hz: $F_{(1,28)} = 2.125$, $p = 0.156$, 0.50 Hz: $F_{(1,28)} = 0.642$, $p = 0.430$), group effect (0.25 Hz: $F_{(1,28)} = 0.769$, $p = 0.388$; 0.33 Hz: $F_{(1,28)} = 1.301$, $p = 0.264$, 0.50 Hz: $F_{(1,28)} = 0.504$, $p = 0.483$) or interaction effect (0.25 Hz: $F_{(1,28)} = 3.291$, $p = 0.080$; 0.33 Hz: $F_{(1,28)} = 1.484$, $p = 0.233$, 0.50 Hz: $F_{(1,28)} = 0.376$, $p = 0.545$) under each speed condition. For the EEG power in high gamma band (Figure 11), there were significant tVNS effect ($F_{(1,28)} = 4.345$, $p = 0.046$), group effect ($F_{(1,28)} = 4.632$, $p = 0.04$) and interaction effect ($F_{(1,28)} = 17.087$, $p < 0.001$) under the 0.25 Hz condition. Post hoc analysis showed that non-anxiety PD group had lower power when they received active tVNS than sham tVNS ($p < 0.001$). In addition, non-anxiety PD group had higher

doi:10.6342/NTU202403646

power than anxiety PD group under sham tVNS ($p = 0.001$). Under the 0.33 Hz condition, there was an significant group effect ($F_{(1,28)} = 4.897$, $p = 0.035$) and interaction effect ($F_{(1,28)} = 5.778$, $p = 0.023$) and but no tVNS effect ($F_{(1,28)} = 2.476$, $p = 0.127$). Post hoc analysis showed that that non-anxiety PD group had lower power when they received active tVNS than sham tVNS ($p = 0.011$). In addition, non-anxiety PD group had higher power than anxiety PD group under sham tVNS ($p = 0.003$). Under the 0.50 Hz condition, there was no significant tVNS effect ($F_{(1,28)} = 2.828$, $p = 0.104$), group effect ($F_{(1,28)} = 3.672$, $p = 0.066$) or interaction effect ($F_{(1,28)} = 0.358$, $p = 0.555$).

Frontal cortex

Under the 0.25 Hz condition, delta power (Figure 12) was affected by tVNS effect ($F_{(1,28)} = 4.443$, $p = 0.044$) and group-by-tVNS interaction effect ($F_{(1,28)} = 7.966$, $p = 0.009$) but no group effect ($F_{(1,28)} = 0.118$, $p = 0.734$). Post hoc analysis showed that non-anxiety PD group had higher power when receiving active tVNS than sham tVNS ($p = 0.002$). However, there was no significant tVNS effect (0.33 Hz: $F_{(1,28)} = 0.844$, $p = 0.366$; 0.50 Hz: $F_{(1,28)} = 0.090$, $p = 0.766$), group effect (0.33 Hz: $F_{(1,28)} = 0.673$, $p = 0.419$; 0.50 Hz: $F_{(1,28)} = 0.325$, $p = 0.573$) or interaction effect (0.33 Hz: $F_{(1,28)} = 2.265$, $p = 0.143$; 0.50 Hz: $F_{(1,28)} = 0.018$, $p = 0.894$) under both 0.33 Hz and 0.50 Hz conditions.

For theta power (Figure 13), there was a significant group effect (0.25 Hz: $F_{(1,28)} = 15.303$, $p = 0.001$; 0.33 Hz: $F_{(1,28)} = 11.066$, $p = 0.002$; 0.50 Hz: $F_{(1,28)} = 15.899$, $p < 0.001$)

doi:10.6342/NTU202403646

but no tVNS effect (0.25 Hz: $F_{(1,28)} = 0.461$, $p = 0.503$; 0.33 Hz: $F_{(1,28)} = 0.713$, $p = 0.406$; 0.50 Hz: $F_{(1,28)} = 0.013$, $p = 0.909$) or interaction effect (0.25 Hz: $F_{(1,28)} = 0.001$, $p = 0.973$; 0.33 Hz: $F_{(1,28)} = 1.022$, $p = 0.321$; 0.50 Hz: $F_{(1,28)} = 1.192$, $p = 0.284$) under all conditions.

For alpha band (Figure 14), there was a significant group effect (0.25 Hz: $F_{(1,28)} = 12.765$, $p = 0.001$; 0.33 Hz: $F_{(1,28)} = 11.555$, $p = 0.002$; 0.50 Hz: $F_{(1,28)} = 16.403$, $p < 0.001$) under each speed condition, but no tVNS effect (0.25 Hz: $F_{(1,28)} = 0.459$, $p = 0.504$; 0.33 Hz: $F_{(1,28)} = 3.049$, $p = 0.092$; 0.50 Hz: $F_{(1,28)} = 3.609$, $p = 0.068$) or interaction effect (0.25 Hz: $F_{(1,28)} < 0.001$, $p = 0.990$; 0.33 Hz: $F_{(1,28)} = 0.007$, $p = 0.933$; 0.50 Hz: $F_{(1,28)} = 0.847$, $p = 0.365$) were observed.

For beta power (Figure 15), there was no significant group effect (0.25 Hz: $F_{(1,28)} = 0.001$, $p = 0.979$; 0.50 Hz: $F_{(1,28)} = 0.189$, $p = 0.667$), tVNS effect (0.25 Hz: $F_{(1,28)} = 0.863$, $p = 0.361$; 0.50 Hz: $F_{(1,28)} = 0.133$, $p = 0.718$) or interaction effect (0.25 Hz: $F_{(1,28)} = 0.005$, $p = 0.944$; 0.50 Hz: $F_{(1,28)} = 0.204$, $p = 0.655$) under both 0.25 and 0.50 conditions. Whereas there was a tVNS effect ($F_{(1,28)} = 4.825$, $p = 0.037$) and group-by-tVNS interaction effect ($F_{(1,28)} = 4.520$, $p = 0.042$), but no group effect ($F_{(1,28)} = 0.035$, $p = 0.852$) under the 0.33 Hz condition. Post hic analysis showed that non-anxiety PD group had lower power when receiving active tVNS than sham tVNS ($p = 0.006$).

For the EEG power in low gamma band (Figure 16), under the 0.25 Hz condition, there was an significant group-by-tVNS interaction effect ($F_{(1,28)} = 6.089$, $p = 0.020$) but

doi:10.6342/NTU202403646

no tVNS ($F_{(1,28)} = 3.154$, $p = 0.087$) or group effect ($F_{(1,28)} = 0.913$, $p = 0.347$). Post hoc analysis showed that anxiety PD group had lower power when receiving active tVNS than sham tVNS ($p = 0.004$). Furthermore, anxiety PD group had higher power than non-anxiety PD group under sham tVNS ($p = 0.047$). However, under both 0.33 and 0.50 Hz conditions, there was no group effect (0.33 Hz: $F_{(1,28)} = 2.436$, $p = 0.130$; 0.50 Hz: $F_{(1,28)} = 1.991$, $p = 0.169$), tVNS effect (0.33 Hz: $F_{(1,28)} = 0.101$, $p = 0.754$; 0.50 Hz: $F_{(1,28)} = 0.162$, $p = 0.690$) or interaction effect (0.33 Hz: $F_{(1,28)} = 0.014$, $p = 0.907$; 0.50 Hz: $F_{(1,28)} = 0.133$, $p = 0.718$). For the EEG power in high gamma band (Figure 17), there was no significant group effect (0.25 Hz: $F_{(1,28)} = 1.779$, $p = 0.193$; 0.33 Hz: $F_{(1,28)} = 2.940$, $p = 0.097$), tVNS effect (0.25 Hz: $F_{(1,28)} = 0.950$, $p = 0.338$; 0.33 Hz: $F_{(1,28)} = 0.803$, $p = 0.378$) and interaction effect (0.25 Hz: $F_{(1,28)} = 0.190$, $p = 0.666$; 0.33 Hz: $F_{(1,28)} = 0.356$, $p = 0.555$) under the 0.25 and 0.33 Hz conditions. In contrast, under the 0.50 Hz condition, there was a group effect ($F_{(1,28)} = 10.445$, $p = 0.003$) but no tVNS effect ($F_{(1,28)} = 0.498$, $p = 0.486$) and interaction effect ($F_{(1,28)} = 0.513$, $p = 0.480$) were observed.

Sensorimotor cortex

Delta power (Figure 18) was affected by tVNS effect ($F_{(1,28)} = 4.522$, $p = 0.042$) under 0.25 Hz, but no group effect ($F_{(1,28)} = 1.659$, $p = 0.208$) and interaction effect ($F_{(1,28)} = 1.643$, $p = 0.210$) were observed. Furthermore, there was no significant group effect (0.33 Hz: $F_{(1,28)} = 0.027$, $p = 0.870$; 0.50 Hz: $F_{(1,28)} = 0.008$, $p = 0.928$), tVNS effect (0.33

doi:10.6342/NTU202403646

Hz: $F_{(1,28)} = 0.967$, $p = 0.334$; 0.50 Hz: $F_{(1,28)} = 0.288$, $p = 0.596$) and interaction effect (0.33 Hz: $F_{(1,28)} = 1.547$, $p = 0.224$; 0.50 Hz: $F_{(1,28)} = 0.070$, $p = 0.793$) under both 0.33 and 0.50 Hz conditions.

Under three speed conditions, theta power (Figure 19) was affected by group effect (0.25Hz: $F_{(1,28)} = 17.569$, $p < 0.001$; 0.33 Hz: $F_{(1,28)} = 14.072$, $p = 0.001$; 0.50 Hz: $F_{(1,28)} = 15.799$, $p < 0.001$), but was not affected by tVNS effect (0.25Hz: $F_{(1,28)} = 0.026$, $p = 0.872$; 0.33 Hz: $F_{(1,28)} = 0.001$, $p = 0.976$; 0.50 Hz: $F_{(1,28)} < 0.001$, $p = 0.983$) and interaction effect (0.25Hz: $F_{(1,28)} = 0.087$, $p = 0.770$; 0.33 Hz: $F_{(1,28)} = 0.690$, $p = 0.413$; 0.50 Hz: $F_{(1,28)} = 0.746$, $p = 0.395$).

Similarly, under three speed conditions, alpha power (Figure 20) was affected by group effect (0.25Hz: $F_{(1,28)} = 11.848$, $p = 0.002$; 0.33 Hz: $F_{(1,28)} = 14.372$, $p = 0.001$; 0.50 Hz: $F_{(1,28)} = 17.422$, $p < 0.001$), but was not affected by tVNS effect (0.25Hz: $F_{(1,28)} < 0.001$, $p = 0.996$; 0.33 Hz: $F_{(1,28)} = 1.167$, $p = 0.289$; 0.50 Hz: $F_{(1,28)} = 0.707$, $p = 0.408$) and interaction effect (0.25Hz: $F_{(1,28)} = 2.399$, $p = 0.133$; 0.33 Hz: $F_{(1,28)} = 2.119$, $p = 0.157$; 0.50 Hz: $F_{(1,28)} = 0.194$, $p = 0.663$).

For beta power (Figure 21), there was no significant group effect (0.25Hz: $F_{(1,28)} = 0.009$, $p = 0.923$; 0.33 Hz: $F_{(1,28)} = 0.072$, $p = 0.790$; 0.50 Hz: $F_{(1,28)} = 0.301$, $p = 0.587$), tVNS effect (0.25Hz: $F_{(1,28)} = 0.315$, $p = 0.579$; 0.33 Hz: $F_{(1,28)} = 1.572$, $p = 0.220$; 0.50 Hz: $F_{(1,28)} = 0.100$, $p = 0.755$) and interaction effect (0.25 Hz: $F_{(1,28)} = 0.068$, $p = 0.796$;

doi:10.6342/NTU202403646

0.33 Hz: $F_{(1,28)}$ = 3.357, p = 0.078; 0.50 Hz: $F_{(1,28)}$ = 0.367, p = 0.550) in each speed condition.

For the EEG power in low gamma band (Figure 22), there was a significant tVNS effect ($F_{(1,28)}$ = 4.783, p = 0.037) but no group effect ($F_{(1,28)}$ = 0.203, p = 0.655) and interaction effect ($F_{(1,28)}$ = 0.055, p = 0.816) in 0.25 Hz condition. However, under both 0.33 and 0.50 Hz conditions, there was no significant group effect (0.33 Hz: $F_{(1,28)}$ = 1.922, p = 0.177; 0.50 Hz: $F_{(1,28)}$ = 1.053, p = 0.313), tVNS effect (0.33 Hz: $F_{(1,28)}$ = 0.004, p = 0.947; 0.50 Hz: $F_{(1,28)}$ = 1.909, p = 0.178) and interaction effect (0.33 Hz: $F_{(1,28)}$ = 0.005, p = 0.946; 0.50 Hz: $F_{(1,28)}$ = 0.694, p = 0.412). For the EEG power in high gamma band (Figure 23), there was a significant group effect ($F_{(1,28)}$ = 13.424, p = 0.001) and marginally significant interaction effect ($F_{(1,28)}$ = 4.151, p = 0.051) but no tVNS effect ($F_{(1,28)}$ = 1.048, p = 0.315) under 0.25 Hz condition. The EEG power in high gamma band was larger in non-anxiety group than anxiety group. Under both 0.33 and 0.50 Hz conditions, there was a significant group effect (0.33 Hz: $F_{(1,28)}$ = 8.900, p = 0.006; 0.50 Hz: $F_{(1,28)}$ = 10.285, p = 0.003) but no tVNS effect (0.33 Hz: $F_{(1,28)}$ = 0.189, p = 0.667; 0.50 Hz: $F_{(1,28)}$ = 0.164, p = 0.688) and interaction effect (0.33 Hz: $F_{(1,28)}$ = 3.141, p = 0.087; 0.50 Hz: $F_{(1,28)}$ = 1.058, p = 0.312).

Parietal-occipital cortex

doi:10.6342/NTU202403646

For delta band (Figure 24), there was no significant group effect (0.25 Hz: $F_{(1,28)}$ = 0.016, p = 0.900; 0.33 Hz: $F_{(1,28)}$ = 0.211, p = 0.650; Hz: $F_{(1,28)}$ = 0.786, p = 0.383), tVNS effect (0.25 Hz: $F_{(1,28)}$ = 2.328, p = 0.138; 0.33 Hz: $F_{(1,28)}$ = 2.429, p = 0.130; Hz: $F_{(1,28)}$ = 0.037, p = 0.849) and group-by-tVNS interaction effect (0.25 Hz: $F_{(1,28)}$ = 3.053, p = 0.092; 0.33 Hz: $F_{(1,28)}$ = 3.162, p = 0.086; Hz: $F_{(1,28)}$ = 0.084, p = 0.774) under the three speed conditions.

For theta power under three speed conditions (Figure 25), there was a significant group effect (0.25 Hz: $F_{(1,28)}$ = 6.818, p = 0.014; 0.33 Hz: $F_{(1,28)}$ = 6.519, p = 0.016; 0.50 Hz: $F_{(1,28)}$ = 10.133, p = 0.004), but no tVNS effect (0.25 Hz: $F_{(1,28)}$ = 2.324, p = 0.139; 0.33 Hz: $F_{(1,28)}$ = 1.025, p = 0.320; 0.50 Hz: $F_{(1,28)}$ = 0.144, p = 0.707) and group-by-tVNS interaction effect (0.25 Hz: $F_{(1,28)}$ = 0.102, p = 0.752; 0.33 Hz: $F_{(1,28)}$ = 0.497, p = 0.487; 0.50 Hz: $F_{(1,28)}$ = 0.282, p = 0.600).

For alpha power (Figure 26), there was a significant group effect (0.25 Hz: $F_{(1,28)}$ = 12.031, p = 0.002; 0.50 Hz: $F_{(1,28)}$ = 11.958, p = 0.002) under the 0.25 and 0.50 Hz conditions, but no tVNS main effect (0.25 Hz: $F_{(1,28)}$ = 0.024, p = 0.878; 0.50 Hz: $F_{(1,28)}$ = 0.047, p = 0.830) and interaction effect (0.25 Hz: $F_{(1,28)}$ = 0.010, p = 0.921; 0.50 Hz: $F_{(1,28)}$ = 0.361, p = 0.553) were observed. However, under the 0.33 Hz condition, there was a significant group effect ($F_{(1,28)}$ = 14.889, p = 0.001) and tVNS effect (0.33 Hz: $F_{(1,28)}$ = 4.731, p = 0.038), but no significant interaction effect ($F_{(1,28)}$ = 0.107, p = 0.746).

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Greater alpha power was observed in the anxiety group. In addition, sham tVNS session had greater alpha power than active tVNS session regardless of the participants have anxiety or not.

For beta power (Figure 27), there was no significant group effect (0.25 Hz: $F_{(1,28)}$ = 0.098, p = 0.757; 0.50 Hz: $F_{(1,28)}$ = 0.031, p = 0.862), tVNS effect (0.25 Hz: $F_{(1,28)}$ = 0.392, p = 0.536; 0.50 Hz: $F_{(1,28)}$ = 0.059, p = 0.810) and interaction effect (0.25 Hz: $F_{(1,28)}$ = 1.707, p = 0.202; 0.50 Hz: $F_{(1,28)}$ = 0.230, p = 0.635) under both 0.25 and 0.50 Hz conditions. In contrast, there was a significant group-by-tVNS interaction effect ($F_{(1,28)}$ = 4.237, p = 0.049) under 0.33 Hz condition, but no group effect ($F_{(1,28)}$ = 0.035, p = 0.853) and tVNS effect ($F_{(1,28)}$ = 1.627, p = 0.213) was observed. Post hoc analysis showed that non-anxiety PD group had lower power when receiving active tVNS than sham tVNS (p = 0.030).

For EEG activity in low gamma band (Figure 28) in each condition, there was no significant group effect (0.25 Hz: $F_{(1,28)}$ = 0.573, p = 0.455; 0.33 Hz: $F_{(1,28)}$ = 1.041, p = 0.316; 0.50 Hz: $F_{(1,28)}$ = 0.332, p = 0.569), tVNS effect (0.25 Hz: $F_{(1,28)}$ = 0.325, p = 0.573; 0.33 Hz: $F_{(1,28)}$ = 0.554, p = 0.463; 0.50 Hz: $F_{(1,28)}$ = 0.206, p = 0.653) and group-by-tVNS interaction effect (0.25 Hz: $F_{(1,28)}$ = 0.601, p = 0.445; 0.33 Hz: $F_{(1,28)}$ = 0.482, p = 0.493; 0.50 Hz: $F_{(1,28)}$ = 0.007, p = 0.935). Similarly, for EEG power in high gamma band (Figure 29) there was no significant group effect (0.25 Hz: $F_{(1,28)}$ = 1.924, p = 0.176; 0.33 Hz:

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$F_{(1,28)} = 2.636$, $p = 0.116$; 0.50 Hz: $F_{(1,28)} = 2.248$, $p = 0.145$), tVNS effect (0.25 Hz: $F_{(1,28)} = 2.066$, $p = 0.162$; 0.33 Hz: $F_{(1,28)} = 0.058$, $p = 0.811$; 0.50 Hz: $F_{(1,28)} = 0.202$, $p = 0.656$) and interaction effect (0.25 Hz: $F_{(1,28)} = 3.881$, $p = 0.059$; 0.33 Hz: $F_{(1,28)} = 1.934$, $p = 0.175$; 0.50 Hz: $F_{(1,28)} = 0.388$, $p = 0.539$) in each speed condition.

doi:10.6342/NTU202403646

Chapter 4

DISCUSSION

Based on the results of behavioral performance, anxiety level, and cortical activity in the present study, our main findings were as follows: 1) Only the anxiety group benefited from tVNS, showing smaller tracking error in active tVNS session with larger JSM. In addition, with faster speed of weight-shifting movement (0.33 Hz and 0.50 Hz), the anxiety group showed a larger weight-shifting amplitude than the non-anxiety group in active tVNS session. 2) Based on correlation findings, PD patients with higher PAS score could benefit more from tVNS. 3) Regardless the speed of weight-shifting movement, anxiety group had greater theta power and alpha power across prefrontal, frontal and sensorimotor cortices. In contrast, the EEG power in high gamma band was greater in the non-anxiety group than the anxiety group. 4) EEG modulation due to tVNS was observed particularly under lower speed conditions (0.25 Hz only or 0.25 Hz and 0.33 Hz) in delta and gamma band.

4.1. tVNS effect on behavior

Based on our behavioral findings, only the anxiety group benefited from tVNS, exhibiting smaller tracking errors and larger JSM (more correction for weight-shifting trajectory) during the active tVNS sessions regardless of the speed of weight-shifting

doi:10.6342/NTU202403646

speed.

In studies by Keute et al. (2020) and Chen et al. (2023), young healthy participants performed a go–no-go-change-task or a cue-target pattern task when they received active tVNS or sham (control) tVNS. The results of this study found the participants had lower proportion of erroneous and missed responses and shorter reaction in active tVNS session, compared with in the control session.[131,132] Keute et al.'s study also found enhanced frontal midline theta activities in go/stop conflicts trials when participants received active tVNS. Because theta activities over frontocentral electrodes is proposed as a marker for control and adaptation processes, the behavior and EEG findings suggested that tVNS could immediately enhance executive control of action. Previous studies proposed that tVNS modulates cognitive control through the activation of the LC-NE system,[134] which enhances attention, response to stress, regulate baseline arousal and to facilitate a variety of sensory-motor and behavioral functions.[135,136,137] During the rhythmic weight-shifting task, participants had to track the target signal by integrating visual information with their movements to achieve good performance.[138,139] Therefore, the reduced tracking error in anxiety PD group might also because of improved sensory processing and attention control. In addition, a previous study reported brief tVNS could increase sensory gating, improving the ability to filter out redundant information.[140] Sensory gating is usually reduced in people with anxiety.[141] When performing the weight-shifting movement, the

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participants had to track the target, and corrected their trajectory constantly. The amount of sensory (visual) input and processing was a lot for people with PD, particularly in the fast-speed condition (0.5 Hz condition). The increased JSM value of weight-shifting trajectory when anxious PD received active tVNS may because they had better cognitive flexibility and sensory gating ability, leading to smaller tracking error in active tVNS session.

Furthermore, it has been reported that tVNS could activate the pedunculopontine nucleus (PPN) in the brainstem.[141] Gait abnormalities in PD are closely linked to alterations in cholinergic neurotransmission, particularly involving the PPN in the brainstem.[142,143] Therefore, some studies supported that tVNS might lead to gait improvement in people with PD.[144,145] For example, Mondal et al.'s study (2019) reported that people with PD, especially in those experiencing FOG, longer step length, faster velocity, reduced step count measured by the GAIRite and decreased stride velocity variability were observed after receiving tVNS for 120 seconds.[146] Another randomized sham-controlled trial conducted by Morris et al. in 2019 demonstrated that active tVNS for 120 seconds could reduce step time variability and step length variability compared to the sham treatment.[147] These benefits are believed to be mediated by cholinergic pathways, potentially involving the nucleus basalis of Meynert and the PPN.

Contrast to our hypothesis, the anxiety group had smaller tracking error and large

doi:10.6342/NTU202403646

weight-shifting amplitude than the non-anxiety group, particularly in active tVNS session. The majority findings of weight-shifting behavior in sham tVNS were similar between anxiety and non-anxiety groups. The difference in weight-shifting behavior between the two groups was pronounced in the fast-speed condition (0.5 Hz condition), implied the tVNS effect might be more dominant under a speed-challenging condition. A previous study proposed that the neurostimulation can rectify abnormal brain network topologies towards a healthier regime, which is particularly effective in individuals with severe baseline abnormalities.[148] This argument may also support that the benefits from neurostimulation would be greater in people with severer disability condition.

4.2. Anxiety level and tVNS benefits

In contrast to our hypothesis, neither the subjective anxiety level nor physiological anxiety level was affected by tVNS in the anxiety group and non-anxiety group (Figure 5). However, we found the anxiety group had higher anxiety subjective anxiety level than the non-anxiety group in the 0.25 Hz and 0.33 Hz condition, particularly in the sham tVNS session, but the phenomenon was not observed in the 0.50 Hz condition. Although most studies proposed faster moving speed is more challenging than slower moving speed, some studies argued that tasks performed at slower speeds are more challenging than faster speeds due to increased cognitive load and the higher cost of time.[149,150,151] For

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example, Krampe et al. (2010) found that older adults showed higher dual-task costs in task time and increased variability when they performed repetitive task with slow speed than with fast speed, highlighting the greater cognitive demands and reduced precision at slower speeds.[150] Similarly, the study by Fujiyama et al. (2013) reported that more cognitive resources was required when older adults performed slow interlimb coordination task than performed fast interlimb coordination task, resulting from the findings of higher attentional load and increased variability of movement frequency of the slow movement condition.[151] Moreover, Berret et al. (2016) demonstrated that participants consumed a higher metabolic and attentional cost when performing slow movements, making them less efficient and more demanding to execute.[149] This increased cost is due to the extended duration of neural processing and sensorimotor control required to maintain and execute slower actions efficiently.[149] Our result of weight-shifting amplitude seemed to be in agree with the concept of more challenging in slower speed condition with (Figure 4). We further examined the speed effect on the weight-shifting amplitude by repeated two-way ANOVA (main effects: speed, tVNS). The results showed that amplitude was indeed smaller in the 0.25 Hz condition than 0.33 Hz and 0.50 Hz condition in both anxiety group (speed effect: $F_{(1,28)} = 41.530$, $p < 0.001$; 0.25 Hz < 0.33 Hz & 0.50 Hz, $p < 0.001$) and non-anxiety group (speed effect: $F_{(1,28)} = 27.337$, $p < 0.001$; 0.25 Hz < 0.33 Hz & 0.50 Hz, $p = 0.001$). The findings may also imply that tracking

doi:10.6342/NTU202403646

accuracy is more challenging of fast rhythmic movements, but the peak amplitude is more challenging of slow rhythmic movements.

In terms of physiological anxiety level, SCL was not affected by the effects of tVNS and group. Some previous studies also found the values of SCL were not varied by tVNS. For example, De Smet et al. (2023) investigated the effects of non-invasive VNS on cognitive function in patients with post-traumatic stress disorder (PTSD).[154] They found that tVNS significantly reduced cognitive rigidity, as reflected by reduced subjective perseverative thinking after psychosocial stress when they receiving active tVNS. Also, tVNS reduced heart rate and blood pressure but did not change the value of SCL. Similarly, Gurel et al. (2020) conducted a study about the tVNS effects on PTSD patients' responses to acute stress.[155] They found that tVNS significantly reduced heart rate but did not affect the value of SCL. These findings implied that SCL might be less sensitive than heart rate and blood pressure for responding a brief tVNS intervention because a review article had reported electrodermal responses are relatively slow in comparison to heart rate responses.[158] The other reason that unchanged SCL in our studies may because that the required speed for weigh-shifting movement was not fast enough. Even in the fasted condition, the weight-shifting speed of 0.5 Hz is like slow walking speed in real-life situations,[2] which may not evoke anxiety.

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4.3. EEG modulation between the anxiety and non-anxiety groups

In our study, we found that both the theta and alpha power were greater in the anxiety group than non-anxiety group across all cortical areas. Theta activity in the frontal region reflects the increased cognitive control demands in stimulus-response conflict and error awareness.[159,160,161] The argument could be partly supported by the JSM of weight-shifting trajectory (Figure 3). Although the values of JSM were not significantly different between anxiety and non-anxiety groups, it seems JSM values were approximately larger in the anxiety group, implying the anxiety devote more attentional control for error correction. Elevated theta power indicates individuals need to enhance cognitive control to adapt to new challenges or correct behavior.[159] Furthermore, elevated theta power in anxious individuals may indicate that their brains are working harder to regulate emotional responses and maintain cognitive control.[160] Therefore, this heightened theta activity likely reflects the additional cognitive resources required to manage anxiety and maintain performance on tasks. In terms of alpha activity, previous studies showed that people with more anxiety had greater alpha power than people with less anxiety.[162,163,164,165] For example, in Knyazev et al. reported resting alpha power positively correlated with anxiety trait score in non-psychology male subjects. Furthermore, the alpha power becoming higher under a threated condition (unexpected loud sound).[164] On the other hand, enhanced alpha band could also reflect an increased devotion to selective

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attention and suppression of sensory information which is irrelevant to the current task.[166] It has been reported that the anxious individuals tend to focus on threat-related information and are easily distracted from current task.[167,168] In the present study, the increased alpha power in the anxiety group might because the threat-related information (i.e., the target speed) was inherent in the rhythmic weight-shifting movement.

In contrast to the findings of larger theta and alpha powers in the anxiety group, high gamma power (50-80 Hz) at sensorimotor cortex was larger in the non-anxiety group (Figure 23). Gamma oscillations sensorimotor cortex was recognized for their role of motor preparation, execution, and sensorimotor integration.[169,170,171,172,173] In Aoki et al.'s study (1999), enhanced high gamma activity was observed when the people with intractable epilepsy performed a target tracking task or threaded a string through tubes compared to the conditions that participants were in rest or just performed wrist extension movement.[169] This suggests that changes in high gamma activity reflect the need for sensorimotor integration and attentional modulation required for the current task. In addition, increased high gamma power reflects the brain's ability to integrate sensory inputs and coordinate motor actions efficiently.[171,173] Although the non-anxiety did not show better weight-shifting performance than the anxiety group in our study, the greater high gamma power may indicate they had better brain ability to integrate sensory information and motor output. The cognitive load of weight-shifting task might lower for

doi:10.6342/NTU202403646

the non-anxiety PD relative to the anxiety PD.

4.4. EEG modulation between active tVNS and sham tVNS sessions

In the present study, the main findings of EEG modulation between active tVNS and sham tVNS sessions were observed in the non-anxiety group. The non-anxiety PD showed larger delta power in active tVNS session and smaller high gamma power at prefrontal area, particularly in the 0.25 Hz and 0.33 Hz condition (Figure 6 and Figure 11). In addition, the anxiety group had smaller frontal activities of low gamma band in active tVNS session in the 0.25 Hz condition (Figure 22).

The mechanism of tVNS involves several brain regions and neurotransmitters.[112,174,175] The primary brain regions affected by tVNS include the nucleus of the solitary tract (NTS) in the medulla, the spinal trigeminal nucleus, the hypoglossal nucleus, the principal sensory trigeminal nucleus, the locus coeruleus, pedunculopontine nucleus, the parabrachial area, the dorsal raphe nuclei, the periaqueductal gray, the red nuclei, and the substantia nigra.[112,174] These areas are associated with afferent vagal inputs and project widely to forebrain regions. In terms of neurotransmitters, tVNS significantly affects the systems of norepinephrine, γ-aminobutyric acid (GABA), and acetylcholine.[175] Studies have shown that tVNS can increase the levels of free GABA in cerebrospinal fluid and enhance the density of GABA

doi:10.6342/NTU202403646

receptors in the epilepsy patients receiving VNS treatment.[176,177] Furthermore, tVNS also leads to an increase in delta band activity.[178] This increase is thought to be related to the activation of subcortical brain structures linked to the vagus nerve, particularly the NTS and other brainstem regions. The activation of these brainstem structures likely enhances delta band activity through GABAergic mechanisms.[179] Delta waves play a crucial role in cognitive processes, particularly in maintaining focus and inhibiting interference.[180] The increased delta activity reflects the inhibitory role of GABA in regulating cortical network activity, aiding in concentration, and reducing external distractions. As we have mentioned before, the slow-speed condition might have high cognitive load for the task. Although tVNS did not change the weight-shifting performance (or led a little damage in amplitude control) in the non-anxiety group, tVNS could improve their attention concentration at cortical level.

In terms of gamma modulation, high gamma power in the prefrontal cortex is integral to various cognitive and emotional processes, particularly visual working memory and emotion recognition.[181,182,183,184] Studies have shown that high gamma activity is closely linked to the retention and manipulation of visual information, where increased high gamma power facilitates the synchronization of neural activity necessary for maintaining visual working memory.[181,182] This synchronization enhances the brain's ability to store and process visual information efficiently, thus supporting tasks that

doi:10.6342/NTU202403646

demand high cognitive load and attention. A decrease in high gamma power in the prefrontal cortex might indicate a reduced demand for visual working memory under active tVNS. This suggests that the brain is allocating its resources more efficiently, focusing less on maintaining high-intensity cognitive functions. In the domain of emotional processing, high gamma in prefrontal cortex is sensitive indicators of emotional states. In addition, increased high gamma activity is often associated with heightened emotion.[183,184] Healthy individuals typically exhibit higher high gamma in response to negative emotions compared to positive ones, reflecting the brain's intensive processing of emotionally charged information.[183] Therefore, a reduction in high gamma activity in the prefrontal cortex can signify a state of emotional relaxation or reduced emotional distress.

Contrary to previous study that the effect of tVNS increase in low gamma power,[185] our result showed the active tVNS decreased low gamma activities at fontal cortex for the anxiety group and at sensorimotor cortex for both groups. Low gamma power is critical for motor functions.[186,187] In the aspect of motor control, low gamma band serve to facilitate kinesthetic afferences from the muscles and joints involved in the movement to the primary sensorimotor cortex, which would be necessary for controlling the ongoing movement.[186] Furthermore, low gamma is typically associated with stable and sustained movements, making them crucial for actions requiring continuous and steady force

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output.[187] Although there is no behavioral change under active tVNS in non-anxiety group. Decreased low gamma activity in motor regions might reflected the decreased task loading of brain resource in voluntary movement execution under active tVNS compared to sham tVNS in non-anxiety group.

4.5. Methodology concerns and study limitations

First, tVNS did not change the anxiety levels significantly neither in anxiety group nor non-anxiety group. This might be due to the relatively short duration of the stimulation in our study, suggesting that longer stimulation periods may be necessary to induce more brain activation and observe significant effects. Additionally, the task speeds we used might not have been challenging enough, as they were relatively slow. Dijkstra's study reported that PD patients with FOG showed a significant decrease in weight-shifting amplitude at the shifting speed above 0.72 Hz.[8] Second, the changes in EEG relative power caused by tVNS were more significant in the non-anxiety group. The changes in brain activity in the anxiety group might involve connectivity between brain regions, which could not be observed in our experiment. More complex EEG analyses are required for exploring these connectivity changes. Lastly, our study only examined the brief therapeutic effects of tVNS. Future research should combine tVNS with posture control training to investigate the long-term intervention effects.

doi:10.6342/NTU202403646

Chapter 5

CONCLUION

The present study demonstrated brief tVNS could improve weight-shifting control in people with PD who had anxiety symptom, although the anxiety level did not reduce with tVNS intervention. In addition, unlike previous studies, we found that weight-shifting control under slow speed seems to increase challenging for people with PD, leading to smaller weight-shifting amplitude. Therefore, it is recommended that postural control training with slow speed also has to be emphasized in clinical practice for people with PD.

doi:10.6342/NTU202403646

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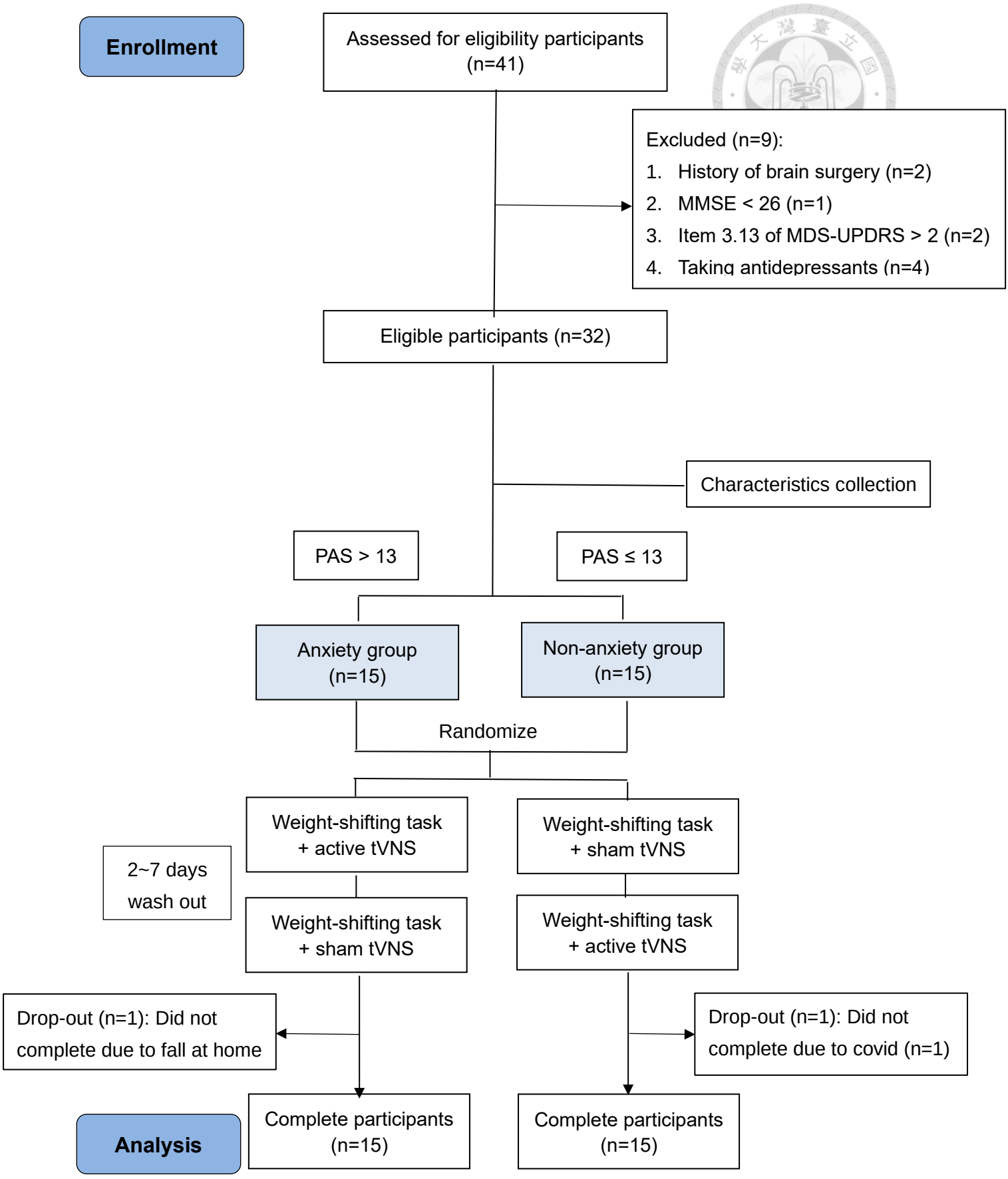

Figure 1. Study procedure of the experiment.

doi:10.6342/NTU202403646

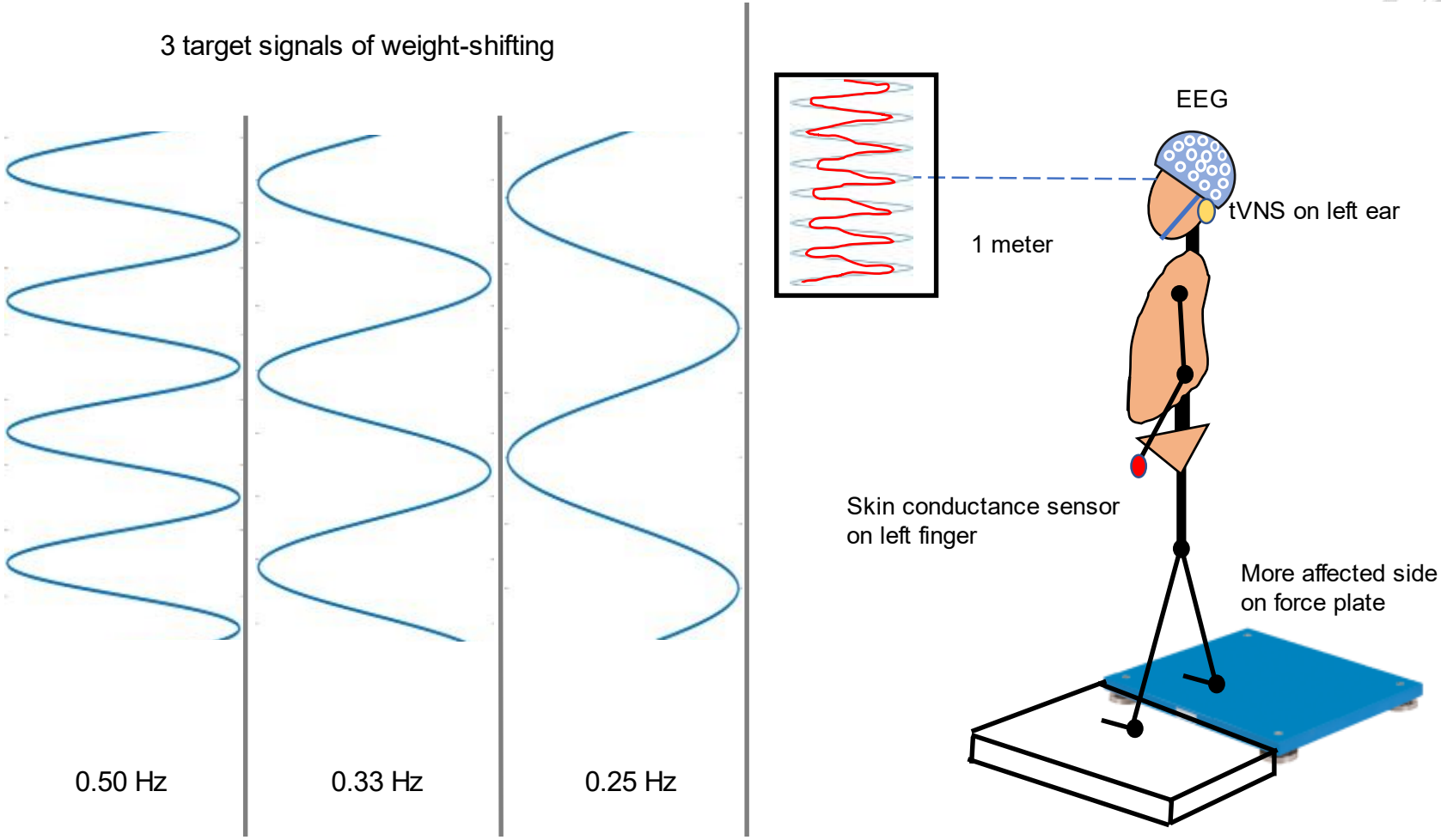

Figure 2. Schematic representation of the experimental setup.

doi:10.6342/NTU202403646

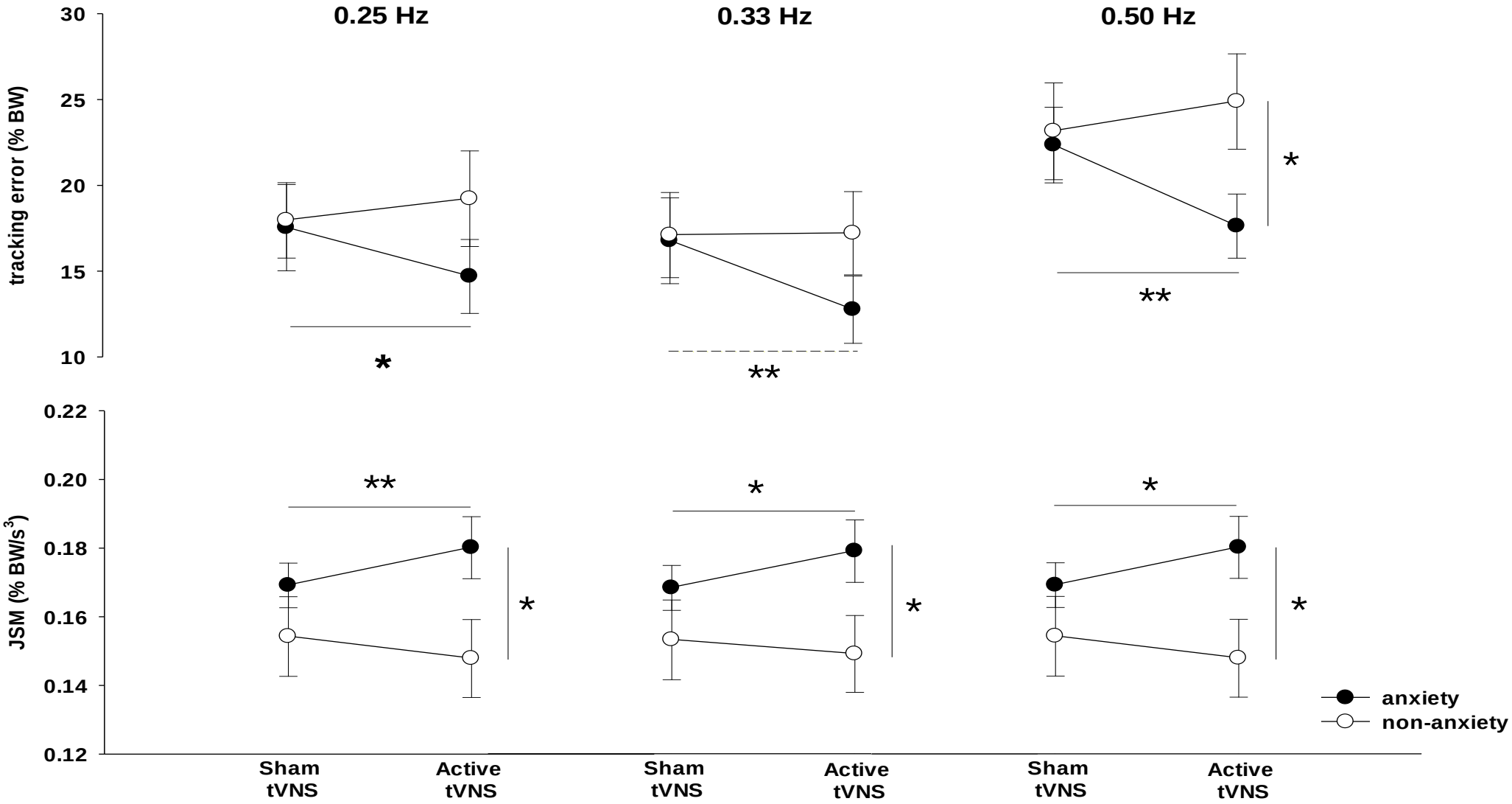

Figure 3. Error and JSM of weight-shifting trajectory.

doi:10.6342/NTU202403646

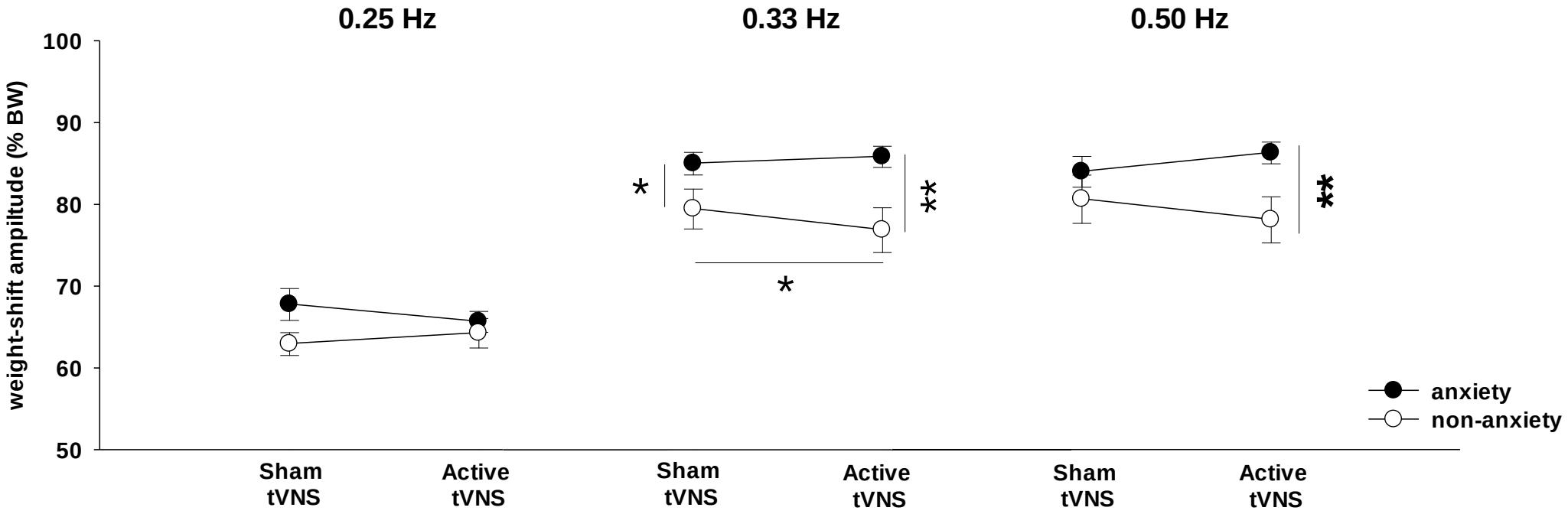

Figure 4. Amplitude of weight-shifting movement.

doi:10.6342/NTU202403646

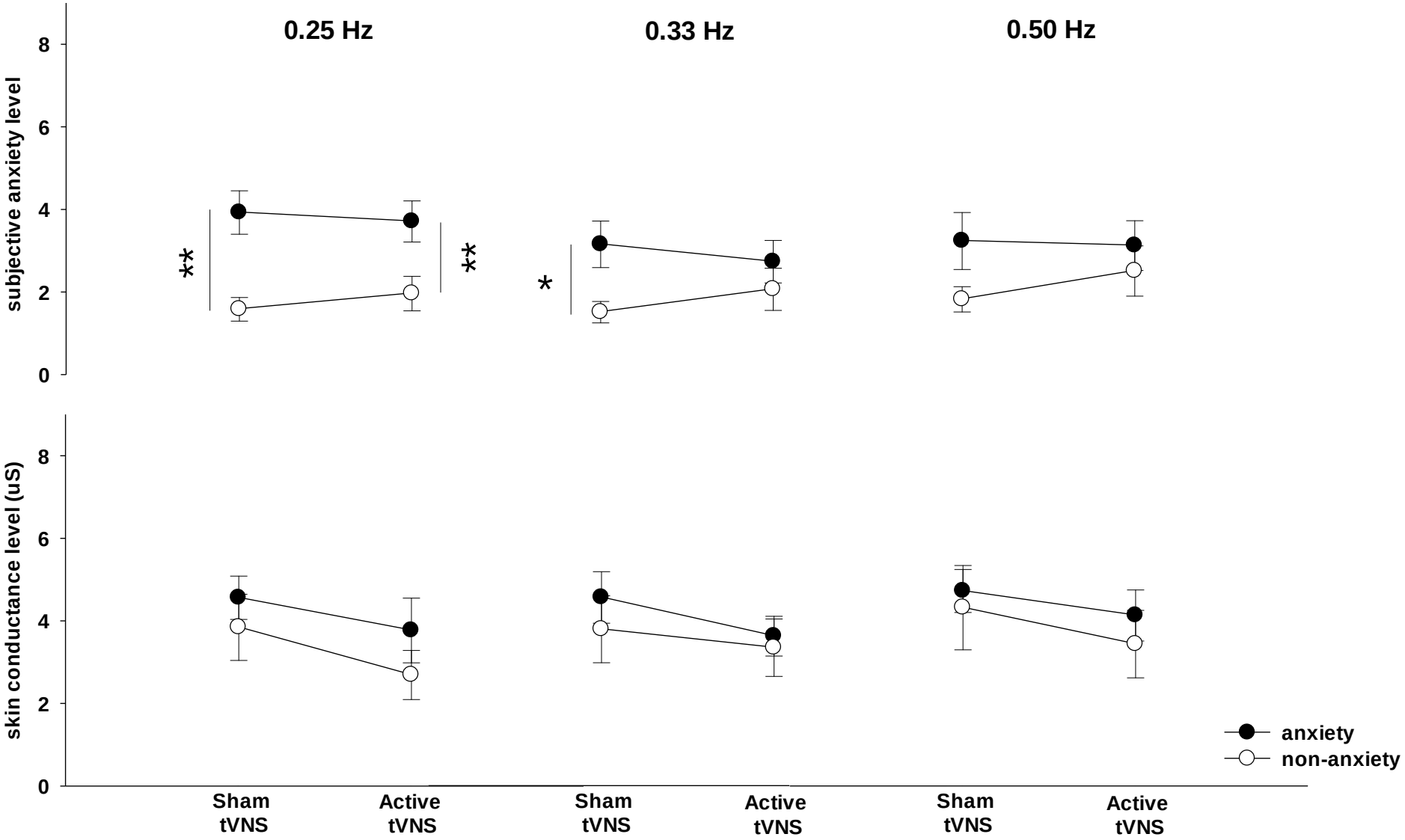

Figure 5. Subjective anxiety level and skin conductance level

doi:10.6342/NTU202403646

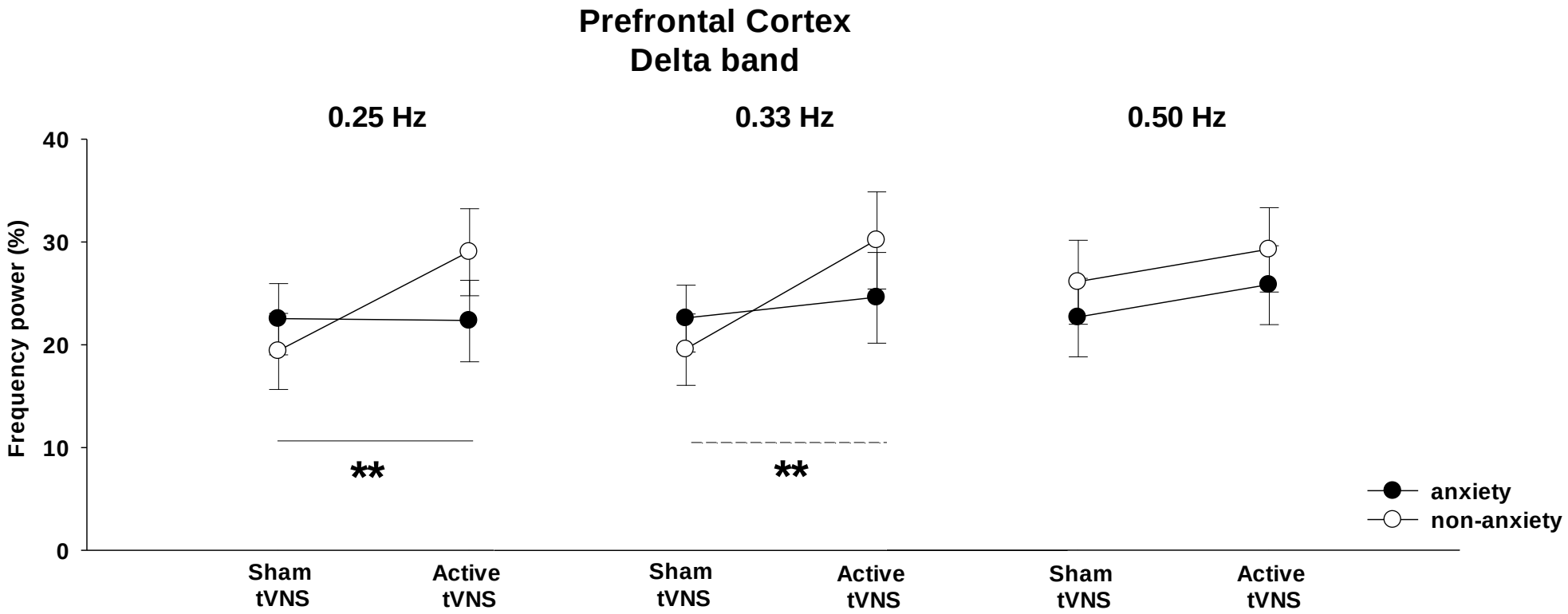

Figure 6. Relative EEG power in delta band at prefrontal cortex.

doi:10.6342/NTU202403646

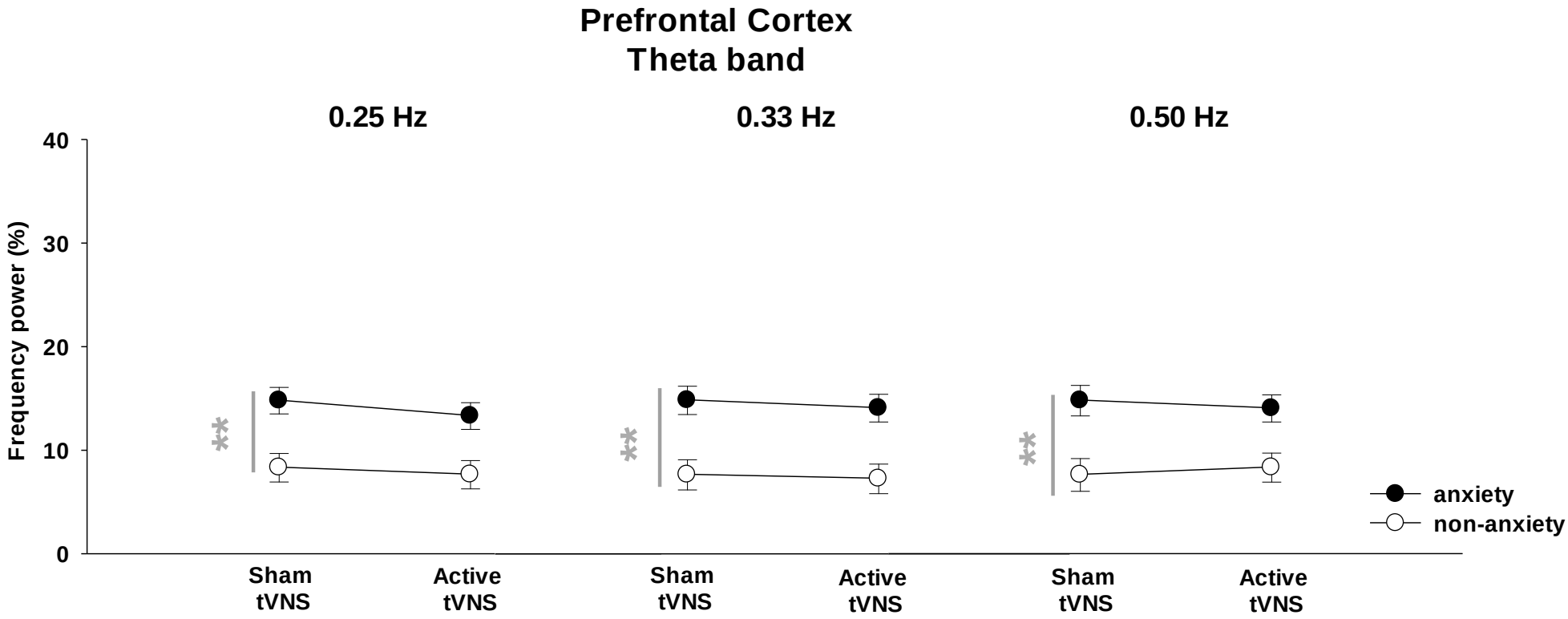

Figure 7. Relative EEG power in theta band at prefrontal cortex.

doi:10.6342/NTU202403646

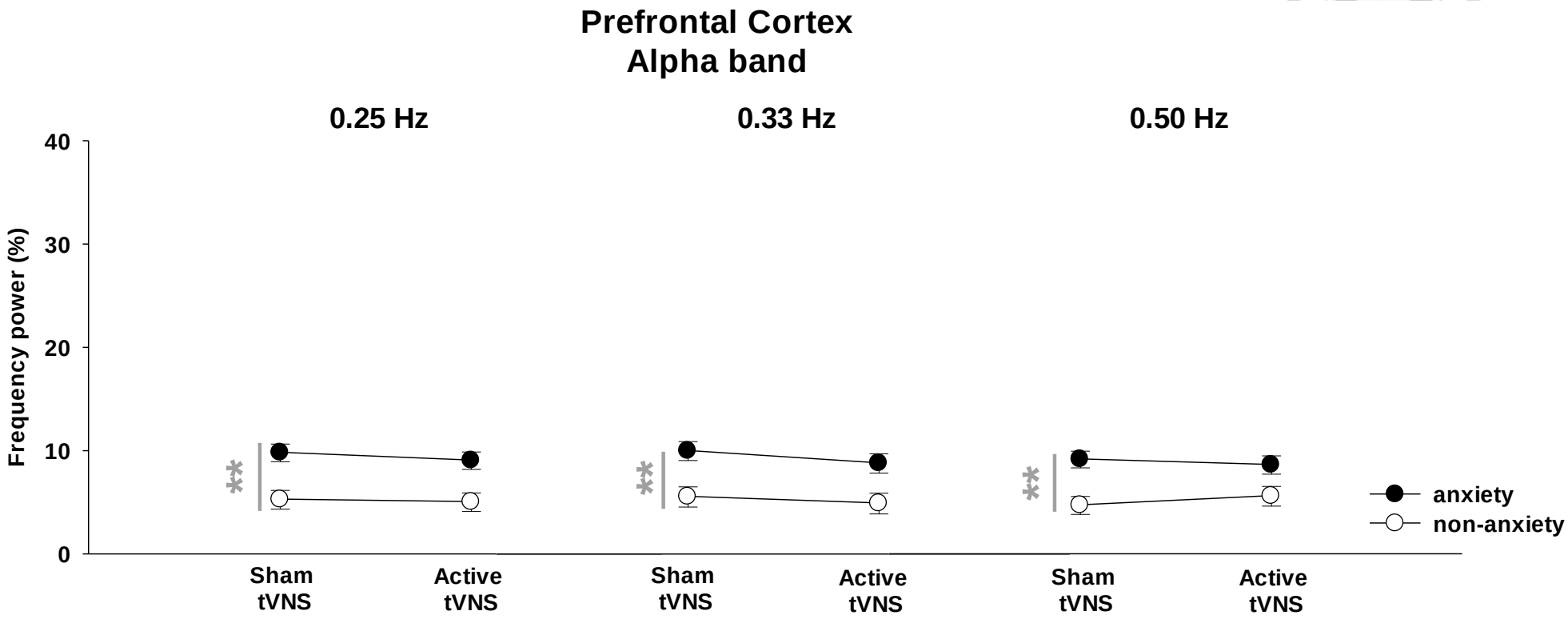

Figure 8. Relative EEG power in alpha band at prefrontal cortex.

doi:10.6342/NTU202403646

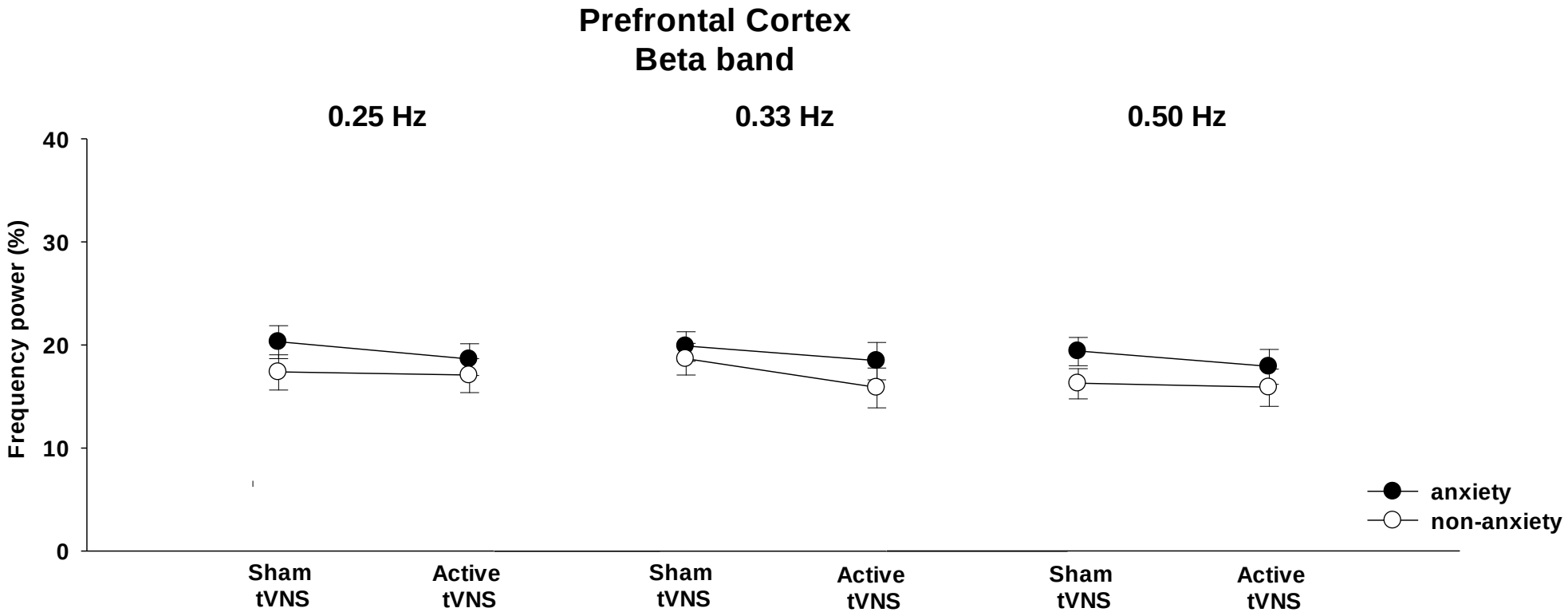

Figure 9. Relative EEG power in beta band at prefrontal cortex.

doi:10.6342/NTU202403646

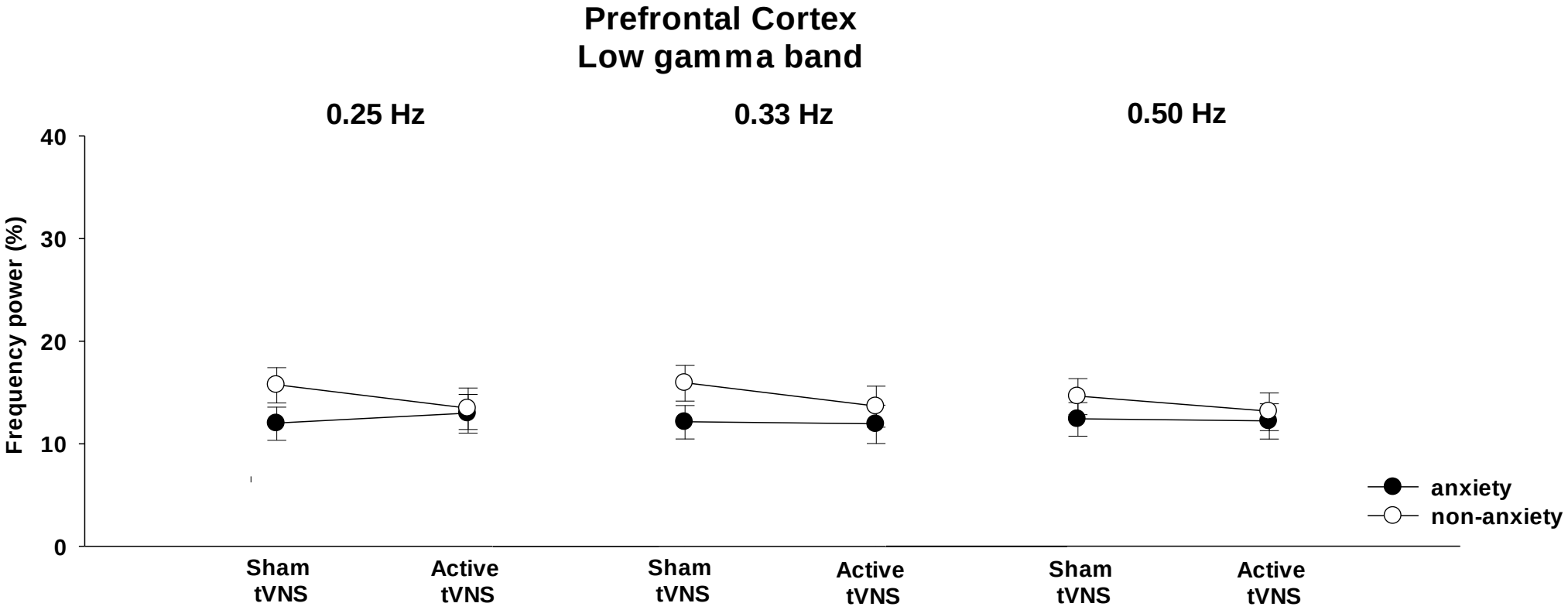

Figure 10. Relative EEG power in low gamma band at prefrontal cortex.

doi:10.6342/NTU202403646

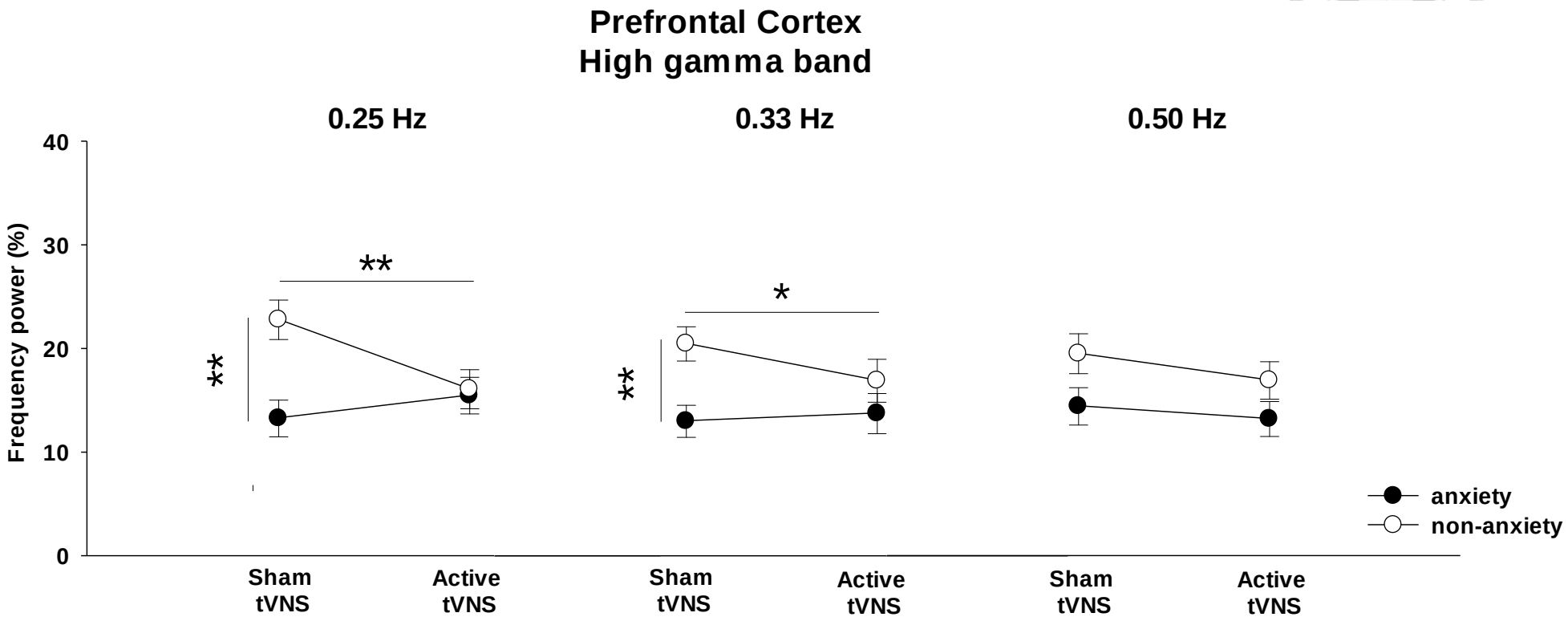

Figure 11. Relative EEG power in high gamma band at prefrontal cortex.

doi:10.6342/NTU202403646

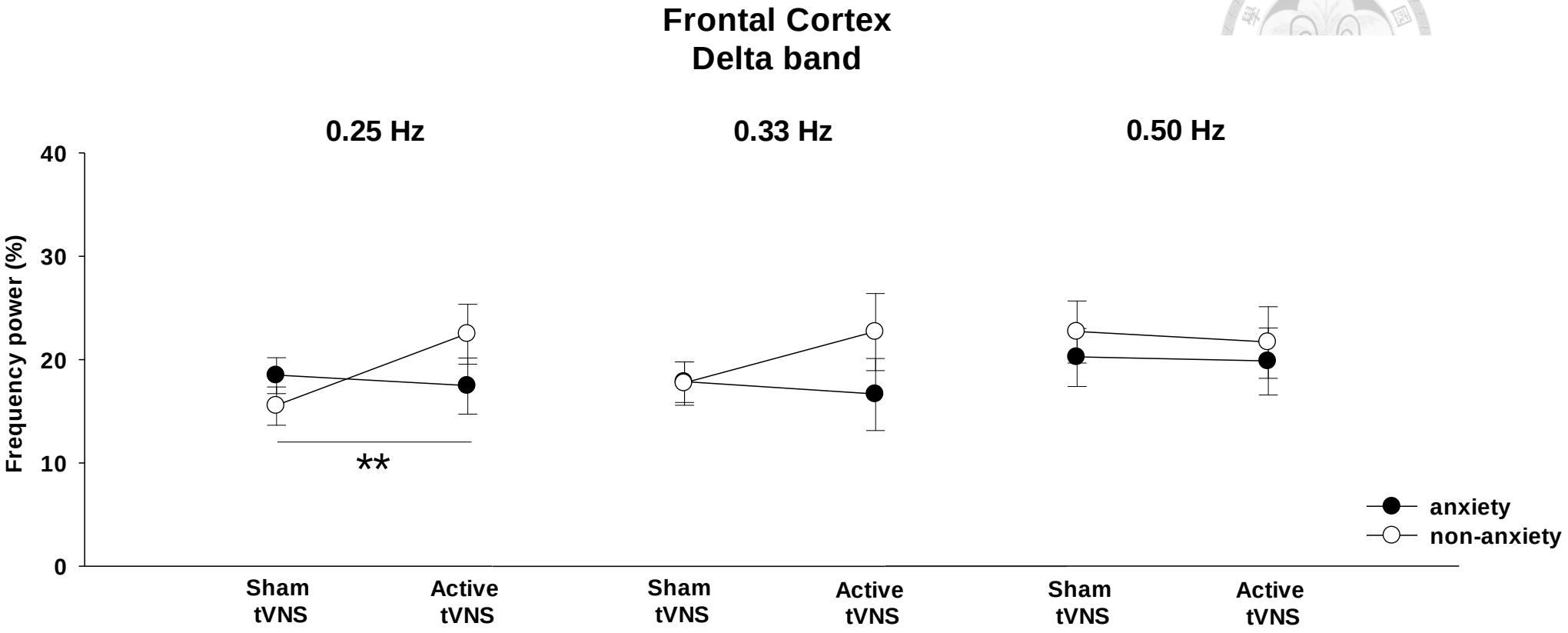

Figure 12. Relative EEG power in delta band at frontal cortex.

doi:10.6342/NTU202403646

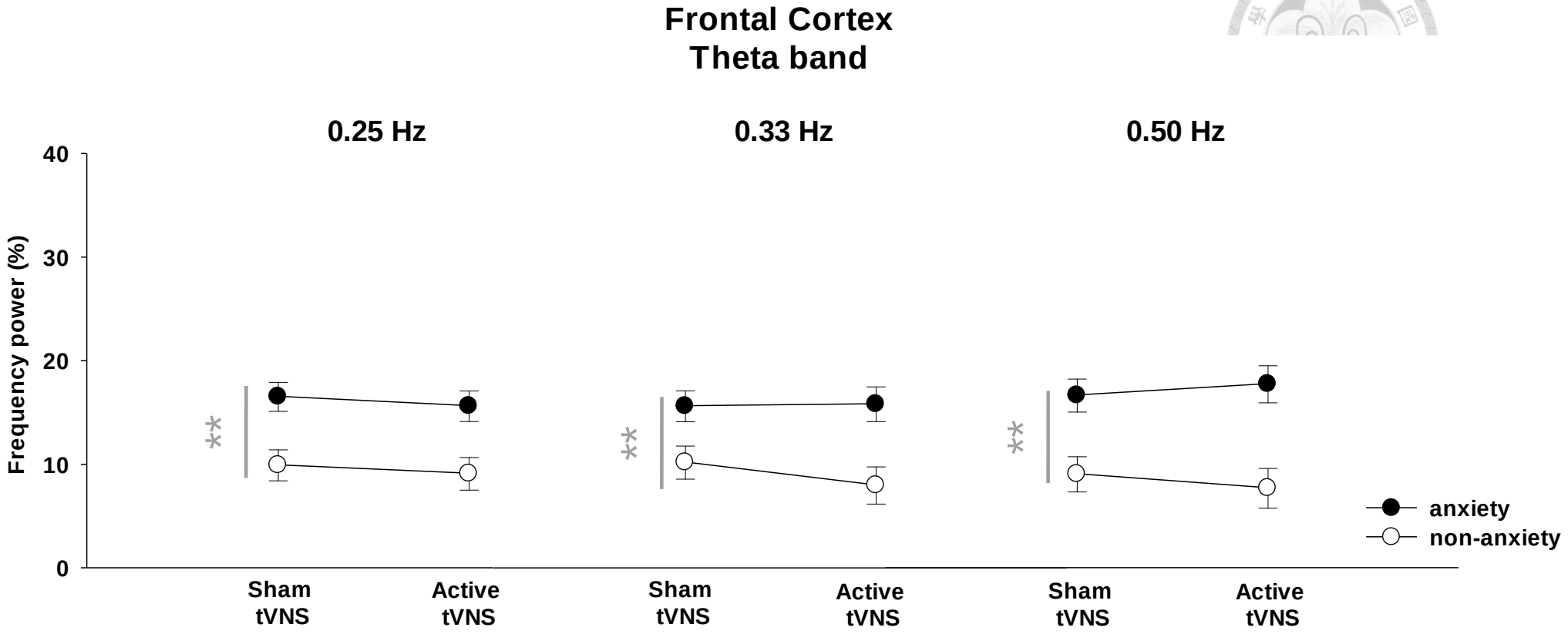

Figure 13. Relative EEG power in theta band at frontal cortex.

doi:10.6342/NTU202403646

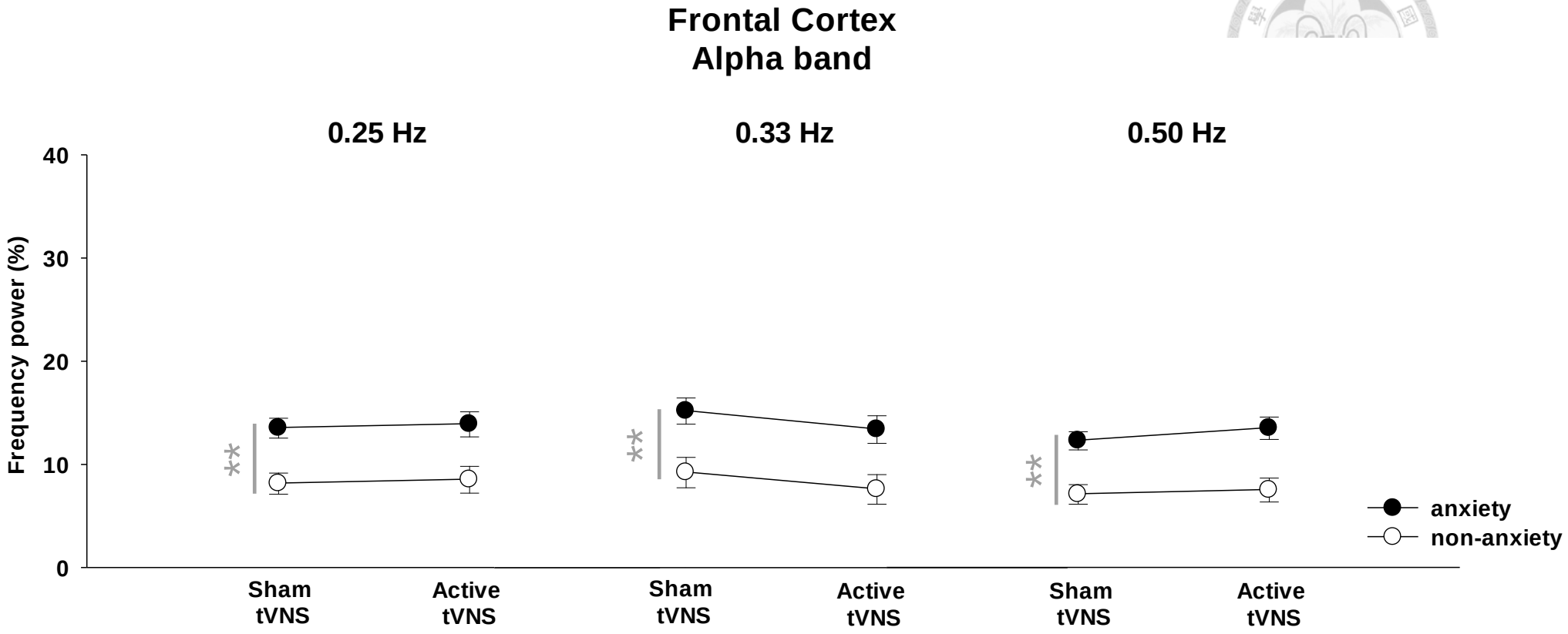

Figure 14. Relative EEG power in alpha band at frontal cortex.

doi:10.6342/NTU202403646

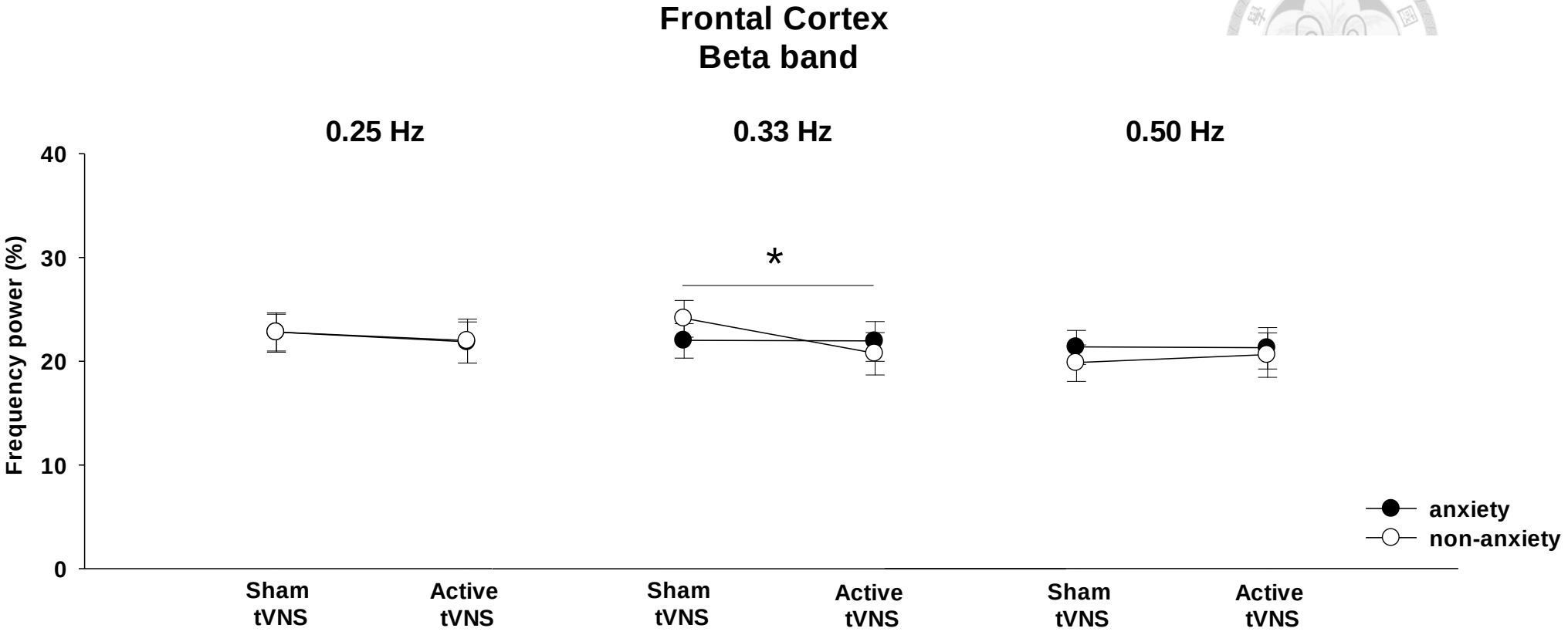

Figure 15. Relative EEG power in beta band at frontal cortex.

doi:10.6342/NTU202403646

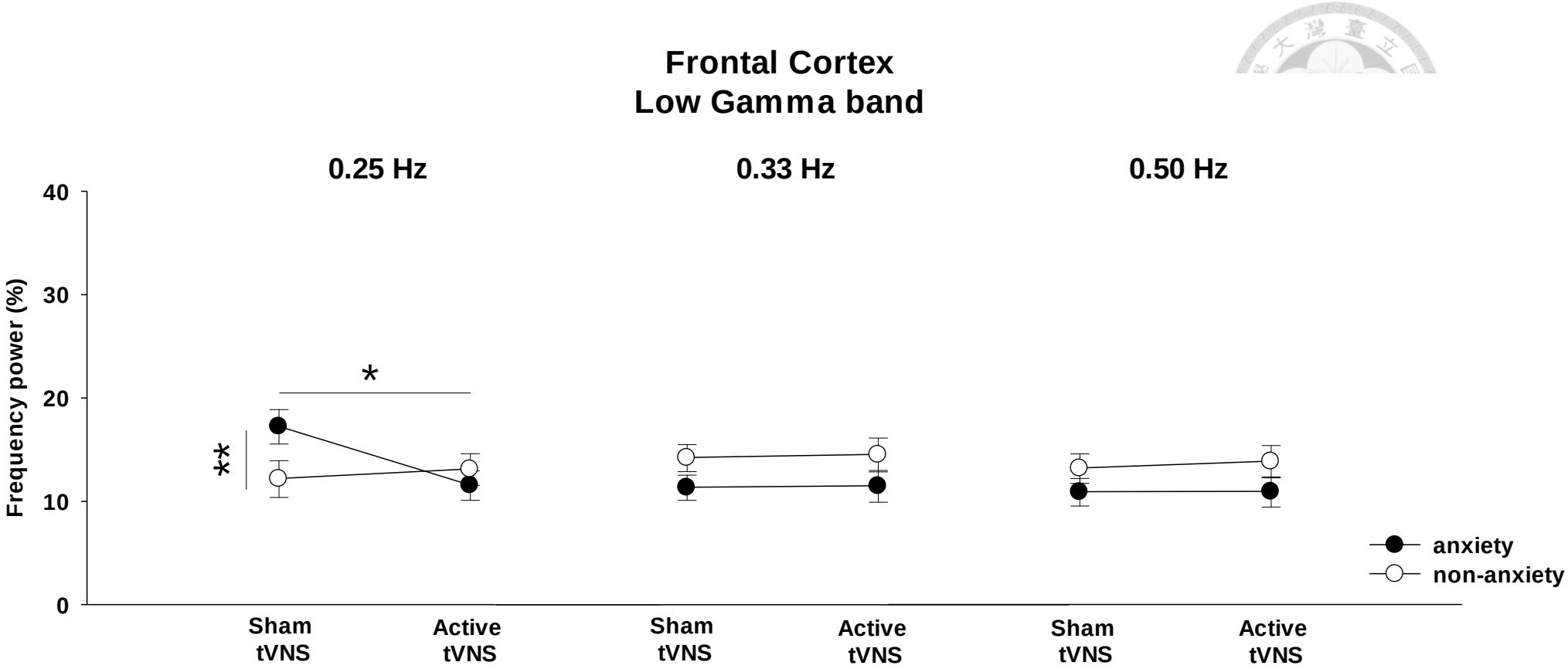

Figure 16. Relative EEG power in low gamma band at frontal cortex.

doi:10.6342/NTU202403646

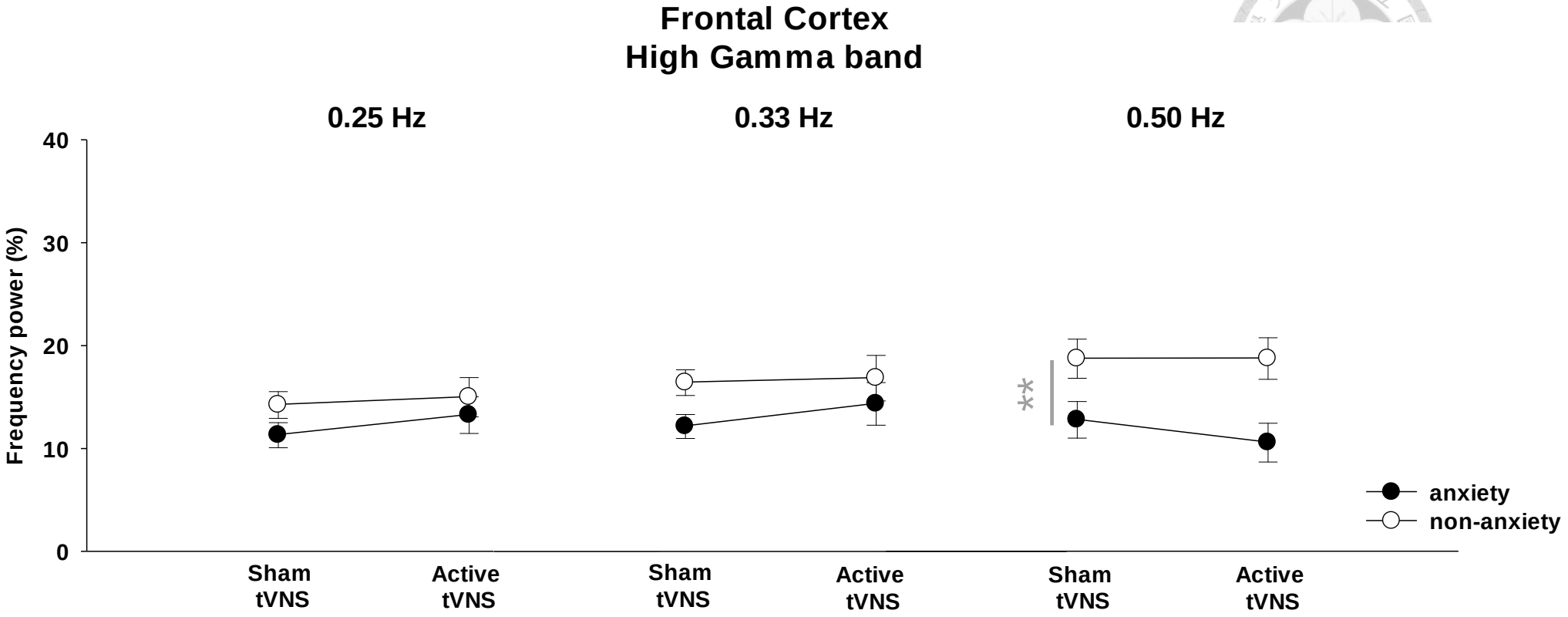

Figure 17. Relative EEG power in high gamma band at frontal cortex.

doi:10.6342/NTU202403646

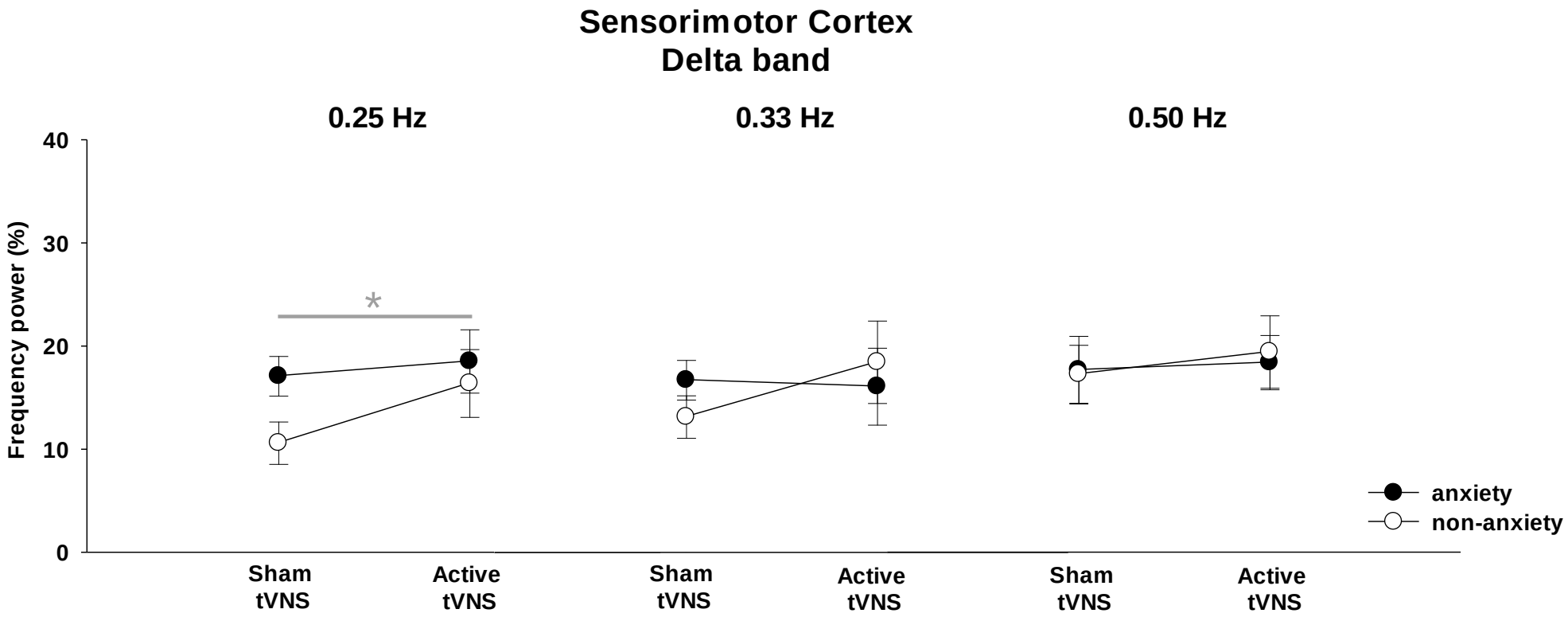

Figure 18. Relative EEG power in delta band at sensorimotor cortex.

doi:10.6342/NTU202403646

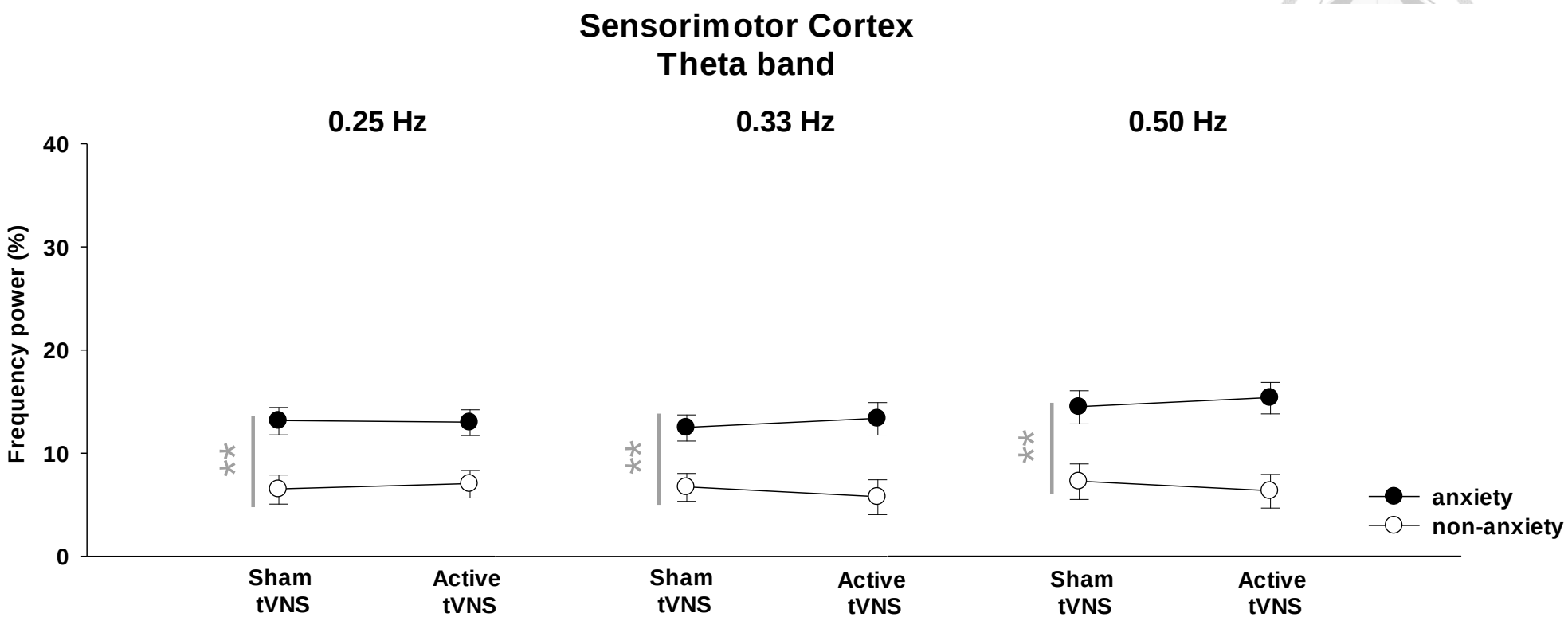

Figure 19. Relative EEG power in theta band at sensorimotor cortex.

doi:10.6342/NTU202403646

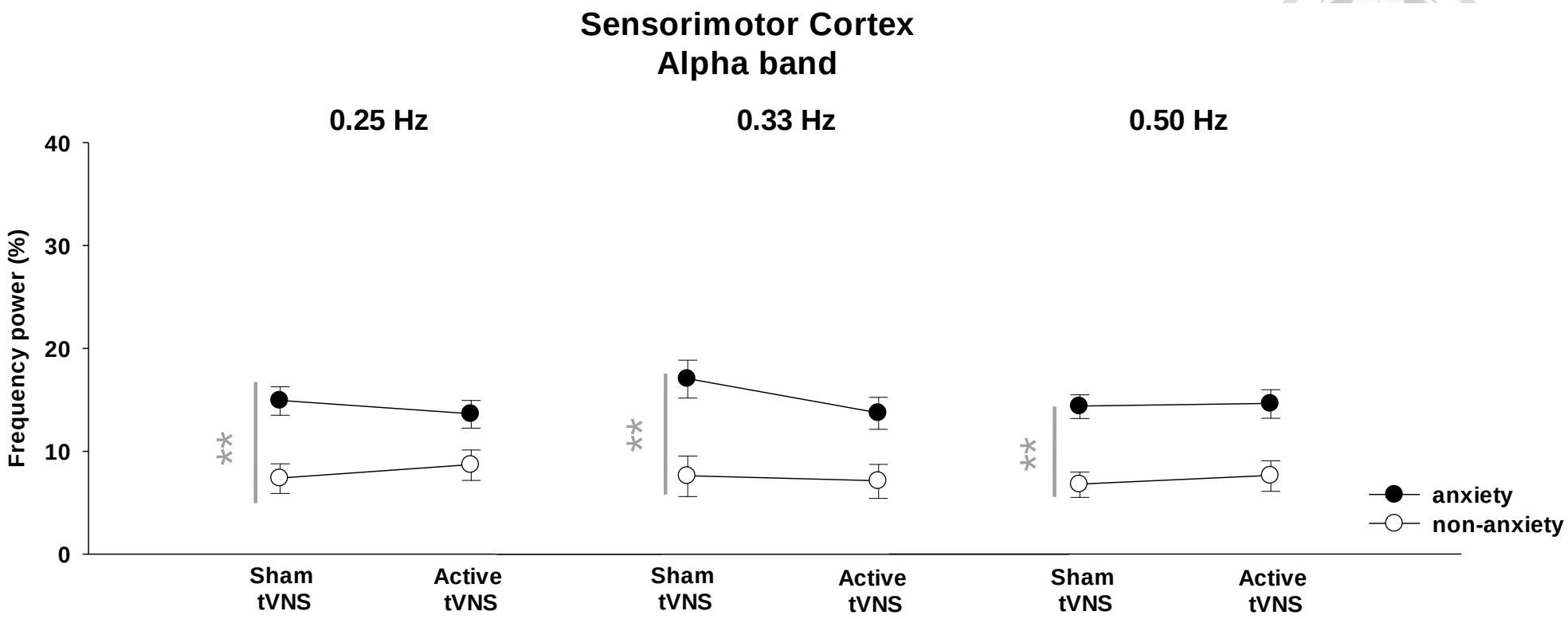

Figure 20. Relative EEG power in alpha band at sensorimotor cortex.

doi:10.6342/NTU202403646

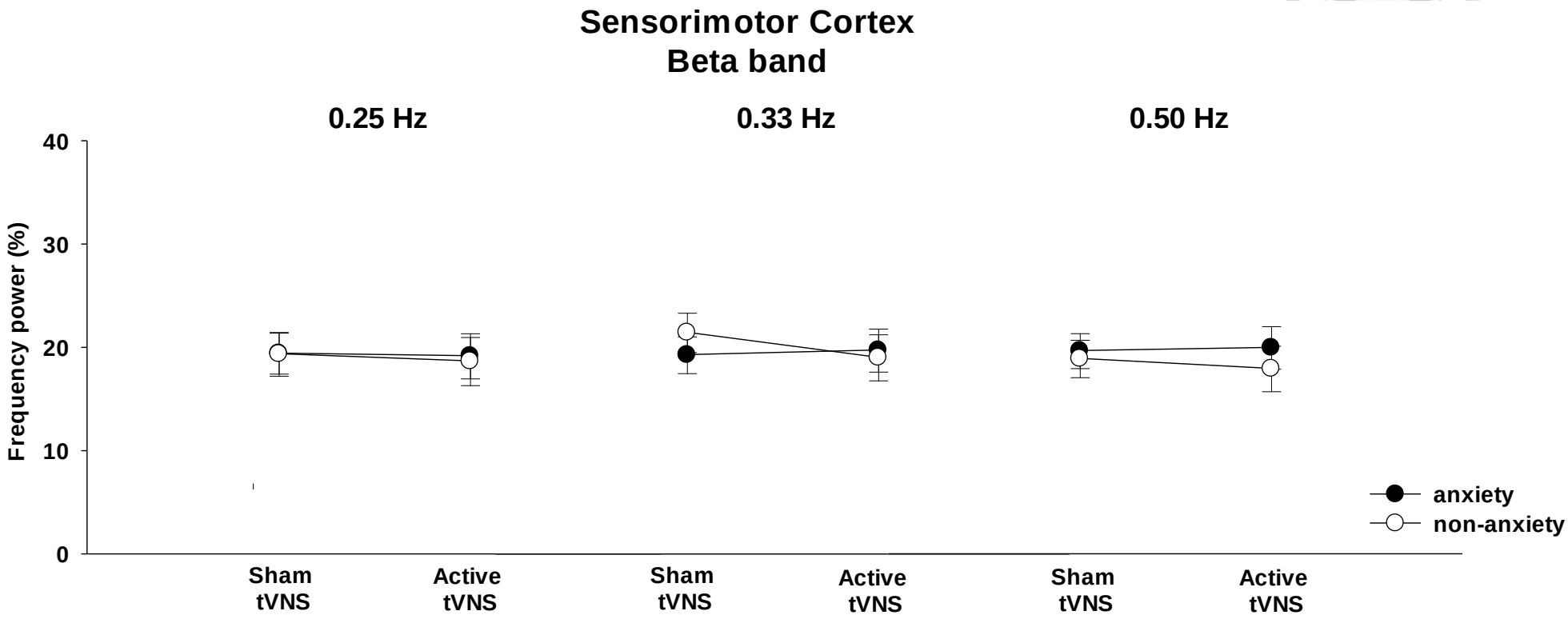

Figure 21. Relative EEG power in beta band at sensorimotor cortex.

doi:10.6342/NTU202403646

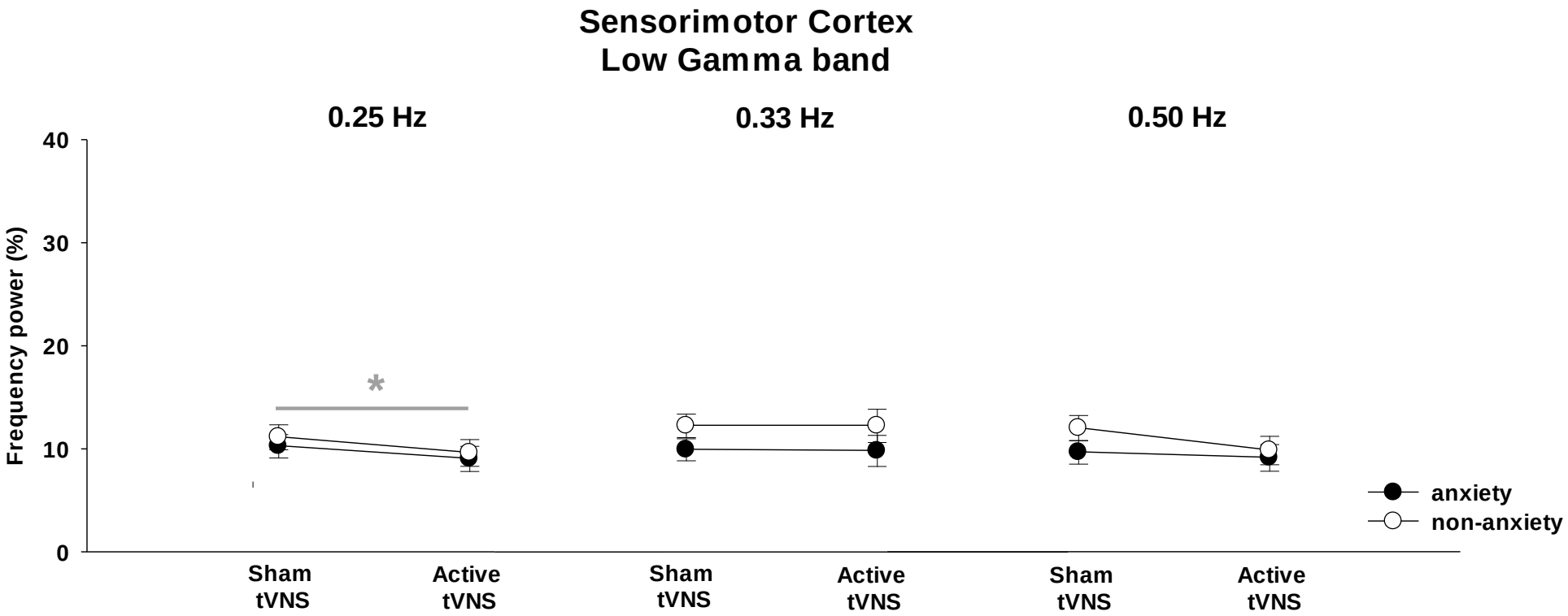

Figure 22. Relative EEG power in low gamma band at sensorimotor cortex.

doi:10.6342/NTU202403646

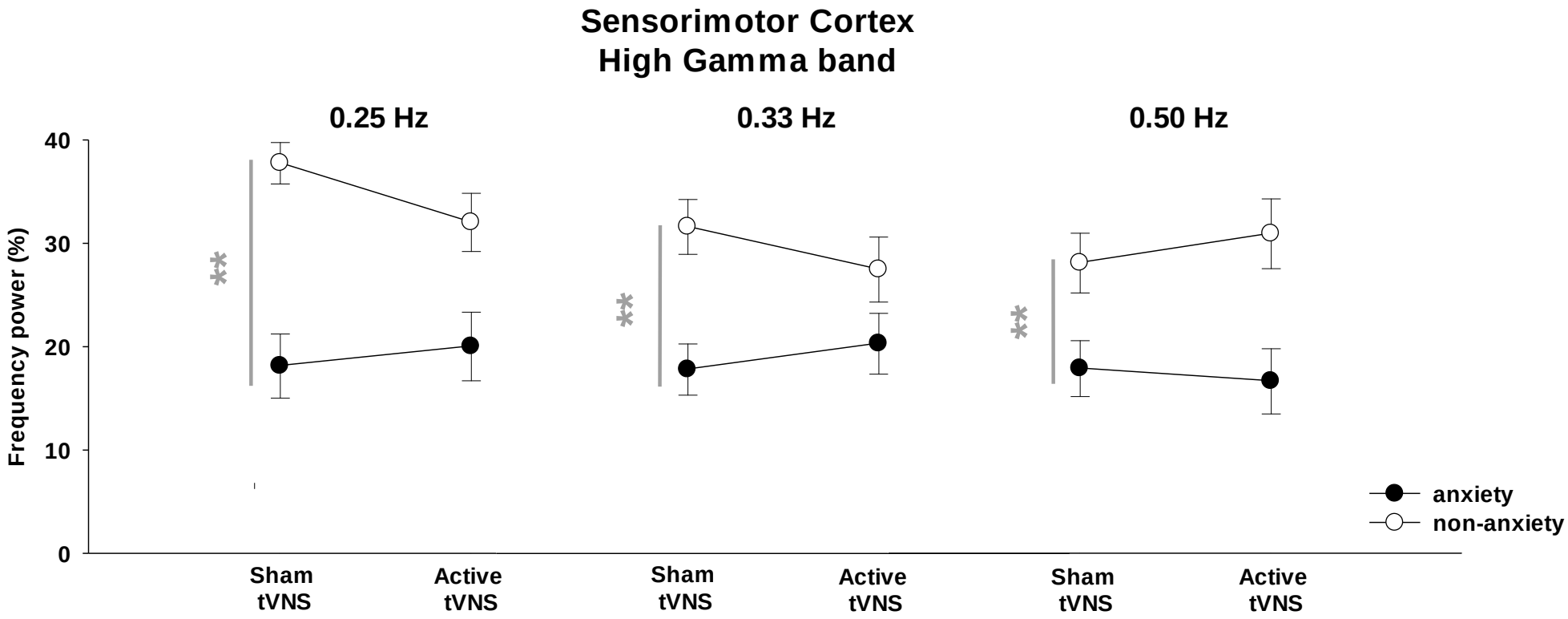

Figure 23. Relative EEG power in high gamma band at sensorimotor cortex.

doi:10.6342/NTU202403646

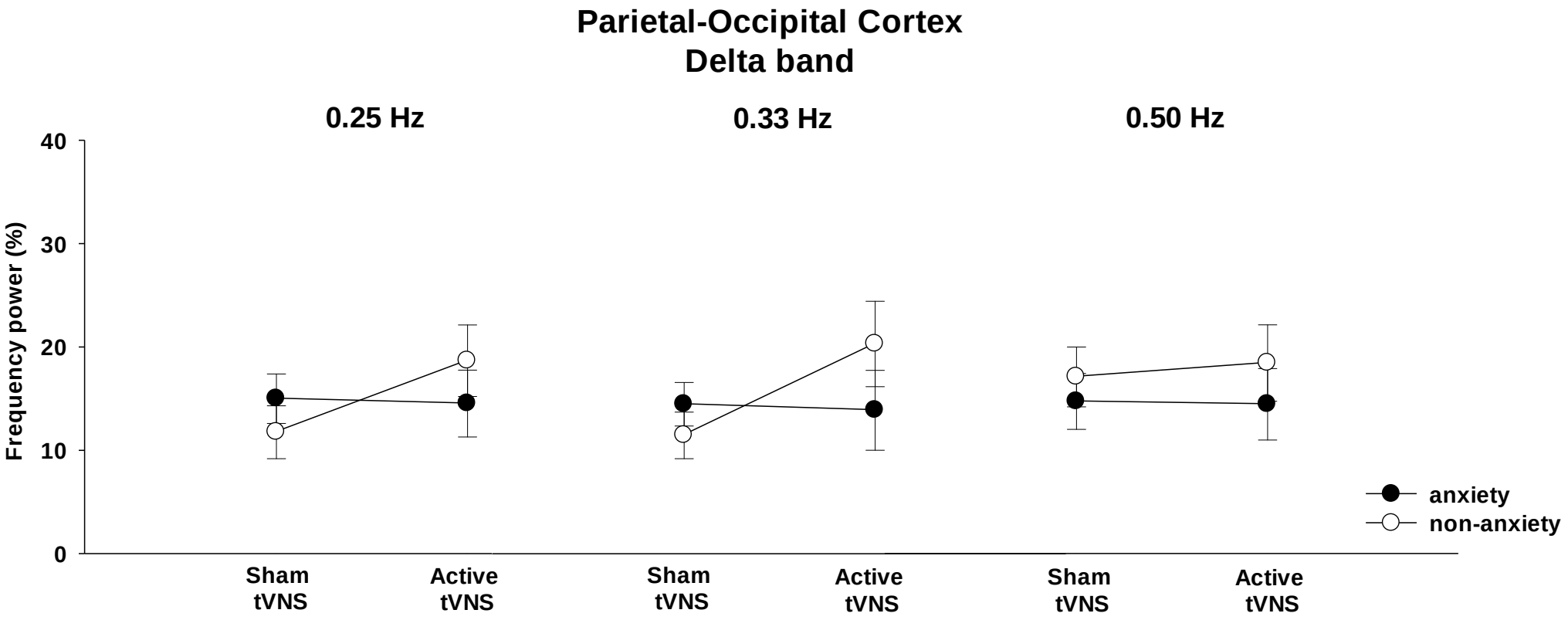

Figure 24. Relative EEG power in delta band at parietal-occipital cortex.

doi:10.6342/NTU202403646

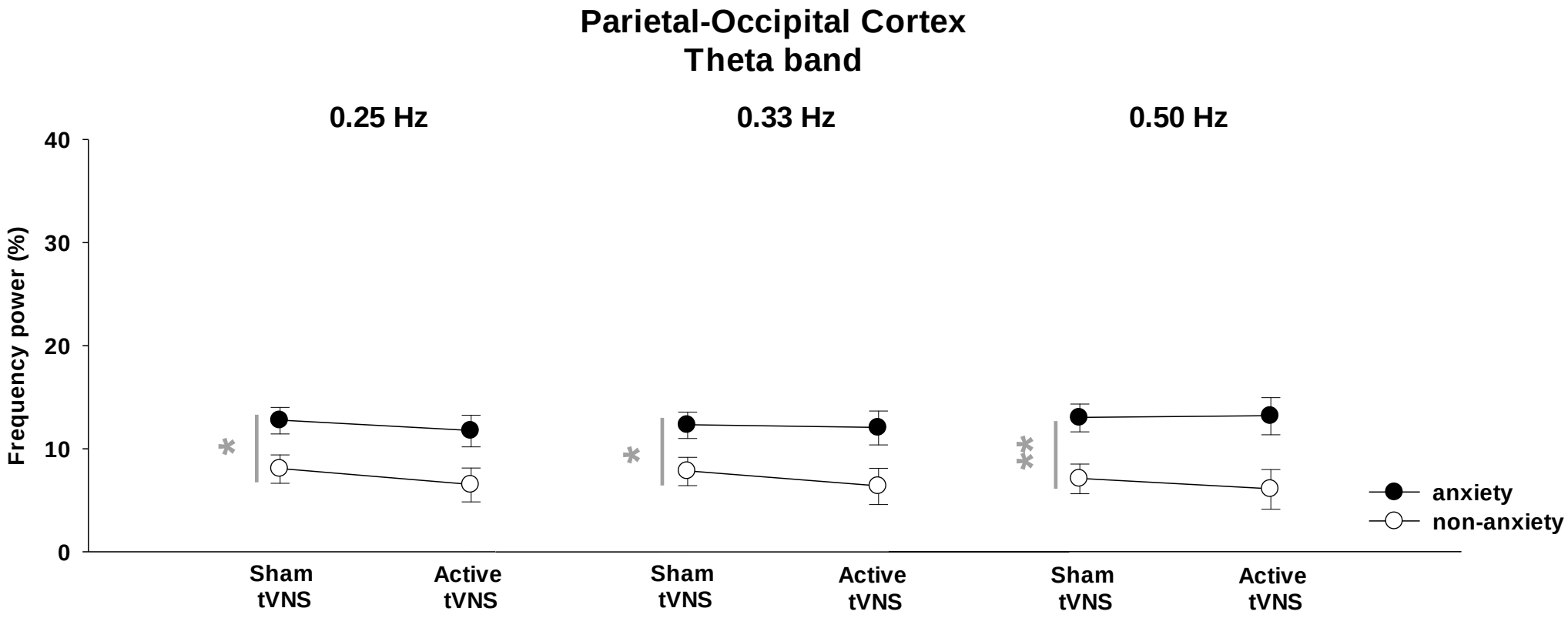

Figure 25. Relative EEG power in theta band at parietal-occipital cortex.

doi:10.6342/NTU202403646

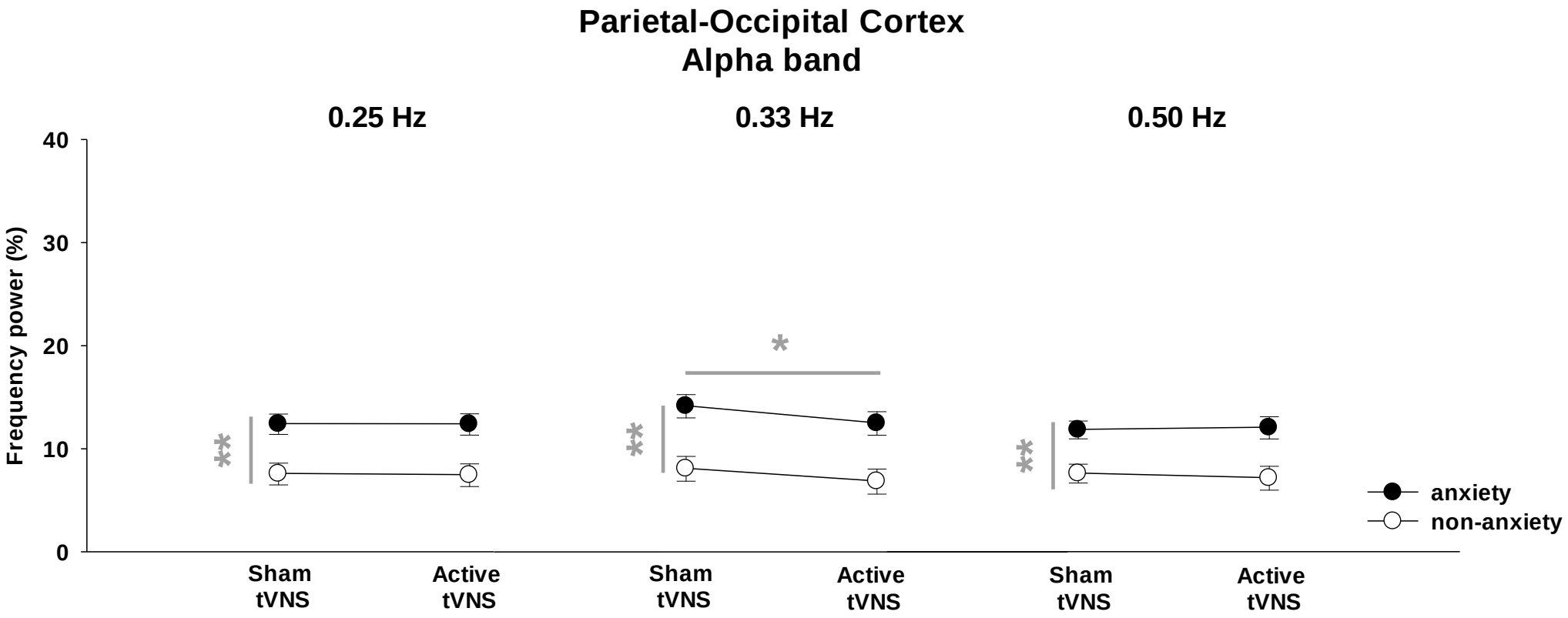

Figure 26. Relative EEG power in alpha band at parietal-occipital cortex.

doi:10.6342/NTU202403646

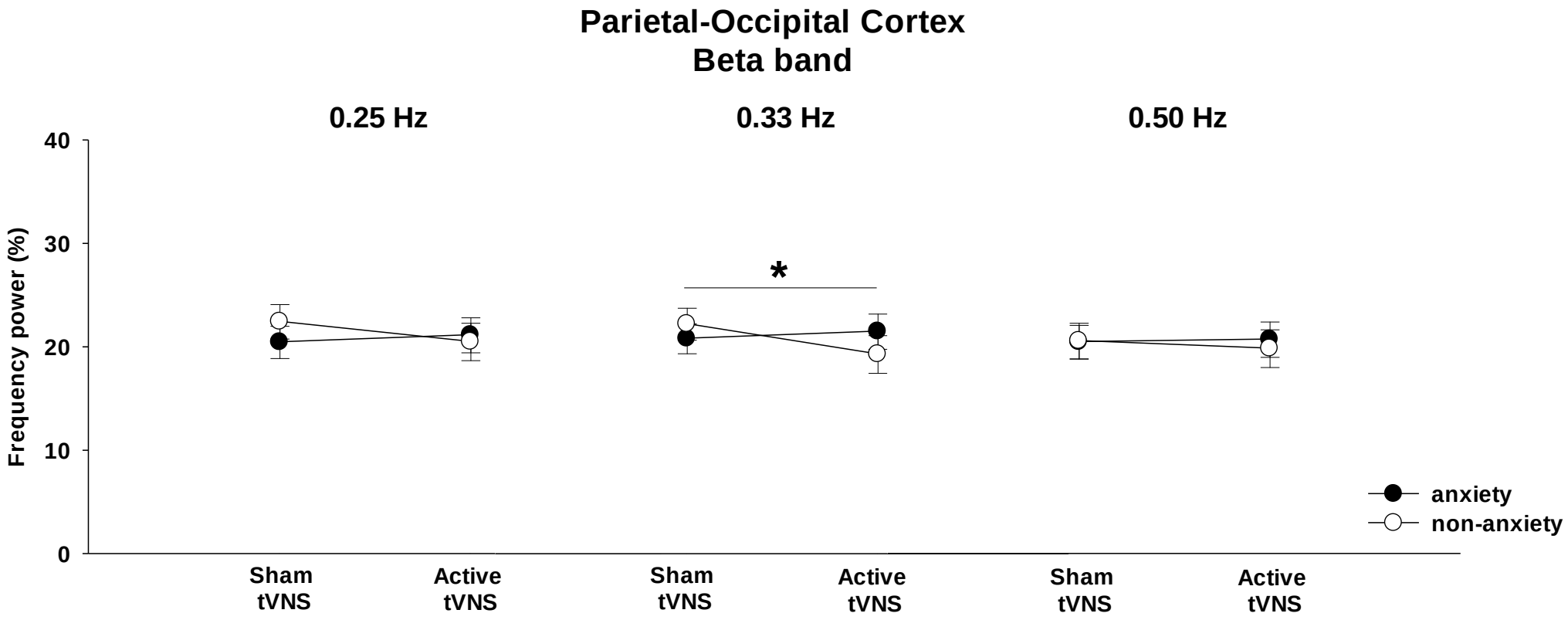

Figure 27. Relative EEG power in beta band at parietal-occipital cortex.

doi:10.6342/NTU202403646

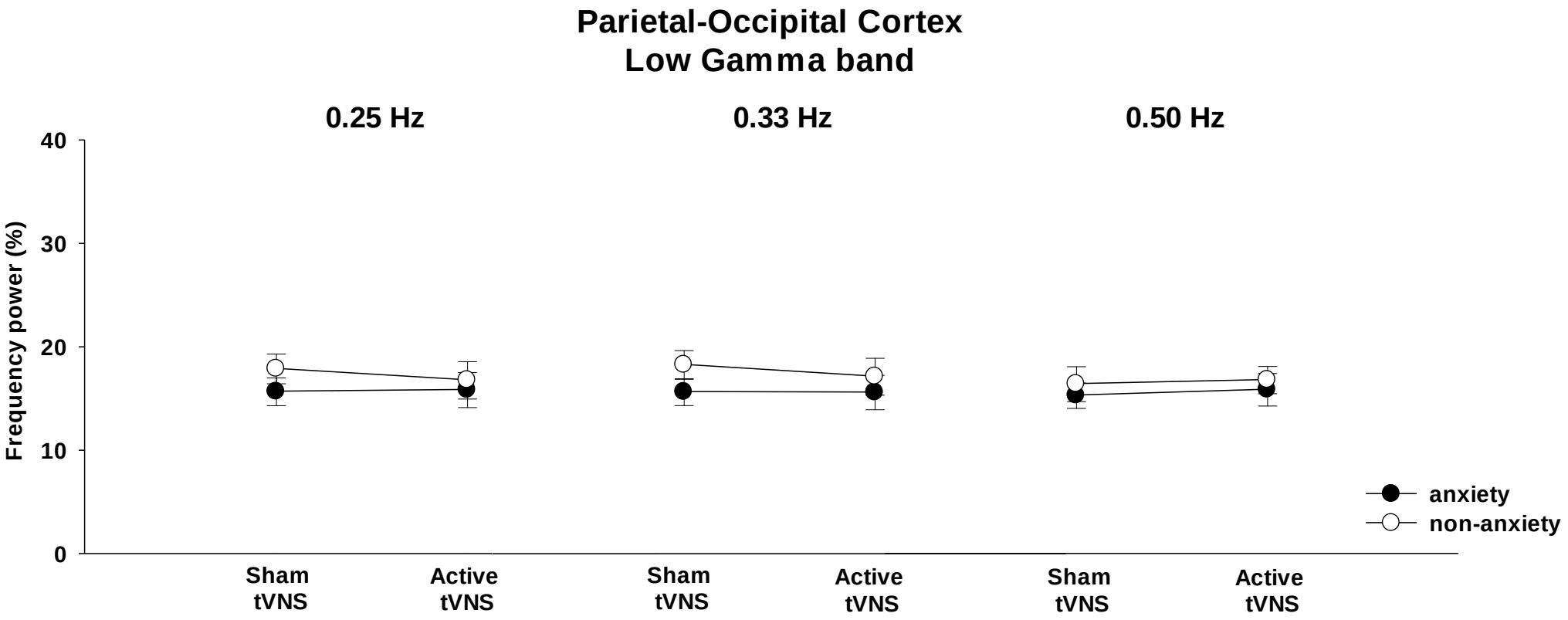

Figure 28. Relative EEG power in low gamma band at parietal-occipital cortex.

doi:10.6342/NTU202403646

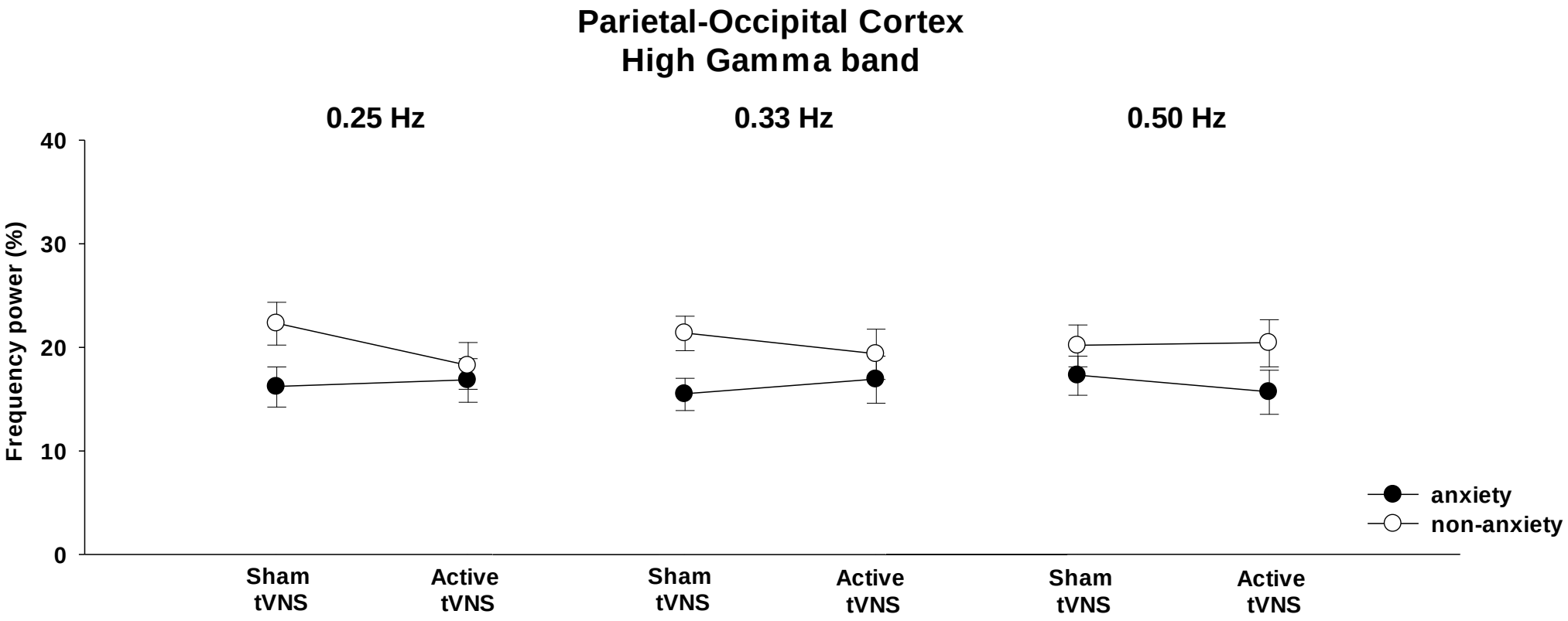

Figure 29. Relative EEG power in high gamma band at parietal-occipital cortex.

doi:10.6342/NTU202403646

Table 1. Participant's demographics and clinical characteristics.

Characteristic	Anxiety group	Nonanxiety group	*p* value
Age (years)	69.07±1.71	67.67±1.88	0.587
Age range (years)	58.5−80.33	61.42−77.09	-
Sex (male/female)	8/7	7/8	0.270
Disease duration (years)	8.86±1.43	8.21±1.02	0.715
Modified H-Y stage	2.37±0.20	2.50±0.24	0.678
MDS-UPDRS part I	4.73±1.07	2.20±0.42	**0.037**
MDS-UPDRS part II	9.33±2.24	6.93±1.77	0.409
MDS-UPDRS part III	15.27±3.32	12.40 ±2.40	0.491
MDS-UPDRS part IV	1.00±0.39	1.13±0.40	0.813
MDS-UPDRS total	30.33±5.78	22.67±4.15	0.291
MMSE	29.00±0.33	28.67±0.39	0.529
PAS	20.13±0.86	6.47±0.87	< **0.001**
LEDD (mg)	341.27±43.65	348.33±32.94	0.898

Note:
MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; PAS: Parkinson anxiety scale; LEDD: L-dopa equivalent daily dose

doi:10.6342/NTU202403646

Table 2. Percentage of the total variance in the EEG data for each cortical area under each condition.

Brain area	Anxiety group (variance, %)	Nonanxiety group (variance, %)	Statistics
0.25 Hz			
Prefrontal	72.02 (2.45)	71.97 (3.07)	$t_{(28)} = -0.043$, $p = 0.966$
Frontal	71.30 (3.43)	73.64 (2.39)	$t_{(28)} = 0.122$, $p = 0.904$
Sensorimotor	72.66 (3.12)	72.43 (2.78)	$t_{(28)} = -0.189$, $p = 0.851$
Parietal-occipital	71.25 (2.67)	72.43 (2.54)	$t_{(28)} = 0.056$, $p = 0.956$
0.33 Hz			
Prefrontal	72.09 (4.23)	73.01 (3.35)	$t_{(28)} = -1.712$, $p = 0.098$
Frontal	73.13 (3.29)	72.47 (3.97)	$t_{(28)} = 1.314$, $p = 0.199$
Sensorimotor	71.99 (3.05)	72.23 (2.45)	$t_{(28)} = -0.433$, $p = 0.668$
Parietal-occipital	72.54 (2.83)	72.85 (2.39)	$t_{(28)} = -0.646$, $p = 0.523$
0.50 Hz			
Prefrontal	72.47 (3.30)	72.61 (3.61)	$t_{(28)} = -0.816$, $p = 0.421$
Frontal	72.58 (3.67)	72.45 (4.23)	$t_{(28)} = 0.238$, $p = 0.813$
Sensorimotor	72.85 (2.86)	72.57 (4.37)	$t_{(28)} = 0.553$, $p = 0.584$
Parietal-occipital	72.62 (2.73)	71.61 (2.65)	$t_{(28)} = 0.712$, $p = 0.428$

doi:10.6342/NTU202403646

Table 3. Correlation between PAS and tVNS induced changes in behavior and anxiety parameters.

Correlation (N=30)	**△tracking error**	**△tracking JSM**	**△amplitude**	**△subjective anxiety level**	**△SCL**
0.25 Hz					
PAS	*r* = -.315	***r* = .469**	*r* = -.181	*r* = -.158	*r* = -.039
	p = .051	***p* = .006**	*p* = .445	*p* = .210	*p* = .423
△subjective anxiety level	*r* = -.026	*r* = -.112	***r* = -.323**	_	*r* = -.208
	p = .448	*p* = .286	***p* = .047**		*p* = .145
△ SCL	*r* = .096	*r* = -.093	*r* =-.016	*r* = -.208	_
	p = .314	*p* = .318	*p* =.468	*p* = .145	
0.33 Hz					
PAS	***r* = -.373**	***r* = .407**	***r* = .380**	***r* = -.340**	*r* = -.164
	***p* = .025**	***p* = .016**	***p* = .023**	***p* = .038**	*p* = .203
△subjective anxiety level	*r* = -.196	*r* = -.291	***r* = -.464**	_	*r* = -.130
	p = .159	*p* = .067	***p* = .006**		*p* = .225
△ SCL	*r* = .181	*r* = -.027	*r* = -.263	*r* = .130	_
	p = .179	*p* = .446	*p* = .088	*p* = .255	
0.50 Hz					
PAS	***r* = -.476**	***r* = .447**	*r* = .268	*r* = -.039	*r* = -.024
	***p* = .005**	***p* = .009**	*p* = .084	*p* = .421	*p* = .453
△subjective anxiety level	*r* = 246	*r* = .156	*r* = -.161	_	*r* = -.021
	p = .103	*p* = .215	*p* = .206		*p* = .457
△SCL	*r* = .058	*r* = -.106	*r* = .301	*r* = -.021	_
	p= .385	*p* = .296	*p* =.060	*p* = .457	

Note: △ = active tVNS – sham tVNS; PAS = Parkinson anxiety scale; SCL = skin conductance level

doi:10.6342/NTU202403646

Appendix 1. Approval of National Taiwan University Hospital Research Ethics Committee.

國立臺灣大學醫學院附設醫院D研究倫理委員會

Research Ethics Committee D
National Taiwan University Hospital
7, Chung-Shan South Road, Taipei, Taiwan 100, R.O.C
Phone: (02)2312-3456 Fax: (02)23951950

臨床試驗/研究計畫變更許可書

許可日期：2023 年 12 月 29 日

倫委會案號：202301082RIND
計畫名稱：探索結合平衡訓練與迷走神經刺激對有焦慮症狀之巴金森患者於重心轉移與行走之訓練成效：於時間限制與空間限制下探討。
試驗機構：國立臺灣大學
部門/計畫主持人：物理治療學系暨研究所　黃正雅教授
上述計畫變更案業經 2023 年 12 月 29 日本院 D 研究倫理委員會第 147 次會議審查同意，符合研究倫理規範。本委員會的運作符合優良臨床試驗準則及政府相關法律規章。

主任委員

蔡甫昌

Permission of protocol amendment of Clinical Trial/Research

Date of approval: Dec 29, 2023

NTUH-REC No.：202301082RIND
Title of protocol：Investigating the effects of combined balance exercise and vagus nerve stimulation on weight-shifting control and ambulation in patients with Parkinson disease and anxiety: under time and space constraints.
Trial/Research Institution：National Taiwan University
Department/ Principal Investigator：School of Physical Therapy / Professor Cheng-Ya Huang

The protocol has been approved by the 147th meeting of Research Ethics Committee D of the National Taiwan University Hospital on Dec 29, 2023. The committee is organized under, and operates in accordance with, the Good Clinical Practice guidelines and governmental laws and regulations.

Daniel Fu-Chang Tsai, M.D. Ph.D.
Chairman
Research Ethics Committee D

Daniel Fu-Chang Tsai

doi:10.6342/NTU202403646