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聽覺提示結合跑步機訓練對巴金森氏症患者於大腦皮質興奮性與步態表現的影響

Effects of Combined Auditory Cues and Treadmill Training on Cortical Excitability and Gait Performance in Parkinson's Disease

高珮容

Pei-Jung Kao

指導教授：陸哲駒 博士

Advisor: Jer-Junn Luh, Ph.D.

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本論文係高珮容君（學號 R05428011）在國立臺灣大學物理治療學系暨研究所完成之碩士學位論文，於民國 107 年 7 月 25 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

研究背景：巴金森氏症是常見的神經退化性疾病，由於基底核的退化性病變導致巴金森氏症患者在自動化動作控制上受損，例如：步態失調。臨床上常使用聽覺提示介入以改善行走步伐變異度高、凍結步態等問題。此外，聽覺提示為基礎的步態訓練對步態的改善效果可能來自於一系列神經塑性的累積。然而，目前鮮少研究顯示巴金森氏症患者經過聽覺提示訓練後其神經生理的改變，另外，也少有研究比較聽覺提示對於有或無步態凍結的巴金森氏症患者之效果。

目的：本研究將探討一次性以聽覺提示為基礎之跑步機訓練對於巴金森氏症患者神經生理與步態表現的影響，藉由經顱磁刺激評估大腦皮質興奮度來顯示神經生理之變化。本研究也探討聽覺提示對於有或無步態凍結之巴金森氏症患者是否有不同影響。

方法：此為隨機交叉試驗，收取 17 位巴金森氏患者(PD)，其中 8 位有凍結步態(FOG)，9 位無凍結步態(nFOG)，且另收取 9 位健康成年人(Control)作為對照組參與本試驗，每組皆以隨機順序接受兩種情形之介入，兩次訓練中間會相隔至少一星期，兩次訓練分別為 30 分鐘之以聽覺提示為基礎之跑步機訓練(AC condition)和沒有聽覺提示之跑步機訓練(NC condition)。每位受試者將接受介入前和介入後的評估。主要評估指標為大腦皮質興奮度，次要評估指標為舒適與最快行走速度下的走路表現。

統計分析：使用變異數分析(analysis of variance)檢測組間介入前、後之變化。

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結果： 在大腦皮質興奮度方面，無論有無聽覺提示，巴金森氏症患者相較於健康人在接受訓練後其皮質寧靜期(cortical silent period, CSP)顯著延長($p<0.001$)，有凍結症狀組只有在合併聽覺提示訓練後有顯著延長的現象(AC: $p=0.032$; NC: $p=0.257$)，而無凍結步態組無論有無聽覺提示介入，其皮質寧靜期都有顯著延長(AC: $p=0.007$; NC: $p=0.008$)。無論有無聽覺提示，巴金森氏症患者與健康人在經過訓練後，顯著減少刺激間距兩毫秒的皮質內抑制(short intracortical inhibition, SICI)以及增加刺激間距十、十二毫秒的皮質內促進(short intracortical facilitation, ICF)，然而有和無凍結步態組在皮質內抑制與促進方面，經過無論有無聽覺提示的訓練後並無顯著差異。在步態表現方面，無論有無聽覺提示，巴金森氏症患者與健康人在訓練後顯著增加舒服行走速度($p=0.006$)與步長($p<0.001$)，此外，無論有無聽覺提示，有凍結步態組與無凍結步態組經過訓練後，皆顯著增加其舒服行走的步長($p=0.002$)，在舒服行走步伐變異度方面，無論有無聽覺提示介入，有凍結步態組經過訓練後，其行走步伐變異度有下降趨勢，而無凍結步態組則呈相反趨勢。

結論： 一次性的跑步機訓練無論有無結合聽覺提示，可以調控巴金森氏症患者之大腦皮質興奮度並且增加舒服行走時的步長與速度。聽覺提示結合跑步機訓練能增強有或無凍結步態者的皮質脊髓抑制，然而，有凍結步態者若接受沒有聽覺提示的跑步機訓練則沒有顯示此效果。

關鍵詞：巴金森氏症、聽覺提示、經顱磁刺激、皮質興奮度、步態、跑步機訓練

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Abstract

Background: Parkinson's disease (PD) is a common neurodegenerative disorder. Dysfunction of dopaminergic cells in basal ganglia leads to deficits in the automatic execution of movements such as gait disturbances. Auditory cues are often used in clinical setting and revealed benefits in ambulation. Moreover, the effects of cueing-based training on gait pattern might come from the accumulation of a series of neuroplasticity through serial motor training. However, current studies provided little information on the changes of neuroplasticity after the patients with PD carried out the cued-based training. Furthermore, it is still uncertain whether PD with or without freezing of gait (FOG) can achieve equal favorable effects from auditory cues.

Purpose: The present study is to investigate the effects of auditory-cued treadmill training for a single session on the neurophysiology and gait performance in patients with PD. Neurophysiology will be evaluated the cortical excitability through transcranial magnetic stimulation (TMS). The study will further explore whether any different effects of auditory cues between freezers and non-freezers.

Methods: This is a crossover study. Freezers (FOG, n=8), non-freezers (nFOG, n=9), and healthy subjects (control, n=9) were recruited in this study. Each subject randomly carried out training with two condition with at least one-week washout interval. Two conditions were 30-minutes of treadmill training with (AC condition) and without rhythmic auditory

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cues (NC condition). All subjects received the baseline and post-treatment assessments. Primary outcome measures included the cortical excitability and the secondary outcome measures included the gait performance in both comfortable and fast walking speed.

Statistical analysis: Repeated measure analysis of variance (RM-ANOVA) was used to determine differences of mean scores of the dependent variables between groups under two condition. The statistical significance was set at $P<0.05$.

Results: PD subjects compared to healthy subjects revealed lengthened CSP duration after training whether with or without auditory cues ($p<0.001$ and $p=0.392$, respectively). Significantly increased CSP duration in AC condition ($p=0.032$), but not in NC condition ($p=0.257$) for the FOG group was found. The nFOG group presented significantly lengthened CSP duration in both AC and NC condition ($p=0.007$ and $p=0.008$, respectively). Both PD and control groups reduced $SICI_{(2ms)}$, increased $ICF_{(10ms)}$, and $ICF_{(12ms)}$ after training whether with or without AC ($p=0.003$, $p=0.009$, and $p=0.009$, respectively), but the FOG and nFOG did not show significant differences in SICI and ICF after training. For the gait performance in comfortable speed, PD and control group showed increased speed ($p=0.006$) and stride length ($p<0.001$) after training whether with or without AC. Moreover, both the FOG and nFOG group increased stride length ($p=0.002$) after treadmill training whether with or without auditory cues. The step time

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CV in the FOG group presented a downward tendency after training, whereas the non-freezers presented an opposite picture.

Conclusion: One-session treadmill training whether with or without auditory cues played a major role in modulated cortical excitability, increased step length, and gait velocity in comfortable walking speed for patients with PD. The auditory cues with treadmill training enhanced the corticospinal inhibition in both freezers and non-freezers. However, this phenomenon cannot be found in freezers when they received treadmill training without cues.

Keyword: Parkinson's disease, auditory cueing, transcranial magnetic stimulation, cortical excitability, gait, treadmill training

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LIST of ABBREVIATIONS

AC	auditory cues
BGTC	ganglia-thalamocortical network
CNS	central nervous system
CSP	cortical silent period
CTC	cerebellar-thalamocortical network
CV	coefficient of variation
CWS	comfortable walking speed
EEG	electroencephalography
EMG	electromyogram
FOGQ	Freezing of gait Questionnaire
FWS	fast walking speed
GABA	γ -aminobutyric acid
GPi	internal segments of the globus pallidus
GPe	external segments of the globus pallidus
ICF	intracortical facilitation
ISI	interstimulus intervals
M1	primary motor cortex

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MEPs	motor evoked potentials
MMSE	Mini-Mental State Examination
MT	motor threshold
NMDA	N-methyl-D-aspartate
PD	Parkinson’s disease
PET	positron emission tomography
RM-ANOVA	repeated measure analysis of variance
rTMS	repetitive transcranial magnetic stimulation
SICI	short intracortical inhibition
SIP	stepping-in-place
SMA	supplementary motor area
SNr	substantia nigra pars reticulata
TMS	transcranial magnetic stimulation
UPDRS	Unified Parkinson's Disease Rating Scale

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Chapter 1 Introduction

1.1 Background

Parkinson's disease (PD) is a common neurodegenerative disorder due to a dopaminergic deficiency in the basal ganglia.[1] The prevalence of PD rises as a growth of aging population. Approximately 0.5-1% of the population ranged from 65 to 69 years of age and rising to 1-3% among people who are older than 80 years of age.[2] Dysfunction of dopaminergic cells in basal ganglia leads to deficits in internal timing and automatic execution of movements[3,4] such as gait disturbances, which are the hallmark of PD.

Parkinsonian gait is characterized by small stride length, decreased gait speed, increased cadence, increased percentage of double leg support, absence of arm swing, and increased stride-to-stride variability.[5-8] Freezing of gait (FOG) is one of the disabling gait disturbances and defined as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk."[9-11] Freezers exhibits more gait instability, which related to stride time variability,[12-15] than non-freezers.[6]

In order to ameliorate the impaired automatic motor performance, the pharmacological management is the primary way and has the capability to relieve certain symptoms; however, motor complications occur after long-term use of medicine, which should not be ignored. Rehabilitation such as physical therapies remains important for

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patients with PD to gain function and decrease the rate of functional decline.

So far, overground gait training with external cues and treadmill training are the common interventions to improve gait disturbances attributed to dysfunction of motor automaticity. Auditory cues are widely applied in clinical studies or practice for PD. Auditory cues provide an external rhythm that bypasses the internal rhythm deficits to prompt more appropriate gait pattern.[16,17] Abundant studies revealed the utilization of auditory cues facilitates the normalization of gait performances in PD such as reduced gait variability and increased stride length.[18,19] However, according to Willems et al.,[7] different effects on improved step length were noted in freezers and non-freezers when they received different frequency of auditory cues. It seems that the freezers and non-freezers may exhibit the different responses in gait to the auditory cues. Insufficient studies investigate that the different responses to the auditory cues in freezers and non-freezers. We are still uncertain whether both types of patients can achieve equal favorable effects on gait performance from auditory cues.

Recently, there has been growing interest in combined auditory cues with treadmill training. Since treadmill training is another common and beneficial intervention to normalize the spatiotemporal gait parameter for PD, cues applied during treadmill walking may potentiate more positive effects on gait in PD compared to traditional intervention.[20,21] Despite this, we are still unclear these different effects of cued treadmill

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training between freezers and non-freezers due to scarcer studies.

After having realized the effects of cueing-based training on gait pattern, it is necessary to dig into how these effects come from and what is the potential mechanism behind the auditory cues. According to the mechanism of learning-induced cortical plasticity in the primary motor cortex (M1), it hypothesized that synaptic plasticity could be modulated through long-term potentiation (LTP) and long-term depression (LTD) depend on different stimuli.[22] An animal study had shown these neurophysiological changes after training is associated with improved motor performance.[23] Moreover, training-induced plasticity may be important to the rehabilitation.[24] Based on the previous research, some neuroplastic changes in the brain might occur before the behavioral changes response to the auditory-cued training. One Positron Emission Tomography (PET) study[25] revealed significant metabolic increment in the cerebellum, parietal and temporal lobes after the patients with PD carried out the auditory cueing-based physical rehabilitation program. Nevertheless, gait parameters except for stride time variability after training did not differ from those obtained before training. It seems that neuroplasticity through cueing-based training plays a crucial role to improve gait disturbances for PD.

In order to explore the neuroplastic effects of cueing-based training in patients with PD, the application of the neuronal imaging techniques is needed. The common neuronal

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imaging techniques for the human to demonstrate neuroplasticity include positron emission tomography (PET), electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Compared to PET and EEG, TMS parameters can be rapidly acquired and provide close monitoring of relatively short-duration neuroplastic changes following experimental manipulation. TMS explore the neuroplasticity as measured through the cortical excitability. Previous studies indicated the patients with PD exhibited abnormal cortical excitability including the reduced cortical silent period (CSP) and a failure of intracortical inhibition.[26] Therefore, it is worth for us to dig into whether auditory cued-based training has an impact on cortical excitability.

Based on our previous laboratory experiment,[27] for the cortical excitability, we investigated significantly lengthened CSP duration and reduced short intracortical inhibition (SICI) at 2ms after PD subjects received stepping-in-place (SIP) training with auditory cues (AC) but not without cues. Additionally, the freezers in comparison of the non-freezers achieved more plastic changes in CSP duration and $SICI_{(2ms)}$ after SIP training with AC. Concurrently, the freezers obtained significantly decreased walking step time CV after training. These findings suggested some changes in neuroplasticity and behavioral performance occurred after training with AC and the freezers and non-freezers may have different responses to the AC. Despite this, SIP is unlike walking, which needs to provide the forward propulsion. We cannot draw the firm conclusion that whether the

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auditory-cued treadmill training could provide similar effects on the cortical excitability and gait performances in freezers.

In general, gait disturbances that related to the dysfunction of automatic motor execution is a major problem for the patients with PD, especially in freezers. Training-induced plasticity may play a crucial role in gait rehabilitation in PD. Therefore, it is worth for us to investigate whether the cortical excitability can be modulated through auditory-cued treadmill training and explore whether any improvement in gait performance after training.

1.2 Purpose and significance

So far, the majority of studies regarding the utilization of auditory cues in PD have focused on overground walking and long-term training for several weeks. Among these studies, the favorable effects of auditory cues on gait were well documented. Moreover, recently, there has been growing interest in the application of auditory cues combined with treadmill walking due to better gait pattern during treadmill walking compared with overground walking. According to the animal study regarding the mechanism of learning-induced cortical plasticity in the primary motor cortex (M1), we may believe that the improvements in gait performances after cueing-based training come from the accumulation of series of neuroplasticity through serial motor training. Thus,

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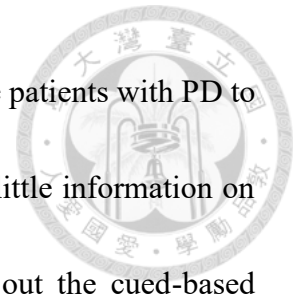

neuroplasticity through motor training may play a crucial role for the patients with PD to improve their gait performances. However, current studies provide little information on the changes in neuroplasticity after the patients with PD carried out the cued-based training. It is uncertain that if any neurophysiological changes occur following the one-session cueing-based training. To explore the neuroplasticity in the human cortex, transcranial magnetic stimulation (TMS) is applied to demonstrate the cortical plasticity. The potential mechanism behind auditory cues through observing the neurophysiological and behavioral changes in response to auditory-cued training can be explored in this study. We can also gain further insight into the different effects of auditory cues in freezers and non-freezers by comparing the results from two types of patients. Therefore, we can choose the appropriate intervention when we apply the auditory cues according to the existence of freezing of gait.

The aims of this study are: (1) to investigate the effects of auditory-cued treadmill training for a single session on cortical excitability in patients with PD; (2) to investigate the effects of auditory-cued treadmill training for a single session on gait performance in patients with PD; (3) to explore whether any different effects of auditory cues on cortical excitability between freezers and non-freezers; (4) to explore whether any different effects of auditory cues on gait performance between freezers and non-freezers

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1.3 Hypotheses

Single session training was used in this study. Therefore, it was considered that the changes in the cortical excitability may be more apparent compared with the changes in gait performances. Furthermore, step time variation, which may relate to the gait stability, in freezers is more impaired than that in non-freezers. Thus, freezers might obtain more benefits from auditory-cued training than non-freezers.

Aim 1: Whether the auditory-cued treadmill training could significantly alter the cortical excitability in PD subjects.

Hypothesis: Compared with treadmill training alone, the auditory-cued treadmill training will significantly alter the cortical excitability in PD subjects than in healthy subjects

Aim 2: Whether the auditory-cued treadmill training could significantly reduce step time variation and improve gait pattern in PD subjects.

Hypothesis: Compared with treadmill training alone, the auditory-cued treadmill training will significantly reduce step time variation and improve gait pattern in PD subjects than in healthy subjects

*Gait pattern include walking speed, cadence, and stride length

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Aim 3: To determine whether auditory-cued treadmill training has different changes in cortical excitability between freezers and non-freezers.

Hypothesis: Compared with treadmill training alone, the auditory-cued treadmill training would have changes in the cortical excitability in both types of patients, and freezers may achieve more alternation than non-freezers.

Aim 4: To determine whether auditory-cued treadmill training has different effects on step time variation and gait pattern between freezers and non-freezers.

Hypothesis: Compared with treadmill training alone, the auditory-cued treadmill training would have favorable effects on step time variation and gait pattern in both types of patients, and freezers may achieve more benefits than non-freezers.

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Chapter 2 Literature Review

2.1 Introduction of Parkinson's disease

2.1.1 Pathophysiology and symptoms

The basal ganglia are a group of subcortical nuclei and they organized connections with external structures such as the basal ganglia-thalamocortical circuit (BGTC).[1] The basal ganglia is considered as a primary substrate for motor learning and controlling behavioral output (e.g., temporal information processing[3] and automatic motor control).[4]

Parkinson's disease (PD) is the progressive neurological degenerative disorders attributed to dysfunction of dopaminergic neurons in the basal ganglia.[28] The cardinal symptoms of Parkinson's disease are rigidity, bradykinesia, tremor, and postural instability.[29] Progressive dopamine deficiency leads to the disturbance of internal rhythmic control and deficits in automatic motor performance such as impaired balance control and gait disturbances, which related to the risks of fall.[30] Additionally, since the basal ganglia have connected to widespread cortical areas, other non-motor symptoms will occur as the disease progressing. These non-motor features contain mood, cognitive problems, sleep disorders, pain, and autonomic disorders, which cause a decline in the quality of life.[31]

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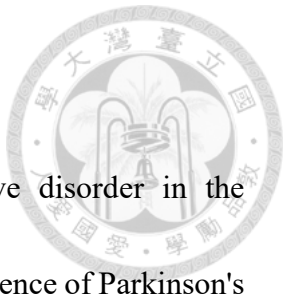

2.1.2 Prevalence and incidence

Parkinson's disease is the second common neurodegenerative disorder in the elderly.[32] Age is the greatest risk factor for developing PD. The prevalence of Parkinson's disease is approximately 0.5-1% of the population older than 65 years of age and rising to 1-3% among people who are older than 80 years of age.[2] Moreover, the prevalence of Parkinson's disease seems higher in Europe and North America compared to Asia and Africa.[33] Gender is another risk factor, with the male-to-female ratio being about 3:2.[34] In Taiwan, the prevalence of Parkinson's disease is 159.8-299.3 per 100,000 and the incidence is 33.5-36.6 per 100,000 in 2002 to 2009.[35] Despite the relatively low prevalence of Parkinson's disease in Asian area, it is still a crucial issue due to the increasing prevalence and incidence in Taiwan.

2.1.3 Freezing of gait

Gait disturbances are the most common complication in patients with PD. Approximately 7% of patients with recently diagnosed of PD[36] and 47% of patients with PD suffer from freezing of gait (FOG).[37] FOG is defined as “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk.”[9-11] There are three different patterns of FOG: (1) trembling in place: alternating tremor of the legs at a frequency of 3–8 Hz;[38,39] (2) shuffling forward with small steps; (3) complete

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akinesia: no observable motion of the limbs or trunk.[11] The third type occurs in low incidence.[40] Patients with FOG would feel as if their feet are glued to the floor. This symptom commonly lasts for several seconds, but the episodes may occasionally exceed 30s.[40] Furthermore, FOG is most commonly observed in the "off" state.[41] It increases the risk of falling.[9]

The pathophysiology of FOG is multifactorial and still not well understood. Most studies classified freezers and non-freezers based on their subjective descriptions of FOG, such as assessed by the New Freezing of Gait Questionnaire (NFOG-Q).[42,43]

2.1.4 Gait patterns in freezers and non-freezers

Dysfunction of dopaminergic cells in basal ganglia circuit affects motor automaticity, such as walking.[4] The features of Parkinsonian gait include decreased gait speed, increased cadence, small stride length, increased percentage of double leg support, absence of arm swing, and increased stride-to-stride variability.[5-8] Among these gait parameters, stride time variability might be considered as the quantitative evaluation of gait instability, since stride time variability is found to be a parameter associated with risk of fall rather than gait speed and stride length.[5,6,13,15] Therefore, The larger stride time variability, the more gait instability for patients with Parkinson's disease.

FOG is a sudden and transient gait disturbance. The cumulative loss of stride length

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and increased cadence are showed before FOG starts to occur.[44] Chee et al.[45] also demonstrated that decreased step length is a precursor of FOG. In this study, freezers who walk on the ground in 100%, 75%, 50%, and 25% of their preferred stride length showed significantly decreased step length and increased step variability compare to non-freezers who walk in the same condition. The gait performance of non-freezers is similar to healthy elders in those conditions. Additionally, between FOG episodes, cadence appears to be similar in freezers and non-freezers whether they are during "on" or "off" medication. However, there is a significantly increased stride time variability in freezers compared to non-freezers regardless of medication.[6] The higher stride time asymmetry in freezers than in non-freezers is also revealed by Plotnik et al.[46] According to the aforementioned findings, a capability of regulating stride time variation in freezers is more impaired than that in non-freezers.

2.2 External cueing as rehabilitative strategy

2.2.1 Auditory cues versus visual cues

Despite the positive effects of pharmacological management for Parkinsonian gait, it still has the side effects and limitation that should not be ignored. Behavioral strategies remain important for patients with PD. As we mentioned above, PD has impaired automaticity of motor control. Behavioral strategies may shift patients' automatic motor

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control to the goal-directed way.[47] External cues, which provide the references for the execution of movement, are the common behavioral strategies for patients to allocate their attention to gait.

External cues contain stimuli of temporal and spatial aspect and they may prompt more appropriate movement timing and amplitude of gait. Auditory cues and visual cues are temporal and spatial stimuli, respectively. A meta-analysis of 25 studies demonstrated auditory cues may provide positive effects in gait speed, cadence, and stride length; whereas visual cues only improve stride length.[48] Although two kinds of stimuli can elicit positive effect in stride length, which is consistently decreased in patients with PD, auditory cues seem more consistent and beneficial in gait performance than visual cues. This result is the same with the previous review.[49] Additionally, comparing the effects of auditory cues to visual cues on gait stability, auditory cues are the effective stimuli to reduce stride time variability, especially for patients in Hoehn and Yahr III to IV.[19]

2.2.2 Effects of auditory cueing on gait for patients with PD

Auditory cues provide the temporal stimuli to regular the timing of gait and coordination of limbs. It is cost efficient and easy to implement. It can be delivered by verbal counting, musical beats, or metronome. There are abundant studies investigated the effects of auditory cue on gait in patients with PD.

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Previous study showed that when patients with PD walked combined with auditory cues, the cadence, step length, and stride time variability are significantly improved than patients walked without cues.[19] Furthermore, auditory cues have immediate effect on gait. Hausdorff et al.[18] instructed patients with PD walking with auditory cues at 100% or 110% of their usual cadence and then immediately evaluated their gait performance without cues. Both frequency of auditory cues improved gait speed and stride length in patients even when cues were removed, but it did not influence gait parameters in healthy elderly. These effects lasted for 15 minutes.

In terms of interventional studies, they combined auditory cues with ground walking or other physical therapies as training.[50,51] The interventional period ranged from one week to eight weeks. All of them demonstrated the beneficial effect on gait in patients with PD after a period of training. However, the frequency of auditory cues applied in these studies did not consistent. Although the therapeutic effects would be influenced by different frequency, insufficient studies demonstrated which frequency is the best.

2.2.3 Different response of auditory cueing in freezers and non-freezers

Although the effects of auditory cues on gait in PD are well documented, the literature assessing the role of auditory cues on FOG are scarcer and controversial. Cubo et al.[52] studied the effects of auditory cues at 100% of usual cadence on FOG in PD during

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"on" medication. Results demonstrated there was no significant difference in the freezing time, average freezing duration, and numbers of freezes between the freezers walking with and without auditory cues. However, since 1996, Enzensberger and Fischer have found a significant reduction in the number of freezing episodes on straight walking when patients walked with metronome during "on" medicine.[53] Another study also showed the presence of auditory cueing at 110% of preferred walking cadence led a significantly reduced number and duration of freezing episodes in freezers during end of dose-period.[8] Furthermore, the different response of auditory cueing in freezers and non-freezers might be influenced by different task. Based on our previous laboratory experiment,[54] non-freezers revealed improved coefficient of variance in fast tapping after auditory-cued tapping training, but not in freezers

Due to the multifactorial nature of FOG, the freezers and non-freezers may exhibit the different responses on gait to the auditory cues. According to Willems et al.,[7] they investigated the effects of auditory cues on gait in the freezers and non-freezers during “on” period. All patients respectively walked with auditory cues at five different frequencies including 80%, 90%, 100%, 110%, and 120% of preferred walking cadence. Results revealed there was no difference in gait speed and stride length between the freezers and non-freezers under different cued conditions. However, they further investigated the gait performance across different cued frequency in each group. For the

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freezers, although their gait speed improved under higher cued frequencies, they performed decreased stride length in 110% cued condition and had larger stride length in 90% condition. Whereas, for the non-freezers, 110% of usual cadence was suitable for them to increase speed and stride length. Due to the small sample size in this study and fewer studies regarding the auditory cues response between the freezers and non-freezers, more evidence is needed to make a clear conclusion.

From the previous literature, it can be seen that the frequency of cueing seems plays an important role in gait for the freezers and non-freezers. Additionally, lack of study investigates the effect of auditory cues on gait instability in the freezers and non-freezers during "off" medication.

2.2.4 Potential mechanism behind auditory cues

Previous sections have demonstrated the clinical effects of auditory cues. It is now necessary to investigate the possible mechanism underlying this effect of auditory cues. Brain areas, such as the basal ganglia, cerebellum, supplementary motor area (SMA), pre-SMA, and premotor cortex, involved in accurate temporal processing that closely related to rhythmical movements.[55] Moreover, there are two brain networks involved in timing movements. One is the basal ganglia–thalamocortical network (BGTC), which is in charge of self-generated movements and attention-dependent evaluation of temporal

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intervals. The other network is cerebellar–thalamocortical network (CTC), which is responsible for matching movements to the external cues.[17] The BGTC network is disrupted in PD due to dysfunction of dopaminergic cells in basal ganglia circuit; whereas, the CTC network spared or is affected lately in PD. Therefore, the beneficial effects of auditory cues may be attributed to driving the residual activity of the BGTC network or compensatory mechanism from the CTC network.[16,17] For the evidence of the compensatory mechanism, del Olmo et al.[25] displayed that not only improvement of gait variability but also enhanced activity of the anterior cerebellum lobe were noted after PD patients received cueing-based physical rehabilitation program for 4 weeks.

Moreover, the central nervous system (CNS) is a dynamically changing system. CNS is capable of adaptation and modification according to the externally environmental inputs, efferent demands, and behavioral influences. Based on the mechanisms of learning-induced cortical plasticity in M1, it was hypothesized that long-term potentiation (LTP) and long-term depression (LTD), which have been termed synaptic plasticity, could modify the synaptic strength of cortical connections depend on the different pattern of stimulation used. LTP and LTD describe the long-lasting enhancement or attenuation in synaptic strength respectively.[22] According to the animal study, results revealed rats achieved a performance with few errors in the reach, grasp or retrieval actions after training, additionally, less LTP was induced from the trained M1, whereas normal levels

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of LTP was induced from the untrained M1.[23] That is, neuroplasticity through motor training was associated with improved motor performance. In human, training-induced plasticity accompanying by improved motor performance has been demonstrated.[56,57] Furthermore, based on the previous research, some neuroplastic changes in the brain might occur before the behavioral changes response to the auditory-cued training. One Positron Emission Tomography (PET) study revealed significant metabolic increment in the cerebellum, parietal and temporal lobes after the patients with PD carried out the auditory cueing-based physical rehabilitation program.[25] Nevertheless, gait parameters except for stride time variability after training did not differ from those obtained before training. According to the aforementioned, we may believe that the improvements in motor performances after cueing-based training is associated with the accumulation of series of neuroplasticity through serial motor training.

To explore the neuroplasticity in the human cortex, the application of the neuronal imaging techniques are needed. The common neuronal imaging techniques for human to demonstrate neuroplasticity include positron emission tomography (PET), electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Among them, TMS explore the neuroplasticity as measured the cortical plasticity. Delvendahl and colleagues[58] suggested that increased and decreased MEP amplitude, which reflects the strength of synaptic transmission, were assumed to present LTP-like or LTD-like synaptic

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plasticity of motor cortex output neurons. However, lack of studies provide the changes of neuroplasticity after the patients with PD carry out the cued-based training. It is uncertain that if any neurophysiological changes occur following the one-session cueing-based training. Through the application of TMS, we can further investigate whether any neuroplasticity occurs before the behavioral improvements.

Overall, despite few studies regarding the mechanism behind auditory cues, the neural mechanism of the beneficial effects of auditory cues might be through the CTC network to compensate the dysfunction of basal ganglia. Furthermore, neuroplasticity induced by motor training may play a crucial role for the patients with PD to improve their gait performances. Thus, the study of the neurophysiological changes has become an important aspect of understanding the effects of auditory cues for PD.

2.3 Treadmill training for patients with Parkinson's disease

2.3.1 Effects of treadmill training on behavior performance

Treadmill training is another common intervention for PD to improve gait performance. For the immediate effects, Pohl and colleagues[59] revealed that one session of treadmill training without body weight support for 30 minutes could improve gait speed and stride length in PD; whereas, the conventional gait therapy could not. Then Bello and colleagues[60] further investigated the effects of one session of treadmill training on gait in

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moderate and advanced PD during "on" medication. They reported that one session of treadmill training for 20 minutes significantly increased overground gait speed and step length, especially in advanced patients (Hoehn and Yahr stage 3). These effects maintained for 5 and 10 minutes after a treadmill session. However, stride time variability did not change after treadmill walking in ether moderate or advanced patients. The speed of treadmill in the above studies was set at each participants' self-selected comfortable speed. For the long-term effects of treadmill programs, they demonstrated the beneficial effect on gait speed and stride length in patients with PD after a period of training, which ranged from four weeks to eight weeks.[61,62] Although some treadmill training in above studies had weight bearing support, Toole and colleagues[63] reported the degree of weight bearing may not be crucial to achieving benefits of gait in patients with PD.

In general, these findings suggest that the treadmill training has therapeutic effects on gait in PD.

2.3.2 Effects of combined treadmill training and cueing (AC, VC, FOG)

Impaired internal rhythmic control, which is related to a dopaminergic deficiency of the nigrostriatal pathway, leads to the higher cadence, shorter step length, and higher stride time variability in PD. The auditory cues can bypass the dysfunctional neural network to improve the cadence, step length, and stride time variability in PD.

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Additionally, treadmill training can also act as an external cue to normalize the spatiotemporal gait parameter in PD.[64] As the patients with PD rely on allocating their attention to gait in order to modulate gait performances, the application of treadmill combined with auditory cues may potentiate positive effects on gait in comparison to single intervention alone.

Research by Chaiwanichsiri and colleagues,[21] they recruited thirty PD subjects and randomly allocated to three groups. One group received treadmill training with music cue for three days a week and home walking program for three days a week (group A). Another group received treadmill training alone for three days a week and home walking program for three days a week (group B). The other group received home walking program for six days a week (group C). The period of intervention was four weeks and followed by self-practice for other four weeks. The results indicated a significantly increased overground step length in group A. Group A had more step length than group B and C, and the effects maintained to the end of the eighth week. However, this study did not report the effects of the combined intervention is the same in freezers as well.

Only one study revealed the effects of treadmill training combined with auditory and visual cues in freezers. Frazzitta and colleagues[20] recruited forty PD subjects with FOG and randomly assigned into two groups. One group received treadmill training associated auditory and visual cues, and the other group received overground walking associated

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auditory and visual cues. Each group carried out training for 20 minutes every day for four weeks. The resulted demonstrated both groups had significant improvements in Unified Parkinson's Disease Rating Scale Motor Section (UPDRS III), Freezing of Gait Questionnaire (FOGQ), 6-minute walking test (6MWT), and gait speed. Cues associated with treadmill provided more improvements in UPDRS III, FOGQ, 6MWT, and gait speed than cues without treadmill. This study suggested the treadmill training associated with auditory and visual cues might provide better effects on gait in freezers compared to conventional treatments.

Although the intervention in Frazzitta et al[20] includes visual cues, this finding still give the possibility that freezers might obtain more positive effects from auditory cues combined with treadmill training. So far, lack of study investigates the different effects on gait between the freezers and non-freezers when they received treadmill training with auditory cues. The study regarding the effects of these interventions through neurophysiologic assessment is scarce. Therefore, more studies are needed to investigate whether there are differences in the neurophysiology and gait performance between the freezers and non-freezers after treadmill training with auditory cues.

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2.4 Transcranial magnetic stimulation

2.4.1 Introduction of transcranial magnetic stimulation (TMS)

In 1985, Barker and his colleagues[65] introduced transcranial magnetic stimulation (TMS) as a safe and non-invasive tool to activate the motor cortex and assess the integrity of the corticomotor pathways. Since its development, the use of TMS was widely applied for neurophysiological examination to explore different neurophysiological mechanisms. Its modulation of cortical excitability was also being developed as a therapeutic tool.[66] In this study, we focus on the diagnostic application of TMS.

The TMS is based on the principle of electromagnetic induction. The TMS machine consists of high-current generators and a magnetic coil, while our brain consists of many neural networks. A brief electric current passes through a magnetic coil, which is placed over the human's head, generating a perpendicular, high-intensity magnetic field, and then the secondary electric field is induced underlying the stimulated site of the brain. The stimuli usually focus on the primary motor cortex (M1). The secondary electric field induced the action potential in the cortical axons, and then the excitation travels along the corticospinal tract to generate muscle twitches or movements of the corresponding muscles according to the motor homunculus. The amplitude of the muscle response to TMS, which termed motor-evoked potential (MEP), is recorded by surface electromyography (EMG). The electrodes of EMG are attached to the muscle belly.

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2.4.2 Common TMS parameters for assessing cortical excitability

Various TMS parameters can provide the different information about cortical excitability, the functional integrity of intracortical neurons, the conduction along the corticospinal tract, and the peripheral neural pathway to the muscles. Such measurements are used to detect the neurophysiological changes of the brain in the setting of the cortical plasticity and brain disorder. Compared to other imaging techniques such as positron emission tomography (PET) and electroencephalography (EEG), TMS parameters can be rapidly acquired and they can provide close monitoring of relatively short-duration neuroplastic changes following experimental manipulation. According to the number of stimuli in a session, the diagnostic application of TMS can be classified into two modes: single-pulse TMS (spTMS) and paired-pulse TMS (ppTMS).[66] The TMS was applied to the primary motor cortex to obtain above assessments. The following are some common TMS parameters that we used in this study.

Single-pulse TMS (spTMS)

- Motor Evoked Potentials (MEPs)

  While TMS is applied to the motor cortex at appropriate stimulation intensity, MEPs are generated through activation of the motor cortex and the corticospinal pathways. The amplitude of MEP reflects the integrity of the cortical tract as well as the excitability of motor cortex, nerve roots, and the conduction along the peripheral

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motor pathway to the muscles.[66] If the TMS is delivered on the M1 under the condition of relaxed target muscle, the MEP that induced is called resting MEP. In contrast, if the TMS is delivered on the M1 under the condition of activated target muscle, the MEP that induced is called active MEP.

- Hot Spot

  The hot spot was defined as the site that can induce the most consistent and prominent MEPs with the shortest latency.[67] It was an optimal stimulation site that represents the target muscle corresponding to the brain. The stimulus intensity was represented by the percentage of maximal stimulator output (MSO).

- Motor Threshold (MT)

  The motor threshold includes resting motor threshold (RMT) and active motor threshold (AMT). The RMT is defined as the minimum stimulus intensity that can induce at least 50μV of MEP in at least 5 of 10 trials under complete muscle relaxation[68], while the AMT is induced under slightly contracted target muscles.[67,68] The MT reflects the neurons' excitability and their local density.[69]

- Cortical Silent Period (CSP)

  The CSP was a period of suppressed EMG activity occurring immediately after the MEP induced by TMS. It is only induced under the condition of activated muscle while the suprathreshold stimulation is delivered. The CSP is defined as the time

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from the end of the active MEP to the return of EMG activity.[66] However, it is difficult to define the end of the MEP in patients with corticospinal tract dysfunction, so some researchers define the CSP as the time interval from stimulus delivery to the return of voluntary activity.[70] The CSP reflects long-lasting corticospinal inhibitory mechanisms. The cortical inhibition is mediated by gamma aminobutyric type B receptors ($GABA_BR$).[71]

Paired-pulse TMS (ppTMS)

- Short Intracortical Inhibition (SICI) and facilitation (ICF)

  The ppTMS can assess the intracortical inhibitory and facilitatory mechanisms through delivering a subthreshold conditioning stimulus (CS) and a suprathreshold test stimulus (TS). A conditioning stimulus is followed by a test stimulus at different inter-stimulus intervals (ISI). Different MEPs responses depend on the stimulus intensity and the ISI. SICI is obtained at ISIs of 1-4ms, which reflects inhibitory effects.[69] In terms of facilitatory effects, the ISI at 7-20ms is applied, which called ICF.[69] SICI is mediated by gamma aminobutyric type A receptors ($GABA_AR$)[72] while ICF is likely mediated through N-methyl-D-aspartate (NMDA) glutamate receptors.[73]

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2.4.3 Abnormal cortical excitability in Parkinson's disease

Since the primary motor cortex (M1) is an important target of basal ganglia output, dysfunction of the basal ganglia–thalamocortical (BGTC) circuit in PD leads to functional disturbances of the motor cortex. Such alteration in cortical excitability of M1 can be assessed through TMS. This imaging technique can detect whether facilitatory or inhibitory changes in motor cortex. The majority of TMS studies focused on the hand area of the more affected brain to investigate the cortical excitability in PD. According to the review of Cantello and colleagues,[74] most studies indicated that RMT in PD was no differences in comparison to the healthy controls. Increased MEP amplitude at resting muscle, shortened duration of CSP, reduced SICI and ICF were found.[74-76] These findings suggested the cortical excitability in PD revealed excessive corticospinal output at rest and reduced intracortical inhibition.

As for the corresponding cortical excitability of the lower limbs area, two studies explored this issue. Tremblay and colleagues[77] recruited 10 patients with PD to investigate the cortical excitability of the quadriceps muscles. As the patients were assessed during "on" medication, decreased RMT, increased MEP amplitude at rest, and longer duration of CSP were noted in comparison to the healthy controls; whereas, when four out of ten patients were evaluated during "off" medication, all parameters except for the duration of CSP were similar to "on" medication. They exhibited the shorter duration

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of CSP during "off" medication compared to "on" medication. It suggested that the dopaminergic medications may normalize the duration of CSP, which reflects the corticospinal inhibition. However, another study reported by Vacherot and colleagues[78] indicated inconsistent results. They recruited 24 patients with PD and 9 healthy controls to explore the cortical excitability of the tibialis anterior muscle. The results displayed that RMT, amplitude of MEP at rest, duration of CSP, and SICI had no differences between groups and medication states. The only reduction in ICF was noted in PD in comparison to the healthy controls and decreased ICF could be partially normalized during "on" medication. The summarized contents are presented in table 1.

Overall, the patients with PD revealed abnormal cortical excitability, especially in the duration of CSP and paired-pulse parameters. The medicine may modulate the cortical excitability. Despite this, there is the paucity of information regarding TMS evaluation over the lower extremity. Therefore, further evidence concerning the changes in the cortical excitability of the lower limbs in PD is needed to draw a clear conclusion.

2.5 Summary of review

Parkinson's disease (PD) is a common neurodegenerative disorder due to a dopaminergic deficiency in the basal ganglia. Dysfunction of dopaminergic cells in basal ganglia leads to deficits in internal timing and automatic execution of movements such as

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gait disturbances. Moreover, freezing of gait (FOG) is one of the disabling gait disturbances. Freezers exhibits more gait instability, which related to stride time variability, than non-freezers. In order to ameliorate the impaired automatic motor performance, the utilization of auditory cues can provide the temporal stimuli to regular the timing of gait. Despite abundant studies concerning the effects of auditory cues on gait in PD, most of them focused on overground walking and long-term training for several weeks and the literature assessing the role of auditory cues on FOG are scarcer and controversial. Treadmill training, which can also act as an external cue, also provides the favorable effects on the gait pattern for patients with PD. More recently, the application of treadmill combined with auditory cues may potentiate positive effects on gait in comparison to treadmill training alone. The potential mechanism behind auditory cues might be through the cerebellar–thalamocortical (CTC) network to compensate the dysfunction of basal ganglia. Furthermore, since neuronal plasticity is associated with improved motor performance, the improved gait pattern after cueing-based trainings may come from the accumulation of series of neuroplasticity through serial motor training. Thus, the neuroplasticity in the brain plays a crucial role for the patients with PD to improved motor performances. In order to explore the neuroplasticity in the brain, transcranial magnetic stimulation (TMS) can be applied to demonstrate the cortical plasticity through assessing the cortical excitability. For the patients with PD, they

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exhibited abnormal cortical excitability, especially in the duration of CSP and paired-pulse parameters, which reflects long-lasting corticospinal inhibitory mechanisms and the intracortical inhibitory and facilitatory mechanisms respectively. However, current studies provide little information on how the auditory cues work in the brain. Furthermore, scarcer studies explores the different effects of auditory cued-based training on neurophysiology and gait performance between freezers and non-freezers. Therefore, it is worth for us to investigate whether the cortical excitability can be modulated through auditory-cued treadmill training and further explore whether there are the different changes in cortical excitability and gait performance between freezers and non-freezers.

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Chapter 3 Methods

3.1 Study design

This is a crossover study. Patients with PD were recruited and classified into freezer group (FOG) and non-freezer group (nFOG) based on the first question of new freezing of gait questionnaire (NFOG-Q).[42] The healthy subjects were also recruited as the control group. All subjects were involved in baseline evaluation and randomly participated in training under two conditions with at least one-week washout interval. Two conditions were treadmill training with (AC condition) and without rhythmic auditory cues (NC condition). The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital (Appendix A).

3.2 Subjects

This study recruited subjects with PD and healthy subjects. Subjects with PD were recruited from the Department of Neurology, the Physical Therapy Center, and the Parkinson Center at National Taiwan University Hospital. Subjects with PD were enrolled if they (1) were 20 years old and over, (2) diagnosed with idiopathic Parkinson's disease by neurologists, (3) classified as stages I through III on the Hoehn and Yahr rating scale, (4) able to walk independently without device, (5) no hearing impairment; (6) able to

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follow instructions (Mini-Mental State Examination score ≧ 24). Participants were divided into the freezer group (FOG) or non-freezer group (nFOG) based on their response to the first question of NFOG-Q: *Did you experience "freezing episodes" over the past month?* We demonstrated a video about freezing episodes to make sure subjects fully understood what freezing symptoms are. Participants were categorized as FOG group if their response was 1. They were placed in nFOG group if their response was 0.

Subjects with PD were excluded if they have (1) past histories of neurological or musculoskeletal disorder that might interfere with ambulation (e.g. stroke), (2) psychological diseases, (3) unstable cardiovascular and respiratory status, (4) dementia, (5) uncorrected visual disturbances that affect gait performance (e.g. blind people), (6) contraindications of receiving TMS assessments including family history of epilepsy, being pregnant, having a cardiac pacemaker, brain trauma, or metal implants in the brain. The purposes and procedures were fully explained to the subjects. Participants signed the informed consent forms (Appendix B) and TMS safety questionnaire (Appendix C) before the experiments.

3.3 Procedure

All participants received treadmill training with (AC condition) and without rhythmic auditory cues (NC condition) in random order by using a computer-generated

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random number. Two conditions were at least one-week washout interval. Basic data collections included age, gender, onset duration, modified Hoehn and Yahr stage, Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Examination (MMSE), New Freezing of Gait Questionnaire (NFOG-Q). The above data were obtained from the subjects' interviews or assessed by the researcher. All participants were evaluated the cortical excitability and motor performance before and after training. Patients were asked to withdraw their dopaminergic drugs overnight at least 8 hours in order to eliminate the influence of medications on the outcome measures. A flow chart of this study is presented in Figure 1.

3.4 Interventions

All participants received a single session of treadmill training in two condition (AC and NC condition) with at least one-week interval. The treadmill (Model AG-2000, Aerogym trading company, Taichung, Taiwan) was used in this study. A suspension with no body weight support was provided for safety concern. We made sure that the suspension would not interfere with participants' walking performance. All participants walked on the treadmill while holding the handrails (Figure 2). The treadmill was set at 0% incline and the training session lasted 30 minutes. Patients could rest 1-3 minutes if they subjectively feeling tired during the training. However, the resting time did not

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include in our intervention time.

3.4.1 Treadmill training with rhythmic auditory cues (AC condition)

We used the metronome from the YouTube as the auditory cues. The cued frequency was set at 110% of subject's comfortable cadence on the treadmill because this cued frequency might provide the beneficial effects on the kinetic characteristic of gait and walking stability based on the previous studies.[18,79,80] Participants were asked to synchronize with the rhythmic auditory cues on the treadmill for 30 minutes. The participants could ask for alternating treadmill speed in order to synchronize with auditory cues.

3.4.2 Treadmill training without rhythmic auditory cues (NC condition)

The treadmill velocity was set at the subject's comfortable walking speed on the treadmill. Participants walked comfortably on the treadmill without auditory cues for 30 minutes.

3.5 Outcome measurements

To determine the effects of treadmill training combining with auditory cues, two domains were evaluated before and after intervention: cortical excitability and motor performance. For the cortical excitability, resting and active amplitude of motor evoked

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potentials (MEPs), cortical silent period (CSP), short intracortical inhibition (SICI), and intracortical facilitation (ICF) were used to record the changes in cortical excitability. For the motor performance, 10-meter walking test was selected to evaluate step time variability and gait pattern.

3.5.1 Primary Outcome measures-Cortical Excitability

Transcranial Magnetic Stimulation (TMS)

The TMS was applied using Magstim BiStim^2 stimulator (The Magstim Company, Whitland, UK) through a double cone coil. Electromyography was recorded using surface electrodes positioned over the tibialis anterior (TA) muscle of the more symptomatic side. Participants were instructed to sit in a comfortable chair with backrest and keep their arms in a relaxed position. They wore the swimming cap, which consisted of one-by-one centimeter points allowing an exact positioning of the TMS coil. The coil was placed over the interhemispheric sulcus and moved around (Figure 3). Once the optimal stimulation site, called "hot spot", was identified, using pen marked the site on the cap to ensure consistent coil placement. After the hot spot was identified, the stimulus intensity would be reduced in steps of 2% maximal stimulator output (MSO) to measure the resting motor threshold (RMT). The RMT was defined as the minimum stimulus intensity that can induce at least 50μV of MEP in at least 5 of 10 trials under complete muscle relaxation.[68]

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Experimenters asked and supervised participants to stay awake during the procedure. Acqknowledge 4.2.1 software (Biopac Inc, California, USA) was used for data acquisition and analysis. Before and after TMS, the participants were asked if they had any adverse effects such as headache, or worsened symptoms.

TMS measurements included amplitude of resting and active MEPs, CSP, SICI, and ICF. Each measurements contained 7 times of stimulus. Each stimulation was separated by at least 5s in order to avoid carryover effects. The followings were the detail of each parameters.

- Resting motor evoked potentials (MEPs): Resting MEPs were measured at 130% of RMT when subjects completely relaxed the target muscle. The MEPs value were recorded the peak-to-peak amplitude of EMG response.
- Cortical silent period (CSP) and active MEP: CSP is a period of suppressed EMG activity following after the MEPs induced by TMS.[67] CSP were measured by single TMS stimulus at 130% of RMT, while subjects executed voluntary contraction of their tibialis anterior muscle. They did dorsifleixon to a given target, and then the stimulus were given in random timing during executing action. CSP duration was recorded from stimulus delivery to the return of voluntary activity. The active MEPs value was recorded the peak-to-peak amplitude of EMG response.
- Short intracortical inhibition (SICI), and intracortical facilitation (ICF): The SICI and

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ICF were obtained using paired-pulse TMS under complete muscle relaxation. The conditioning stimulus (CS) was set at 80% of RMT, and the test stimulus (TS) was set at 130% of RMT. The interstimulus intervals (ISIs) included 2, 3, 7, 10, and 12ms. The ISIs of 2 and 3ms represented SICI and the ISIs of 7, 10 and 12ms represented ICF.[81] Different interstimulus intervals were randomly given. The SICI and ICF were recorded through the peak-to-peak amplitude of the EMG response and were divide by the mean value of MEP. They were expressed as the percentage of MEP.

3.5.2 Secondary Outcome measures-Gait Performance

10-meter walking test

All participants walked on a 10-m walkway in two conditions: (1) comfortable walking speed (CWS); (2) fast walking speed (FWS). Each condition included three walking trial. The spatiotemporal parameters of gait were recorded by two inertial sensor system Physilogs® (GaitUp, Switzerland). The participants wore the sensors that attached to the shoes during walking test (Figure 4). These inertial sensor system Physilogs® had an excellent test-retest reliability.[82]

The measures included step time variability, walking speed, cadence, and stride length. Step time variability was quantified using the coefficient of variation (CV) of step time, which was calculated as follows: (standard deviation of the step time/mean of the

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step time) x100.

3.6 Statistical analysis

Descriptive statistics were performed to present demographic characteristic of the three groups and be expressed as mean ± standard deviation. The Shapiro-Wilk test and the Levene's test was conducted respectively to test variables for the normality of distribution and homogeneity. Independent t-test was used for between-groups comparison on demographic and clinical characteristics. Mann-Whitney U test was applied on those variables that violate the normality. In order to determine the effects of auditory-cued treadmill training on the neurophysiological parameters and gait performance for PD, we used the three-way repeated measures (RM) analysis of variance (ANOVA) with factors 'Group' (PD, and healthy controls), 'Cue' (with and without auditory cues), and 'Time' (baseline and posttest). To further investigated the different effects of auditory-cued training between freezers and non-freezers, the three-way repeated measures analysis of variance (ANOVA) with factors 'Groups' (freezers and non-freezers), 'Cue' (with and without auditory cues), and 'Time' (baseline and posttest) was carried out. The statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

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Chapter 4 Results

4.1 Demographics and baseline characteristics of patients and healthy adults

Subjects with PD were recruited from April 2018 to July 2018 through department of Neurology and Physical Therapy Center of National Taiwan University Hospital. Twenty-seven patients met the inclusion criteria, but 9 patients refused to participate in this study. Eighteen patients agreed to withdraw their medication for at least 8 hour before the experiments. Nine patients were allocated to freezer (FOG) group and the other nine patients were allocated to non-freezer (nFOG) group. Nine healthy subjects participated in this study. All of subjects understood the experimental procedures and signed the consent form. One subjects in the FOG group dropped out during training due to fatigue even if he took a rest. Therefore, 8 subjects in the FOG group, 9 subjects in the nFOG group, and 9 subjects in the control group completed the two training across one week. No one reported any adverse event or discomfort. The flow chart is presented in Figure 1.

Subjects' baseline demographic information and clinical characteristics are summarized in Table 2. There were no statistically differences between the PD and control group in age (p =0.766) and MMSE (p =0.862). Comparison between the FOG and nFOG group also showed there were no significant differences in disease duration (p =0.906), Hoehn and Yahr scale (p =0.703), and UPDRS-motor part (p =0.155). The FOG group

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presented significantly poorer performance on MMSE (p =0.034) and NFOGQ (p <0.001) compared to nFOG group.

4.2 Transcranial magnetic stimulation

The TMS variables were compared between the PD and control group first. Then the comparison between the FOG and nFOG group was conducted.

4.2.1 Motor evoked potentials

The 2x2x2 three-way RM-ANOVA analysis demonstrated there were no significant differences in MEP (p =0.801) and active MEP (p =0.645) between the PD and control group (Table 3) as well as between the FOG and nFOG group (MEP: p =0.132; active MEP: p =0.699) (Table 4).

4.2.2 Cortical silent period

RM-ANOVA analysis yielded no Group x Cue x Time interaction on CSP duration for a comparison of the PD and control group (p =0.283), but significant effects of the group x time interaction (p =0.031) and time (p <0.001) were noted (Table 3). Post hoc analysis indicated that CSP duration significantly increased in the PD group (p <0.001) after training, but not in the control group (p =0.392).

Furthermore, for a comparison of the FOG and nFOG group, RM-ANOVA analysis

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revealed no Group x Cue x Time interaction on CSP duration (p =0.283). However, a significant time main effect for lengthened CSP duration in FOG and nFOG group (p <0.001) was noted (Table 4).

4.2.3 Intracortical inhibition and facilitation

RM-ANOVA analysis yielded no Cue x Group x Time interaction on $SICI_{(2ms)}$, $SICI_{(3ms)}$, $ICF_{(7ms)}$, $ICF_{(10ms)}$, and $ICF_{(12ms)}$ (all variables: p >0.05) between the PD and control group (Table 5 and Figure 5, 6). Nevertheless, there were significant time main effects for $SICI_{(2ms)}$ (p =0.003), $ICF_{(10ms)}$ (p =0.009), and $ICF_{(12ms)}$ (p =0.009), indicating both the PD and control groups decreased $SICI_{(2ms)}$, increased $ICF_{(10ms)}$, and $ICF_{(12ms)}$ after training.

Moreover, RM-ANOVA analysis demonstrated there were no significant differences between the FOG and nFOG group in any of the variables for ppTMS (Table 6 and Figure 7).

4.3 Gait performance

The gait variables were compared between the PD and control group first. Then the comparison between the FOG and nFOG group was conducted.

4.3.1 Comfortable walking speed (CWS)

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RM-ANOVA analysis revealed there were no significant effect of Cue x Group x Time interaction on step time CV, speed, cadence, and stride length in CWS for a comparison of the PD and control groups. A significant time main effects were found for speed (p =0.006) and stride length (p <0.001), indicating both the PD and control groups increased speed and stride length after training (Table 7).

In terms of a comparison of FOG and nFOG group, RM-ANOVA analysis yielded no significant Cue x Group x Time interaction effect on step time CV, speed, cadence, and stride length (all variables: p >0.05) in CWS (Table 8). A significant time main effect on stride length (p =0.002) were found, indicating both the FOG and nFOG group increased stride length after training. Moreover, a significant effect of Group x Time interaction on step time CV (p =0.034) was noted. 2x2 (Group x Time) RM-ANOVA analysis for the FOG and nFOG group further indicated there was no Group x Time interaction (p =0.056) on step time CV as well as group (p =0.077) and time (p =0.751) main effect. However, the step time CV in the FOG group presented a downward tendency after training, whereas the non-freezers presented an opposite picture (Figure 9).

4.3.2 Fast walking speed (FWS)

RM-ANOVA analysis yielded no significant Cue x Group x Time interaction effect on step time CV, speed, cadence, and stride length in FWS for a comparison of the PD

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and control groups (Table 9). A significant time main effect was found for decreased cadence (p =0.038) after the PD and control groups receiving the training. There were significant effects of Cue x Group interaction (p =0.035) and Cue main effect (p =0.013) in step time CV. 2x2 (Cue x Group) RM-ANOVA analysis for the PD and control group further showed there was no significant Cue x Group interaction but a significant cue main effect was found for step time CV (p =0.041), indicating both PD and control groups presented decreased step time CV in AC condition. Additionally, 2x2x2 (Group x Cue x Time) RM-ANOVA analysis yielded a significant effect of Cue x Group interaction for stride length (p =0.023). Further analysis through 2x2 (Cue x Group) RM-ANOVA revealed there were Cue x Group interaction (p =0.011) and group main effect (p <0.001). The cue main effect did not yield significant (p =0.253). Post hoc analysis revealed the PD group had significant shorter stride length in comparison of the control group (p <0.001).

In terms of comparison of FOG and nFOG group, RM-ANOVA analysis demonstrated that there was no significant effect of Cue x Group x Time on step time CV, speed, cadence, and stride length in FWS. The main effect of Cue and Time did not reach significant in all of the above variables (Table 10).

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Chapter 5 Discussion

This study aims at investigating the effects of auditory-cued treadmill training for a single session on the cortical excitability and gait performances in patients with PD. Moreover, due to the multifactorial nature of FOG, some evidence indicated that the freezers and non-freezers had different neural images, motor performances, and responses to interventions. However, scarcer studies investigated the differential effects of auditory-cued intervention between patients with and without FOG. This study probed into the effects of auditory-cued treadmill training and further compared the changes in cortical excitability and gait performances between these two groups of patients.

5.1 Effects of auditory-cued treadmill training on cortical excitability

Two major findings were found in this study. First, either treadmill training alone or auditory-cued treadmill training significantly lengthened the CSP duration in PD, but not in healthy adults (Table 3 and Table 11). Several studies revealed the CSP duration is shorter in PD in comparison with healthy adults,[74,83] which reflects the reduced corticospinal inhibition. This finding suggested treadmill training whether with or without auditory cues are capable of inducing increased corticospinal inhibition in PD. Since the corticospinal inhibitory mechanism is mediated by γ-aminobutyric acid ($GABA_B$) receptors,[71] we supposed that treadmill training whether with or without auditory cues

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may modulate the $GABA_B$ neural network.

Accumulating evidence indicated that GABA receptors play a crucial role in the pathogenesis of PD. $GABA_B$ receptor levels are increased in the internal segments of the globus pallidus (GPi)/ pars reticulate (SNr) and decreased in the external segments of the globus pallidus (GPe), which seem to be compensatory responses for the hypoactive direct pathway and hyperactive indirect pathway in PD.[84] Based on the animal study, treatment with baclofen, which acted on the $GABA_B$ receptor, significantly improved locomotor and attenuated the neuro-inflammation in rats with MPTP induced Parkinson's disease.[85] It suggested that modulation of $GABA_B$ receptor-mediated responses may provide benefits on improved parkinsonian symptoms. In our study, the lengthened CSP duration after treadmill training whether with or without auditory cues may be associated with changes in motor performance.

Furthermore, our finding in training-induced lengthened CSP duration in PD is consistent with previous studies. Fisher et al.[62] revealed lengthened CSP duration was found in PD after high-intensity treadmill training for 24 sessions over 8 weeks, whereas the low-intensity exercise group and zero-intensity education group did not. Concurrently, they found PD subjects presented increased gait speed and step length after high-intensity treadmill training. Yang et al.[86] indicated both the rTMS plus treadmill training and treadmill training alone for 12 sessions over 4 weeks could induce prolongation of CSP

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duration in PD. They also found PD obtained increased fast walking speed after training. Both the studies showed lengthened CSP duration accompanied by gait improvement; however, the precise role that corticospinal inhibition plays in motor performance remains unclear.

We further explored whether the different effects of auditory-cued treadmill training existed between the freezers and non-freezers. The results demonstrated both types of patients achieved enhanced corticospinal inhibition as long as they carried out one-session treadmill training. Based on the previous study from our laboratory, the freezers rather than non-freezers had significantly lengthened CSP duration after auditory-cued stepping-in-place (SIP) training, but not SIP training alone. Since the effects of auditory cues did not obviously demonstrate in this study, in order to compare with the previous data, we tried to deeply analyze the CSP data for the freezers and non-freezers in two condition (AC and NC). In this study, we found that the non-freezers had significantly lengthened CSP duration in AC and NC conditions after training (p=0.007 and p=0.008, respectively), whereas the freezers attained significantly lengthened CSP duration only in AC condition (AC: p=0.032; NC: p=0.257) (Table 4 and Figure 8). It seems that the effects of auditory cues have more impact on corticospinal inhibition for the freezers.

The second finding in our study was that both PD and control groups presented reduced $SICI_{(2ms)}$, increased $ICF_{(10ms)}$ and $ICF_{(12ms)}$ after treadmill training whether with

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or without AC (Table 5 and Table 11). SICI and ICF reflect interneuron influences in the cortex. SICI represents intracortical inhibition mediated via $GABA_A$ receptors,[72] whereas ICF represents intracortical facilitation that is likely mediated through N-methyl-D-aspartate (NMDA) glutamate receptors.[73] Patients with PD are revealed a failure of the inhibitory cortical circuit,[26] therefore, their nature brain is in excessive excitatory status. In our study, reduced SICI and increased ICF represented less inhibition and more facilitation in the cortical level after training. However, there is only one study revealed increased SICI after long-term intervention in PD.[86] Yang et al. demonstrated PD subjects achieved increased SICI after rTMS plus treadmill training for 12 sessions over 4 weeks.[86] Our study different from Yang et al. may be due to different interventional duration. If PD subjects received more sessions of auditory-cued treadmill training, the similar outcome regarding changes in SICI may be found after training. For the ICF, although one research indicated modulated ICF through drug therapy is relative to improved gait speed and stride length,[87] it is still unclear how ICF changes and what it works after one-session intervention in PD.

Despite current explanation to changes in SICI and ICF for PD is unclear, some research suggested healthy subjects obtained changes in cortical plasticity of the leg area after one-session motor training. Similar to our finding, Perez et al.[56] revealed the healthy subjects presented reduced SICI after motor skill training involving ankle control

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movements for a 32-min single session but not in non-skill and passive training. Yamaguchi et al.[88] also demonstrated the healthy subjects represented reduced SICI after receiving one-session 7-min low-intensity active pedaling exercise rather than passive pedaling and repetitive ankle dorsiflexion. It seems that changes in cortical plasticity play a crucial role in motor training. Reduced SICI after one-session treadmill training whether with or without AC in our study may be a precursor of long-term plasticity in the brain.

5.2 Effects of auditory-cued treadmill training on gait performance

In our study, the step time CV in comfortable walking speed had no improvement in PD and control groups after they carried out training under both AC and NC condition (Table 7 and Table 11). Nevertheless, we found a trend for different effects in step time CV in comfortable walking speed between the freezers and non-freezers (Figure 9 and 10). The freezers presented a downward trend in step time CV under both AC and NC condition, whereas the non-freezers presented an opposite picture. Additionally, the participated freezers felt more comfortable when the auditory cues were given in treadmill training. Based on previous research, not only the auditory cues but the treadmill acts as the external cues.[64] The freezers in comparison of the non-freezers may more rely on external cues to enhance gait rhythmicity and reduced gait variability through goal-directed control.

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Moreover, according to the resource-competition model,[89] attention is assumed as a capacity-limited resource. When performing automatic controlled task combined with another cognitive task, both tasks compete for the same attentional resource. If the attentional requirements of both tasks exceed their capacity, the concurrent tasks interfere with each other and lead to adverse effects on the performance. Therefore, the non-freezers presenting obviously increased step time CV after treadmill training with AC may be attributed to the outcome of attentional resource-competition and these impact carried over to overground walking.

In terms of stride length in comfortable walking, we found all the participants increased stride length after the training whether with or without the auditory cues. These results suggest the effects of the treadmill training carry over into an improvement in overground walking. These results are consistent with the previous studies that revealed improved overground-gait performances after one-session of treadmill training.[59,60]

5.3 Treadmill may act as another external cues

The results revealed that one-session treadmill training whether with or without auditory cues had an obvious impact on modulated cortical excitability and increased step length in comfortable walking speed for PD subjects. That is, the obvious effects on the cortical excitability and gait performance mainly come from the treadmill training. Some

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studies indicated treadmill may act as external cues.[64,90] Therefore, insignificant effects of auditory cues on cortical excitability and gait performance in this study may be attributed to the treadmill training, which played as another external cue.. However, we could still find some effects of auditory cues, which had the impact on CSP duration in freezers. Thus, if PD subjects would like to achieve more benefits from the auditory cues to enhance stable rhythm of the movements during treadmill training, increased training sessions may be needed. The previous research in the next section supports this opinion.

5.4 Impact of the interventional duration on the effects of the auditory-cued treadmill training

So far, the research regarding the auditory-cued treadmill training includes two characteristics. One is often investigating gait performance and the other is carried out the intervention for a period of time (from 4 weeks to 8 weeks). This is the first study explored the effects of the one-session auditory-cued treadmill training compared to the treadmill alone on the cortical excitability and gait performance in PD, and further dig into distinguishing the differences between the freezers and non-freezers.

For the gait performance, the study by Chaiwanichsiri et al.[21] indicated the PD subjects, who received music-cued treadmill training plus home walking program, had increased step length after training for 8 weeks. In contrast, PD subjects, who received

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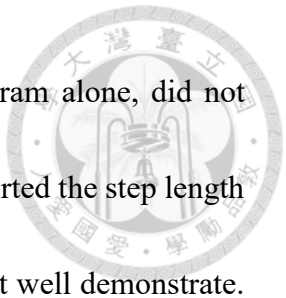

treadmill alone plus home walking program or home walking program alone, did not show the positive effects on gait as training with cues. Our study reported the step length increased after training, but the benefit from the auditory cues did not well demonstrate. This may implicate that a single session of auditory-cued treadmill training is not enough to cause obvious effects on the gait performance. If we would like to reproduce the effects that the auditory-cued treadmill training is superior to the treadmill training alone, the PD subjects may require more sessions of training to embed learned rhythm into walking.

For the freezers, there was only one research revealed the effects of external-cued treadmill training on gait performance. The work by Frazzitta and colleagues[20] indicated the freezers had improved gait speed and decreased FOG-Q after treadmill training associated auditory and visual cues for every day over four weeks rather than external-cued overground-walking training. This finding indicated the freezers may achieve more positive effects from treadmill training combined with the external cues. Nevertheless, in our study, the benefits from one-session auditory-cued treadmill training is not enough to demonstrate the obvious effects on gait in the freezers and fewer different effects are noted between the freezers and non-freezers. These findings may implicate again that the duration of the auditory-cued treadmill training should be considered.

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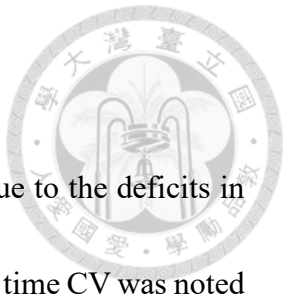

5.5 Clinical implication

Gait disturbance is a major concern for the patients with PD. Due to the deficits in internal timing and automatic execution of movements, increased step time CV was noted during PD subjects walking, especially in the freezers. To improve their temporal stride regulation, the utilization of auditory cues is a well-documented way to prompt their gait pattern more regular. Moreover, through detecting the changes in neuroplasticity as measured through cortical excitability, we could understand whether the interventions are effective and further explore the different effects of auditory cues between the freezers and non-freezers.

This study revealed that modulated cortical excitability, increased step length and gait velocity in comfortable walking speed were noted in patients with PD after one-session treadmill training whether with or without auditory cues. This may be due to treadmill training played as another external cue. The effects of a single session treadmill training with auditory cues can be only found in the CSP duration of the freezers. Compared to other long-term interventional research, one-session auditory-cued treadmill training may not be enough to demonstrate the obvious effects of auditory cues. If PD subjects would like to achieve more benefits from the auditory cues to enhance stable rhythm of the movements during and after treadmill training, increased interventional duration will be considered.

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5.6 Limitation and future study

There are two limitations in this study. First, the sample size is not sufficient in this study. Although the changes of CSP duration in AC condition in PD subjects reached medium effect size, the achieved power was 0.5. The patients with PD have variations, therefore a larger sample size is needed in order to get a reliable power.

Second, 110% of the subject's comfortable cadence on the treadmill may not be the best auditory-cued frequency in the treadmill training. We selected the 110% as our intervention according to the previous studies, which indicated that the cued frequency at 110% of cadence during comfortable overground walking might provide better effects on step length, gait speed, and step time CV.[18,79,80] Nevertheless, it is uncertain that whether this cued frequency could provide similar effects during treadmill walking. So far, there is no study about the effects of different auditory-cued frequency in the treadmill training for PD.

For the future study, research regarding long-term auditory-cued treadmill training and further investigating the different effects of auditory cues on neurophysiology and gait performance between the freezers and non-freezers should be needed. Furthermore, exploring the utilization of appropriated auditory-cued frequency during treadmill walking should be taken into account. Finally, the type of auditory cues is a noteworthy issue. Metronome we used is easily applied. Nevertheless, recently, there has been

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growing interest in action-relevant sounds, such as music and footstep sounds.[91] This is the potential factor that may influence the interventional efficiency. Thus, we should also take this into consideration in the future.

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Chapter 6 Conclusion

This is the first study to investigate the immediate effects of auditory-cued treadmill training for one-session on cortical excitability and gait performance in patients with PD. Moreover, this study further explored the different effects of auditory cues in freezers and non-freezers. The results showed that one-session treadmill training whether with or without auditory cues played a major role in modulated cortical excitability, increased step length and gait velocity in comfortable walking speed in PD subjects. We also found the auditory cues with treadmill training enhanced the corticospinal inhibition in both freezers and non-freezers. However, this phenomenon cannot be found in freezers when they received treadmill training without cues. Additionally, the freezers had a tendency to perform decreased step time CV after training. In contrast, the non-freezers had a tendency to perform increased step time CV after training.

In summary, the auditory-cued treadmill training may be a treatment strategy to be considered in clinical application. However, research regarding long-term training, choice of cued frequency, and type of auditory cues is needed.

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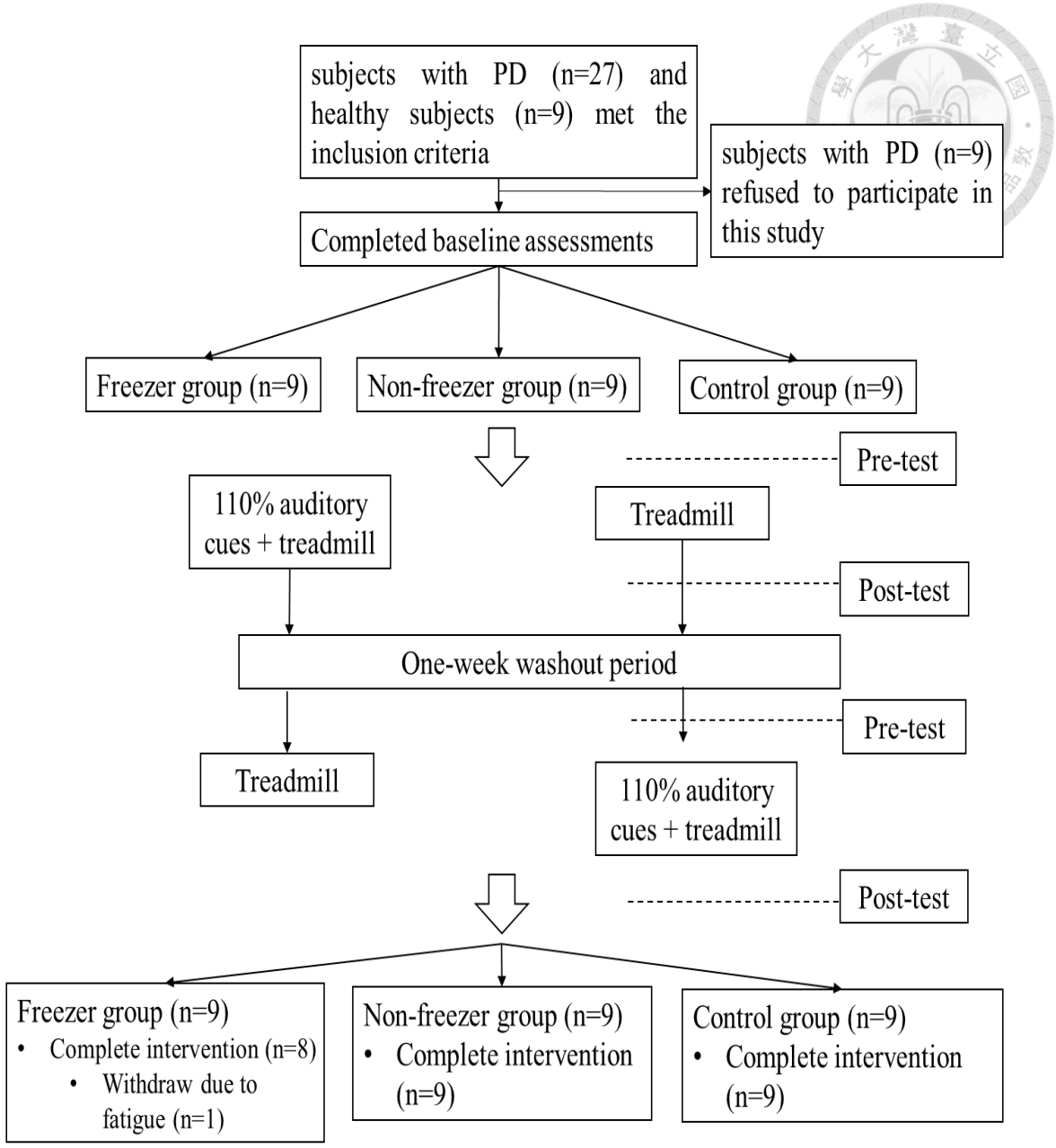

Figure 1. Flowchart of the study

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(A) (B)

Figure 2. Treadmill training from (A) lateral view, and (B) posterior view

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(A)

(B)

(C)

Figure 3. Transcranial magnetic stimulation (TMS).

(A) a double cone coil; (B) setting of the TMS; (C) the placement of the coil over the scalp

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(A) (B)

Figure 4. The placement of the inertial sensor system Physilogs® on the subject from (A) lateral view, and (B) anterior view

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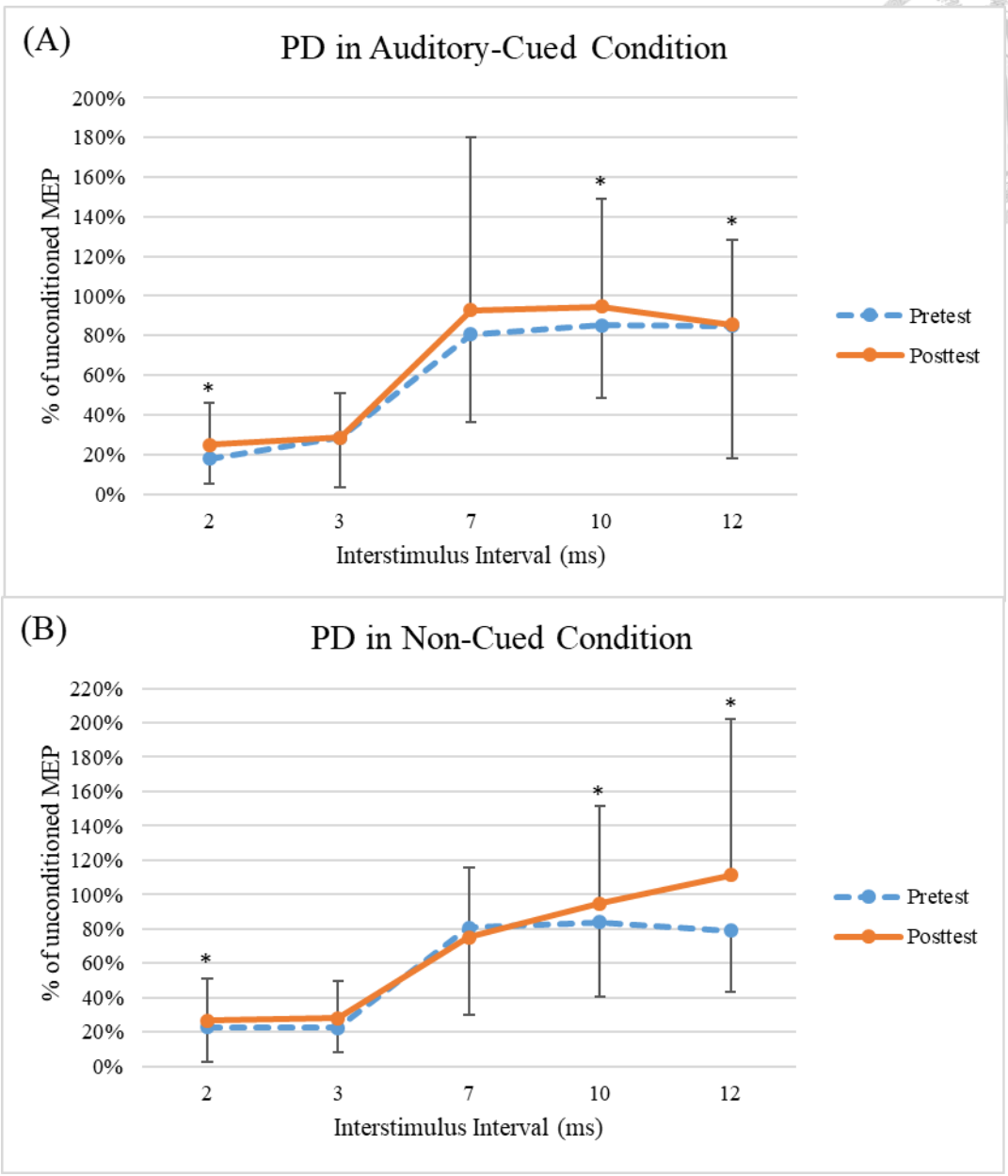

Figure 5. Paired-pulse TMS in the PD group (A, B).

(A) under auditory-cued condition; (B) under non-cued condition. MEP: motor evoked potentials; dotted line represents pretest and the solid line represents the posttest;

*: $p<0.05$ on time main effect for a comparison of PD and control group by RM-ANOVA

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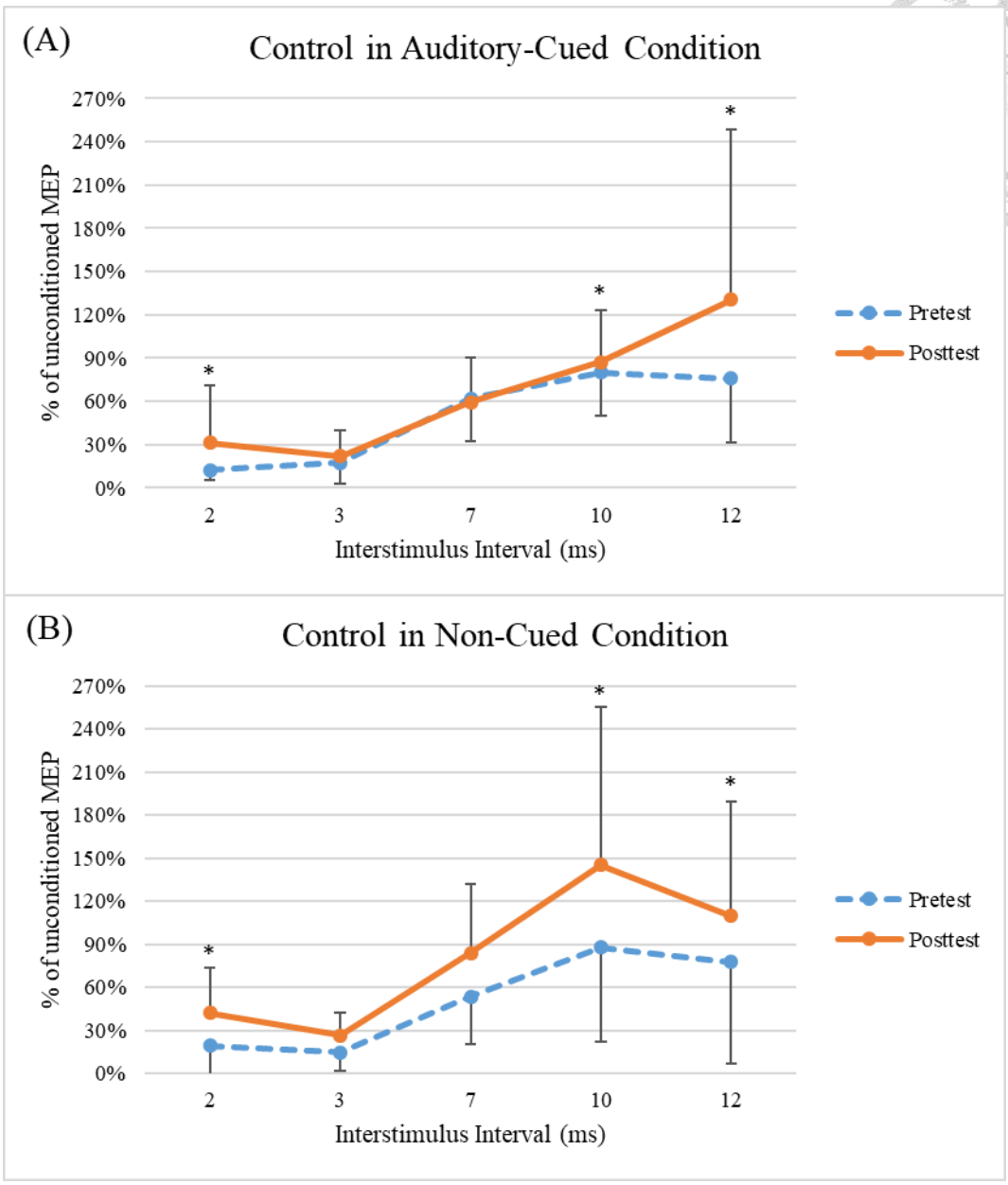

Figure 6. Paired-pulse TMS in the control group (A, B).

(A) under auditory-cued condition; (B) under non-cued condition. MEP: motor evoked potentials; dotted line represents pretest and the solid line represents the posttest;

*: $p<0.05$ on time main effect for a comparison of PD and control group by RM-ANOVA

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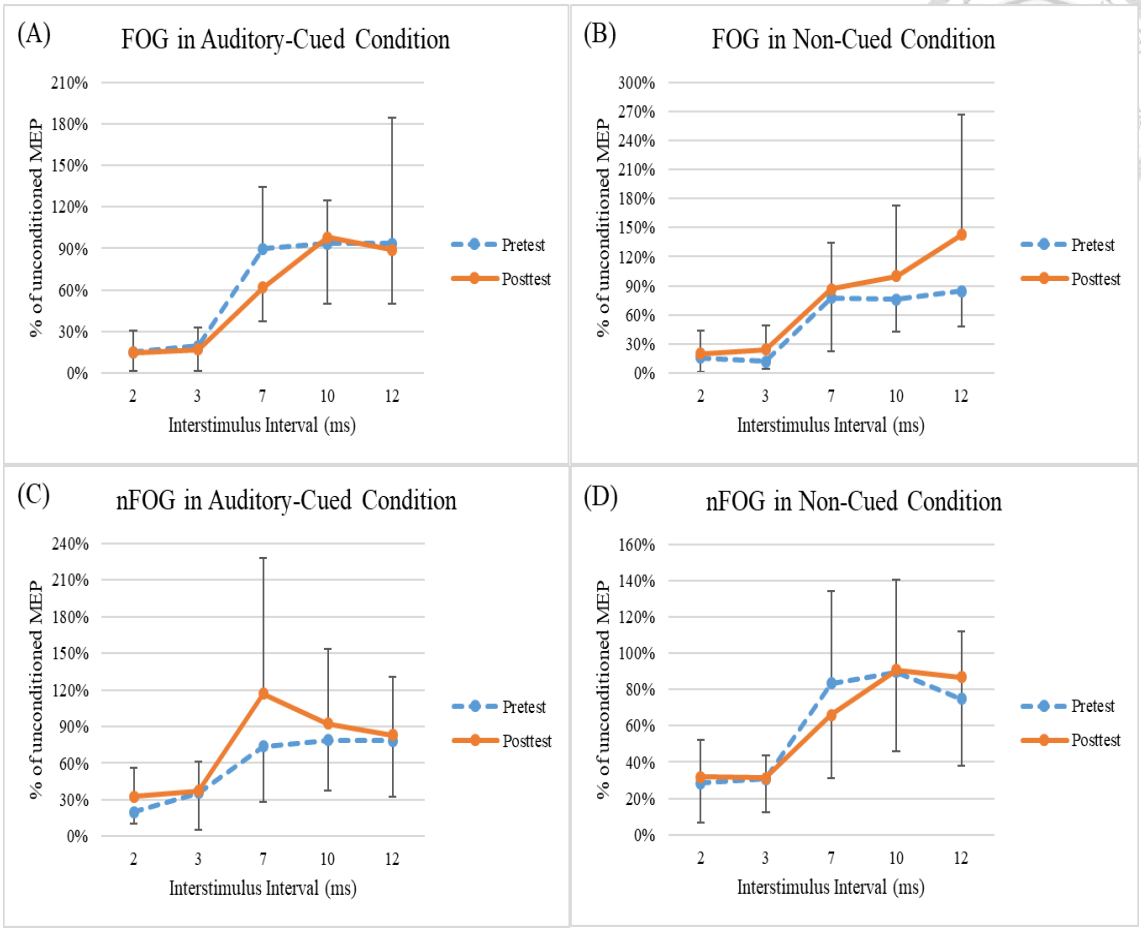

Figure 7. Paired-pulsed TMS in the freezer (A, B) and non-freezer group (C, D). MEP: motor evoked potentials; dotted line represents pretest and the solid line represents the posttest

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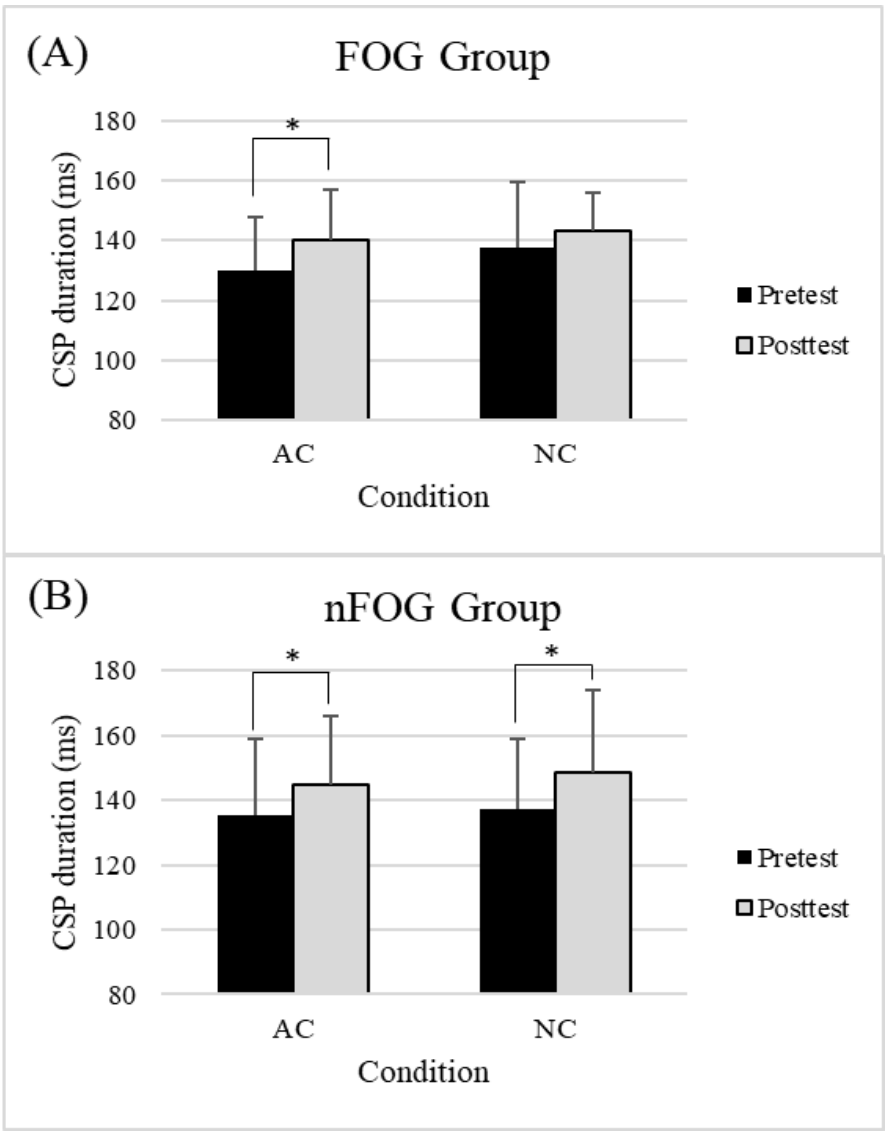

Figure 8. CSP duration in the freezer (A) and non-freezer (B) group

CSP: cortical silent period; *: p <0.05

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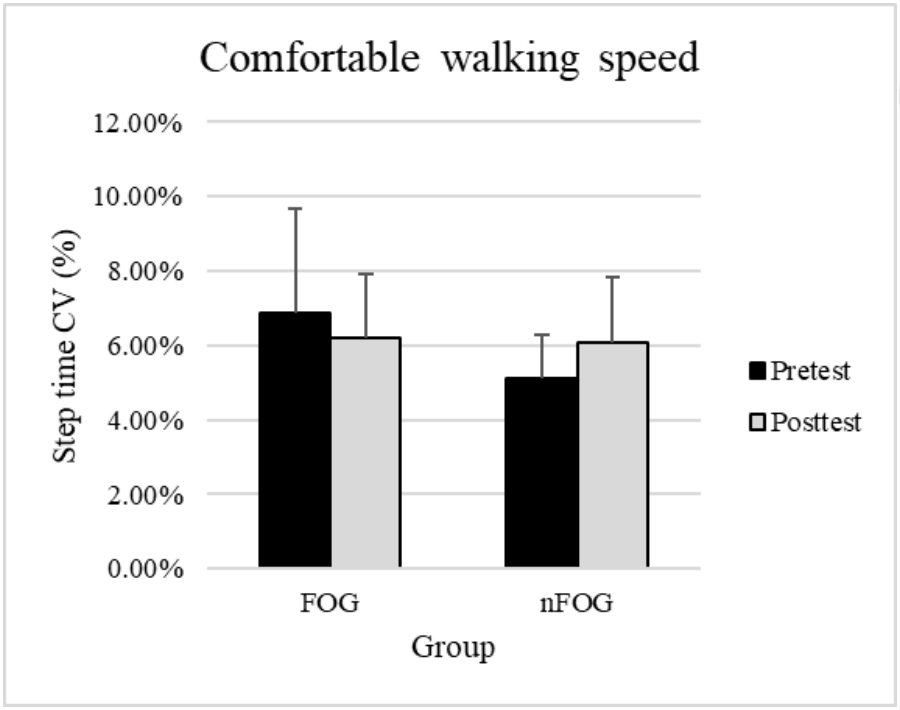

Figure 9. Step time CV of CWS in the freezer and non-freezer group

Step time CV: coefficient of variation of step time; CWS: comfortable walking speed

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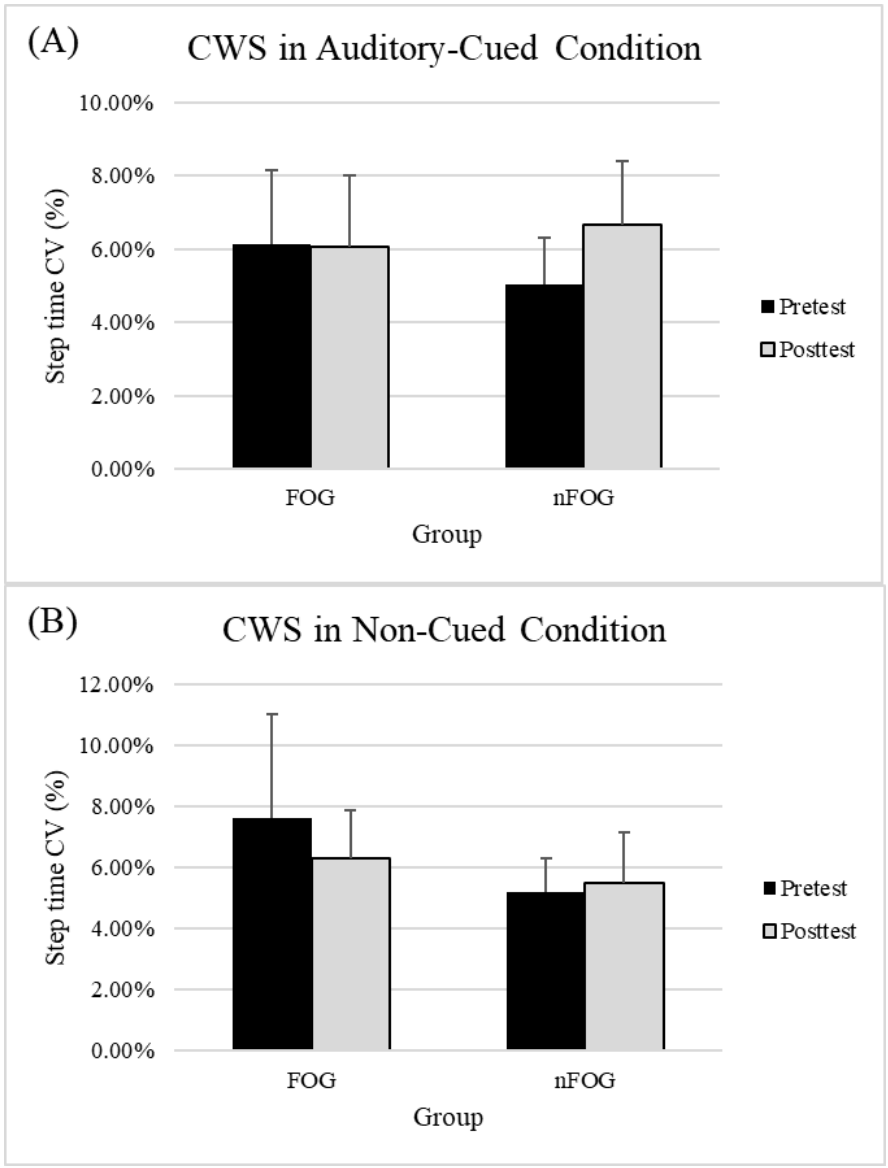

Figure 10. Step time CV of CWS in the freezer and non-freezer group under AC (A) and NC (B) condition

Step time CV: coefficient of variation of step time; CWS: comfortable walking speed

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Table 1. Summary of the cortical excitability in PD

TMS measure	Compare to healthy subjects	
	Upper extremity[74]	Lower extremity[77,78]
Resting motor threshold (RMT)	Similar	Reduced / Similar
Motor evoked potentials (MEPs)	Increased	Increased
Cortical silent period (CSP)	Reduced	Reduced / Similar
Short intracortical inhibition (SICI)	Reduced	Similar
Intracortical facilitation (ICF)	Similar	Reduced

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Table 2. Demographics and clinical characteristics of healthy subjects and patients with Parkinson's disease

	PD			Control (n=9)	b/t PD and C	b/t F and NF
	FOG (n=8)	nFOG (n=9)	total		*p* value	*p* value
Demographics						
Age, yrs	66.88±8.89	63.89±7.79	65.29±8.20	67.33±7.05	0.766	0.471[a]
Gender, M/F	6/2	4/5	10/7	5/4		
More affected side, L/R	4/4	3/6	7/10	-		
Disease duration, yrs	7.63±3.46	7.44±2.70	7.53±2.98	-		0.906[a]
Hoehn & Yahr scale-total	2.56±0.32	2.50±0.35	2.53±0.33	-		0.703
Stage 2, n	1	2	3	-		
Stage 2.5, n	5	5	10	-		
Stage 3, n	2	2	4	-		
Cognitive function						
MMSE	28.38±1.06	29.44±0.73	28.94±1.03	28.38±1.06	0.862	0.034*
Motor function						
UPDRS-III	18.50±3.51	15.78±2.44	17.06±3.21	-		0.155
NFOG-Q	19.50±6.50	0±0	-	-		0.000*

Note:

FOG: freezer group; nFOG: non-freezer group; Control: healthy group; M: male; F: female; L: left; R: right; MMSE: Mini-Mental State Examination; UPDRS-III: Unified Parkinson's Disease Rating Scale-motor part; NFOG-Q: New Freezing of Gait Questionnaire

Values are expressed as mean ± standard deviation; Mann-Whitney U test was used for the between-group comparison

a: independent t-test; *: $p < 0.05$

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Table 3. Single-pulse TMS in PD and control group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
MEP, μV										
PD	827.74±634.54	854.75±661.86	911.56±517.90	851.33±677.90	0.801	0.794	0.929	0.260	0.427	0.709
Control	623.24±372.96	664.67±543.54	770.66±385.76	675.39±648.13						
AMEP, μV										
PD	2240.90±667.32	2312.42±610.35	2168.30±646.92	2132.00±764.46	0.645	0.686	0.086	0.624	0.665	0.153
Control	2843.57±971.49	2662.65±910.46	2840.91±726.43	2656.65±651.61						
CSP, ms										
PD	133.00±20.77	142.63±18.98	137.28±21.14	146.29±20.38	0.283	0.201	0.031*	0.212	0.924	0.000*
Control	134.28±12.95	140.91±20.03	133.71±17.91	132.28±13.95						

Note:

AC: auditory-cued condition; NC: non-cued condition; MEP: motor evoked potentials; AMEP: active motor evoked potentials; CSP: cortical silent period; PD: patients with Parkinson's disease group; Control: healthy group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ examined by three-way RM-ANOVA

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Table 4. Single-pulse TMS in freezers and non-freezers group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
MEP, μV										
FOG	828.93±601.98	966.60±695.89	851.39±401.66	710.13±504.58	0.132	0.073	0.853	0.325	0.757	0.833
nFOG	826.81±695.10	767.75±662.35	958.37±613.42	961.16±799.80						
AMEP, μV										
FOG	2074.37±791.41	2200.69±719.86	1932.67±444.48	1891.10±723.00	0.699	0.582	0.769	0.412	0.394	0.786
nFOG	2370.43±567.51	2399.32±538.92	2351.57±741.73	2319.36±783.22						
CSP, ms										
FOG	130.16±17.72	140.00±17.20†	137.36±22.11	143.36±12.57	0.443	0.793	0.477	0.790	0.360	0.000*
nFOG	135.21±23.68	144.68±21.04†	137.22±21.70	148.57±25.43†						

Note:

AC: auditory-cued condition; NC: non-cued condition; MEP: motor evoked potentials; AMEP: active motor evoked potentials; CSP: cortical silent period; FOG: freezer group; nFOG: non-freezer group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ examined by three-way RM-ANOVA; ; †: $p < 0.05$ for within-group comparison by paired t-test.

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Table 5. Paired-pulse TMS in PD and control group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
$SICI_{(2ms)}$, %										
PD	17.85±12.43	24.91±21.20	22.93±20.65	26.73±24.49	0.687	0.567	0.064	0.967	0.208	0.003*
Control	12.52±7.04	31.44±39.87	19.56±23.45	42.49±31.66						
$SICI_{(3ms)}$, %										
PD	28.63±25.09	28.45±22.62	22.58±14.19	28.23±21.41	0.927	0.540	0.470	0.413	0.756	0.156
Control	17.54±14.30	22.12±17.78	14.92±12.87	26.80±15.69						
$ICF_{(7ms)}$, %										
PD	80.69±44.65	92.79±87.15	80.88±51.02	75.12±40.75	0.202	0.497	0.494	0.699	0.982	0.285
Control	61.95±29.94	59.54±31.22	53.61±32.69	84.25±47.72						
$ICF_{(10ms)}$, %										
PD	85.19±36.52	94.74±54.09	83.78±43.14	94.64±56.64	0.135	0.112	0.152	0.117	0.128	0.009*
Control	80.06±30.27	87.07±35.93	87.98±66.12	145.38±109.94						
$ICF_{(12ms)}$, %										
PD	84.91±67.01	85.58±42.61	78.89±35.72	111.15±90.93	0.320	0.340	0.213	0.864	0.979	0.009*
Control	76.04±44.48	130.56±118.00	78.00±70.95	110.09±79.54						

Note:

AC: auditory-cued condition; NC: non-cued condition; SICI: short intracortical inhibition; ICF: intracortical facilitation; PD: patients with Parkinson's disease group; Control: healthy group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ examined by three-way RM-ANOVA

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Table 6. Paired-pulse TMS in freezers and non-freezers group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
$SICI_{(2ms)}$, %										
FOG	14.91±15.72	14.76±13.32	15.71±14.44	20.01±23.84	0.366	0.916	0.453	0.748	0.346	0.211
nFOG	20.13±9.54	32.81±23.43	28.55±23.71	31.95±25.06						
$SICI_{(3ms)}$, %										
FOG	19.64±12.83	17.01±15.38	12.11±7.74	24.23±25.24	0.454	0.453	0.719	0.518	0.428	0.551
nFOG	35.62±30.51	37.35±24.05	30.71±12.73	31.34±18.88						
$ICF_{(7ms)}$, %										
FOG	89.66±44.79	61.79±24.86	77.65±55.58	86.75±47.63	0.053	0.391	0.315	0.618	0.652	0.871
nFOG	73.72±45.93	116.89±110.83	83.40±50.48	66.08±34.67						
$ICF_{(10ms)}$, %										
FOG	93.44±30.93	97.98±47.81	76.15±33.50	99.66±72.72	0.276	0.572	0.614	0.817	0.889	0.128
nFOG	78.76±40.95	92.23±61.28	89.72±50.56	90.74±44.84						
$ICF_{(12ms)}$, %										
FOG	93.59±91.05	88.79±38.60	84.18±35.93	142.56±124.40	0.399	0.295	0.339	0.295	0.290	0.079
nFOG	78.17±45.67	83.08±47.66	74.78±37.16	86.72±48.59						

Note:

AC: auditory-cued condition; NC: non-cued condition; SICI: short intracortical inhibition; ICF: intracortical facilitation; FOG: freezer group; nFOG: non-freezer group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ examined by three-way RM-ANOVA

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Table 7. Gait performance with comfortable walking speed in PD and control group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
CV, %										
PD	5.55±1.71	6.37±1.80	6.34±2.70	5.88±1.63	0.098	0.950	0.267	0.976	0.673	0.558
Control	6.40±0.85	5.20±2.18	5.99±1.89	6.03±2.14						
Speed, m/s										
PD	0.98±0.21	1.00±0.20	0.96±0.20	0.99±0.21	0.521	0.950	0.212	0.843	0.637	0.006*
Control	1.19±0.19	1.27±0.17	1.19±0.17	1.25±0.17						
Cadence, steps/min										
PD	114.71±8.14	114.37±7.25	113.96±6.61	112.52±7.76	0.426	0.244	0.134	0.093	0.970	0.835
Control	111.44±10.87	114.10±9.78	114.15±7.35	113.83±8.18						
Slength, m										
PD	1.00±0.21	1.03±0.21	0.99±0.20	1.04±0.21	0.662	0.543	0.736	0.347	0.383	0.000*
Control	1.26±0.18	1.30±0.15	1.23±0.17	1.29±0.15						

Note:

AC: auditory-cued condition; NC: non-cued condition; CV: coefficient of variation of step time; Slength: stride length; PD: patients with Parkinson's disease group; Control: healthy group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ by three-way RM-ANOVA

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Table 8. Gait performance with comfortable walking speed in freezers and non-freezers group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
CV, %										
FOG	6.13±2.02	6.06±1.95	7.64±3.41	6.31±1.59	0.984	0.128	0.034*	0.190	0.657	0.712
nFOG	5.03±1.28	6.64±1.73	5.19±1.11	5.50±1.67						
Speed, m/s										
FOG	0.94±0.28	0.96±0.27	0.89±0.24	0.92±0.25	0.825	0.185	0.998	0.698	0.584	0.080
nFOG	1.01±0.15	1.04±0.13	1.03±0.14	1.06±0.14						
Cadence, steps/min										
FOG	116.20±7.28	115.60±6.12	113.62±8.06	112.05±9.08	0.932	0.207	0.791	0.458	0.286	0.203
nFOG	113.39±9.05	113.28±8.34	114.27±5.52	112.94±6.92						
Slength, m										
FOG	0.95±0.27	0.97±0.26	0.90±0.23	0.97±0.25	0.631	0.214	0.910	0.238	0.739	0.002*
nFOG	1.05±0.14	1.09±0.16	1.06±0.15	1.11±0.15						

Note:

AC: auditory-cued condition; NC: non-cued condition; CV: coefficient of variation of step time; Slength: stride length; FOG: freezer group; nFOG: non-freezer group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ by three-way RM-ANOVA

doi:10.6342/NTU201802784

Table 9. Gait performance with fast walking speed in PD and control group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
CV, %										
PD	6.3±1.91	5.86±1.97	6.18±2.33	6.34±2.49	0.084	0.035*	0.184	0.207	0.013*	0.114
Control	4.70±1.59	4.99±1.83	8.49±4.57	5.16±2.15						
Speed, m/s										
PD	1.28±0.30	1.26±0.26	1.28±0.28	1.28±0.26	0.646	0.543	0.641	0.195	0.922	0.203
Control	1.68±0.26	1.63±0.26	1.65±0.30	1.64±0.28						
Cadence, steps/min										
PD	127.96±11.38	126.64±9.67	127.25±9.27	125.60±7.73	0.652	0.124	0.853	0.493	0.400	0.038*
Control	130.79±11.04	129.82±9.54	134.48±5.66	131.94±7.50						
Slength, m										
PD	1.17±0.25#	1.17±0.24†	1.18±0.24#	1.20±0.24†	0.380	0.023*	0.492	0.109	0.300	0.458
Control	1.51±0.22	1.48±0.22	1.44±0.25	1.47±0.22						

Note:

AC: auditory-cued condition; NC: non-cued condition; CV: coefficient of variation of step time; Slength: stride length; PD: patients with Parkinson's disease group; Control: healthy group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ by three-way RM ANOVA; #: $p < 0.05$ for between-group comparison of baseline by independent t test; †: $p < 0.05$ for between-group comparison of posttest by independent t test

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Table 10. Gait performance with fast walking speed in freezers and non-freezers group

	AC		NC		Cue x Group x Time	Cue x Group	Group x Time	Cue x Time	Cue	Time
	Baseline	Posttest	Baseline	Posttest						
CV, %										
FOG	6.38±1.77	5.68±2.53	6.88±2.04	6.81±2.81	0.969	0.090	0.699	0.573	0.528	0.798
nFOG	6.23±2.12	6.03±1.44	5.57±2.52	5.92±2.25						
Speed, m/s										
FOG	1.20±0.39	1.18±0.35	1.20±0.37	1.20±0.33	0.823	0.975	0.981	0.430	0.513	0.471
nFOG	1.35±0.19	1.33±0.13	1.36±0.18	1.35±0.17						
Cadence, steps/min										
FOG	125.84±10.94	124.90±9.39	125.37±7.87	123.95±7.86	0.928	0.895	0.735	0.818	0.462	0.095
nFOG	129.84±12.07	128.19±10.19	128.92±10.54	127.07±7.76						
Slength, m										
FOG	1.10±0.32	1.10±0.29	1.11±0.30	1.14±0.29	0.775	0.657	0.860	0.508	0.182	0.174
nFOG	1.23±0.17	1.24±0.18	1.23±0.17	1.25±0.18						

Note:

AC: auditory-cued condition; NC: non-cued condition; CV: coefficient of variation of step time; Slength: stride length; FOG: freezer group; nFOG: non-freezer group

Values are expressed as mean ± standard deviation; *p* value was displayed; *: $p < 0.05$ by three-way RM ANOVA

doi:10.6342/NTU201802784

Table 11. Comparison of PD and control group in cortical excitability and gait performance

Cortical excitability		**Gait performance**		
			Comfortable walking speed	Fast walking speed
Resting MEP	PD and control: Similar in AC and NC	Step time CV	PD and control: Similar in AC and NC	PD and control: Decreased in AC
CSP	PD: Increased in AC and NC Control: Similar in AC and NC	Speed	PD and control: Increased in AC and NC	PD and control: Similar in AC and NC
$FSICI_{(2ms)}$	PD and control: Increased in AC and NC	Cadence	PD and control: Similar in AC and NC	PD and control: Decreased in AC and NC
$SICI_{(3ms)}$	PD and control: Similar in AC and NC	Stride length	PD and control: Increased in AC and NC	PD had decreased stride length than control
$ICF_{(7ms)}$	PD and control: Similar in AC and NC	-	-	-
$ICF_{(10ms)}$	PD and control: Increased in AC and NC	-	-	-
$ICF_{(12ms)}$	PD and control: Increased in AC and NC	-	-	-

Note:

AC: auditory-cued condition; NC: non-cued condition; CV: coefficient of variation of step time

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Appendix A. Clinical trial/research approval

國立臺灣大學醫學院附設醫院C研究倫理委員會
Research Ethics Committee C
National Taiwan University Hospital
7, Chung-Shan South Road, Taipei, Taiwan 100, R.O.C
Phone: 2312-3456 Fax: 23951950

臨床試驗/研究許可書

許可日期：2018 年 4 月 23 日

倫委會案號：201802068RINC
計畫名稱：節律性聽覺提示合併步態訓練對於巴金森氏症患者大腦皮質興奮性及動作表現的效果。
試驗機構：國立臺灣大學
部門/計畫主持人：物理治療學系　陸哲駒助理教授
上述計畫業經2018 年 4 月 2 日本院 C 研究倫理委員會第 102 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。
本臨床試驗/研究許可書之有效期限為 1 年(自 2018 年 4 月 23 日至 2019 年 4 月 22 日止)，計畫主持人須依國內相關法令及本院規定通報嚴重不良反應事件及非預期問題，並應於到期日至少 6 週前提出持續審查申請表，本案需經持續審查，方可繼續執行。

主任委員

蔡甫昌

Clinical Trial/Research Approval

Date of approval: Apr 23, 2018

NTUH-REC No.：201802068RINC
Title of protocol：Effects of Rhythmic Auditory Cueing with Locomotion Training on Cortical Excitability and Behavior in Patients with Parkinson's Disease.
Trial/Research Institution：National Taiwan University
Department/ Principal Investigator：School of Physical Therapy / Assistant Professor Jer-Junn Luh

The protocol has been approved by the 102nd meeting of Research Ethics Committee C of the National Taiwan University Hospital on Apr 2, 2018. The committee is organized under, and operates in accordance with, the Good Clinical Practice guidelines and governmental laws and regulations.

The duration of this approval is one year (from Apr 23, 2018 to Apr 22, 2019). The investigator is required to report Serious Adverse Events and Unanticipated Problems in accordance with the governmental laws and regulations and NTUH requirements and apply for a continuing review not less than six weeks prior to the approval expiration date.

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

Daniel Fu-Chang Tsai

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國立臺灣大學醫學院附設醫院C研究倫理委員會

Research Ethics Committee C
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/研究許可書
Clinical Trial/Research Approval

Date of approval: Apr 23, 2018

計畫文件版本日期 Version date of documents：

(1) ***計畫書 Protocol:*** *version 2.0 2018/03/17*
(2) ***中文摘要 Chinese protocol synopsis:*** *version 2.0 2018/03/17*
(3) ***同意書 ICF:****3.0/2018.04.15*
(4) ***個案報告表 CRF:***
(5) ***主持人手冊 IB:***
(6) ***問卷 Questionnaire:***
經顱磁刺激安全問卷(TMS): *Date:20180116*
(7) ***招募文宣 Advertisement of subject Recruitment:***
Version:1.0 版本日期:2018.01.16
Version 1.0, 2018/02/20
(8) ***其他文件 Other documents:***
巴金森症量表(Unified Parkinson's Disease Rating Scale, UPDRS): *版本 1.0 日期: 2018.03.17*
新凍結步態量表(New Freezing of Gait Questionnaire): *Version: 1.0 Date:2018/0317*
認知功能評估量表(MMSE): *Version: 1.0 Date:2018/02/01*

doi:10.6342/NTU201802784

Appendix B. Informed consent form

病歷號：
姓　名：
生　日：西元　　年　月

國立臺灣大學醫學院附設醫院
National Taiwan University Hospital

臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201802068RINC

請詳細閱讀內容，待主持人或其授權人員向您說明後，再簽署同意書　　第 1 頁

計畫名稱

中文：節律性聽覺提示合併步態訓練對於巴金森氏症患者大腦皮質興奮性及動作表現的效果

英文：Effects of Rhythmic Auditory Cueing with Locomotion Training on Cortical Excitability and Behavior in Patients with Parkinson's Disease

試驗機構：台灣大學物理治療研究所	委託單位/藥廠：無 研究經費來源：自籌
試驗主持人：陸哲駒	職稱：物理治療師
協同主持人：吳瑞美	職稱：主治醫師/教授
24 小時緊急聯絡人：高珮容	電話：0961-160-629

（若撥打時暫時未接通，請以簡訊或語音留言，研究人員將儘速與您聯繫）

受試者姓名：　　病歷號碼：

您被邀請參與此臨床試驗/研究，這份表格提供您本試驗/研究之相關資訊，試驗主持人或其授權人員將會為您說明試驗/研究內容並回答您的任何疑問，在您的問題尚未獲得滿意的答覆之前，請不要簽署此同意書。您不須立即決定是否參加本試驗/研究，請您經過慎重考慮後方予簽名。您須簽署同意書後才能參與本試驗/研究。如果您願意參與本試驗/研究，此文件將視為您的同意紀錄。即使在您同意後，您仍然可以隨時退出本試驗/研究而不需任何理由。

(一)試驗/研究目的：

本研究目的在於以同步化的聽覺提示合併步態訓練進行介入，探討聽覺提示對於巴金森氏症患者的大腦皮質興奮度、動作節律性問題，例如：原地踏步動作、行走變異程度是否會有顯著性的改善。

(二)研究背景或藥品/醫療技術/醫療器材現況：

1. 本品/技術資料：

本研究所採用的聽覺提示介入為臨床上常使用的治療手法，用以增進行走能力以及減輕凍結步態情形，目前已有許多研究指出配合固定頻率的聽覺提示能夠有效改善巴金森氏症患者在執行節律性動作(如行走)的問題，並能增進行走功能以及降低步伐間的變異程度，藉以減少跌倒的危險。以上實驗內容皆不涉及使用藥品、醫療技術、醫療器材。

2. 本品上市狀況：

本研究使用的經顱神經磁刺激是一種非侵入性的研究用影像學工具，可用來了解健康人與神經損傷患者大腦神經皮質興奮性。此項技術已於國內外各大研究單位使用多年，探討不同疾病、行為、心理等神經生理機制，目前已有相當多的研究及臨床證據，且極少有不良反應。經顱磁刺激的原理為，以磁場通過頭頂上的圓形線圈，經過大腦皮層進一步引發您下肢的動作，故在刺激的同時，會感到您下肢的抽動，此為正常現象。我們會於您小腿前側上放置表面肌電圖以偵測動作大小。而經顱磁刺激使用的為磁場，

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故並無幅射的危害。而表面肌電圖是置於皮膚表面的電極，用以測量，並無能量輸入，也無侵入性。唯每一次的磁場發射通過頭頂上的圓形線圈時，皆會有類似空氣槍的聲音，可能感到不適的情形大多是在施測過程中頭皮或臉部肌肉有輕微的收縮或刺痛感。此經顱磁刺激器可能伴隨癲癇風險，若有體內有心臟節律器或體內有任何神經刺激器則不可接受此評估，此外，若本身有大範圍的缺血性傷痕、失眠、本身或家族史中有癲癇風險，則需要由專業人員小心執行。而本研究若您符合本身或家族史中有癲癇風險此項則會無條件退出此試驗。經顱磁刺激器已於國內上市，且取得衛生福利部使用許可證（衛署醫器輸字第014086 號），許可項目為常規之檢查項目。可能發生之風險的發生率與處理方法詳述於同意書(五)。

(三)試驗/研究之納入與排除條件：

執行本研究計畫的醫師或相關研究人員將會與您討論有關參加本研究的必要條件。請您配合必須誠實告知我們您過去的健康情形，若您有不符合參加本研究的情況，將不能參加本研究計畫。

➢ 有凍結症狀組以及無凍結症狀組

1. 納入條件(參加本試驗/研究的條件):
(1)年滿20歲的成年人。
(2)經確診為原發性巴金森氏症的患者(侯恩和葉爾期第一期至第三期，為巴金森症狀嚴重程度，共五期)。
(3)無聽覺障礙(能夠聽見口語聲並正常對談)。
(4)能夠獨立行走。
(5)能夠了解指令並遵從指示（簡易心智量表≧24)

2. 排除條件(若您有下列任一情況，您將無法參加本試驗/研究):
(1)罹患巴金森氏症以外的其他神經疾病。
(2)患有肌肉骨骼疾病影響走路表現者。
(3)被診斷有任何精神疾病者。
(4)不穩定的心血管疾病以及呼吸系統疾病。
(5)有失智症狀。
(6)患有視覺障礙影響其步態表現者
(7)有癲癇的病史或直系血親有癲癇病史。
(8)腦部曾受過創傷，如手術開刀、腦瘤、中風或植入顱內金屬物者。
(9)體內裝有心律調節器或其他電刺激器。
(10)曾因不明原因昏厥、常偏頭痛者。
(11)懷孕

**為減低巴金森氏症之藥物對本研究造成的影響，會請您在非藥效時期進行實驗(即OFF

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期)，即於進行本實驗前8小時停藥，在每次實驗評估結束之後會請您立即服藥；但若您有個人因素之考慮，本研究並不强求。本研究會全程於台大物理治療研究所進行。

➢ 健康受試者

1. 納入條件(參加本試驗/研究的條件):
   (1)年滿20歲的成年人。
   (2)無聽覺障礙(能夠聽見口語聲並正常對談)。
   (3)能夠獨立行走。
   (4)能夠了解指令並遵從指示（簡易心智量表≧24)。

2. 排除條件(若您有下列任一情況，您將無法參加本試驗/研究):
   (1)罹患神經相關疾病。
   (2)患有肌肉骨骼疾病影響走路表現者。
   (3)被診斷有任何精神疾病者。
   (4)不穩定的心血管疾病以及呼吸系統疾病。
   (5)有失智症狀。
   (6)患有視覺障礙影響其步態表現者
   (7)有癲癇的病史或直系血親有癲癇病史。
   (8)腦部曾受過創傷，如手術開刀、腦瘤、中風或植入顱內金屬物者。
   (9)體內裝有心律調節器或其他電刺激器。
   (10)曾因不明原因昏厥、常偏頭痛者。
   (11)懷孕

**巴金森氏症患者預期於台大巴金森氏症中心以及巴金森之友會招募；而健康受試者預期於醫院大廳公佈欄或是社區招募。

(四)本試驗/研究方法及相關程序：

本研究預計招募 51 位受試者，有三個組別: 有凍結症狀組、無凍結症狀組以及控制組，各組別分別收錄 17 位受試者，三個組別都會接受兩次的實驗，實驗順序以丟硬幣隨機決定。在實驗進行前，我們會先進行基本資料的收集，項目如下:年齡、性別、發病年齡、侯恩和葉爾期(Modified Hoehn& Yahr，為巴金森症狀嚴重程度)、目前用藥情形、是否有凍結現象、巴金森症量表(Unified Parkinson's Disease Rating Scale, UPDRS)之第三部分(動作)、簡易心智量表(Mini Mental State Examination, MMSE)、新步態凍結量表(New Freezing of Gait Questionnaire, NFOG-Q)、跌倒頻率、症狀較嚴重側。以上基本資料皆為口頭詢問，無侵入性。巴金森相關測試基本資料收集如下:

doi:10.6342/NTU201802784

項目	測試時間	測試地點
巴金森症狀衡量表(第三部分：動作)	20 分鐘	公衛大樓三樓姿勢控制研究室
簡易心智量表	10 分鐘	
新步態凍結量表	15 分鐘	

每個組別都會接受兩次的實驗，間隔為一個星期，實驗程序為如下(隨機順序):

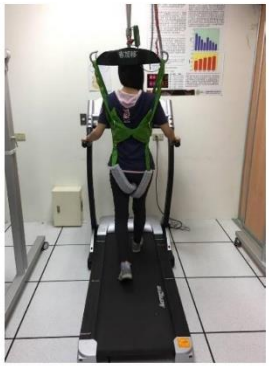
(一)聽覺提示合併跑步機訓練: 同步化聽覺提示介入，聆聽等時性節律(110%步頻)，在以受試者舒適的跑步機速度下，同時按照節律的頻率作出對應同步化之步頻，進行 30 分鐘的介入。

(二)無聽覺提示合併跑步機訓練: 在以受試者舒適的跑步機速度下，進行30分鐘的介入。

*以上介入中若您感覺疲累時，可以中途休息，然而，真實介入時間仍長達 30 分鐘內，休息時間不算在介入時間中。

*在進行跑步機訓練時，基於安全考量，會請受試者穿戴懸吊裝置，此懸吊裝置並不會提供受試者減輕體重、降低試驗難度，只是用來保護受試者，以防步態訓練的過程中受試者反應不及跌倒。此外，受試者在進行跑步機訓練時，可以因安全考量而雙手扶著跑步機的扶手，不會影響試驗進行。[圖一、圖二]

[圖一] 步態訓練側面圖



[圖二] 步態訓練背面圖

在實驗前後，我們皆會進行評估以了解聽覺提示對於步態表現的效果，評估的項目包含動作測試以及經顱磁刺激評估(地點位於公衛大樓三樓物理治療所)，簡介如下:

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(一)動作測試，包含原地踏步以及行走步伐：包含舒適速度下之原地踏步以及舒適速度下和快速之行走，此測試會請您穿戴兩個小型的步態感測器在腳踝處紀錄步態表現，身旁會有受過訓練的物理治療師隨時保護您的安全。[圖三、圖四]

[圖三] 步態感測器

[圖四] 步態評估

(二)經顱磁刺激器：我們會先請您戴上泳帽，將圓形線圈會擺放在頭部中間的位置，並以防水筆標記在泳帽上，確保在試驗過程中經顱磁刺激的線圈都在相同的位置。經顱磁刺激屬於非侵入性的評估工具，其無痛又安全，近二十年常應用於精神、神經與復健領域上的大量研究中，可評估大腦皮質興奮性，即大腦的皮質的活動情況。經顱磁刺激的原理為，以磁場通過頭頂上的圓形線圈，經過大腦皮層進一步引發您下肢的動作，故在刺激的同時，會感到您下肢的抽動，此為正常現象。我們會於您小腿前側上放置表面肌電圖以偵測動作大小。而經顱磁刺激使用的為磁場，故並無輻射的危害。而表面肌電圖是置於皮膚表面的電極，用以測量，並無能量輸入，也無侵入性。唯每一次的磁場發射皆會有類似空氣槍的聲音，請您不用過於擔心。在接受經顱磁刺激時會有兩位物理治療師在旁已隨時監控您的身體狀況，若在接受經顱磁刺激時您有任何身體不適，我們會立即停止實驗並陪同您去就診，若有緊急狀況，會立即帶您前往急診就醫。

總體而言本研究的流程如下表，每一次的實驗時間約需兩小時半左右:

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	前測	實驗	後測 (介入後立即)	後測 (介入後1hr)
實驗動作		走路		
評估項目	1. 經顱磁刺激評估 (30) 2. 原地踏步步伐的變異程度 (5) 3. 行走步伐的變異程度 (5) *前測經顱磁刺激評估因需尋找大腦反應熱點，故花費較多時間	在跑步機上行走	1. 經顱磁刺激評估 (20) 2. 原地踏步步伐的變異程度 (5) 3. 行走步伐的變異程度 (5)	1. 經顱磁刺激評估 (10) 2. 原地踏步步伐的變異程度 (5) 3. 行走步伐的變異程度 (5)
預估時間 (min)	30+5+5	30	20+5+5	10+5+5

**本試驗不會採集您的檢體。

**若您曾在本院醫療體系各總、分院就醫，我們也會檢閱該院與本研究有關之病歷資料，以獲得完整之醫療資訊。

**本研究全程皆會有至少兩名受過專業訓練的物理治療師在旁保護您的安全，訓練時會使用懸吊裝置綁在您身上確保不會跌倒；物理治療研究所與台大醫院非常接近，若在實驗過程中您有任何不適合繼續實驗之情形，會立即停止實驗介入並通報主持人，並陪同您至台大醫院就醫，待檢查確定無礙後，您將無條件退出試驗。

於評估及治療期間，請您遵照研究人員的指示，配合回答或填寫相關問題。在進行測驗時務必請您放輕鬆，不要有任何壓力。您的回答不會對您的權益產生任何影響。

(五)可能發生之風險及其發生率與處理方法：

1. 與試驗藥物/醫療器材/醫療技術相關的風險（本試驗使用藥物/器材/醫療技術的副作用）：

本研究的各項檢查皆屬於非侵入式檢查，已被應用在人體上。

經顱磁刺激在本研究只使用於評估而非治療用，每個項目單次評估僅會有單發或是雙發的刺激，相較於治療性經顱磁刺激(約一至兩千發)對於受試者的影響會小很多；根據文獻以及研究經驗，接受經顱磁刺激評估可能感到不適的情形大多是在施測過程中頭皮或臉部有輕微的收縮或刺痛感，也可能因頭皮肌肉收縮而引起輕度短時間的頭痛或頭暈。另外，關於重覆性經顱磁刺激可能會導致少於1%的成年人癲癇發作、精神上的異常症狀等風險，在本實驗使用的參數(用作評估)上，過去的文獻回顧中並無發現類似例子，故請您不用過度憂慮。

而本實驗亦嚴格篩選受試者，確定您並非不適合使用經顱磁刺激的族群才讓您參加本實驗，以降低可能造成的風險。在接受經顱磁刺激之前，我們會先示範在您的手，讓您感受磁刺激的強度，並會詢問您是否能夠接受磁刺激施用於頭部；而實驗過程中，亦會不定時詢問並記錄您會否有任何不良的反應(如頭昏、頭痛、嘔吐，脖子痛，刺激部位是否發癢、刺痛、發紅，或任何不適)。若在試驗過程中您有產生明顯不適的反應，將立即停止實驗介入並通報主持人，並陪同至台大醫院就醫，待檢查確定無礙後，您將無條件退出試驗。

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2. 與試驗/研究過程相關的風險：

在來往住處以及物理治療研究所由於需請您搭車前來，我們希望能夠有家屬陪同您以確保安全，在進行實驗時，皆會有兩位受過專業訓練的物理治療師在旁維護您的安全，必要時會使用懸吊帶預防跌倒情形發生。

(六)其他替代療法及說明：

針對巴金森氏症的常規治療方式包含肌力訓練、運動訓練、行走訓練以及功能性訓練等等，若有復健需求可尋求您的主治醫師，並請醫師評估是否需要轉介您接受物理治療介入。

此實驗為獨立兩次的聽覺提示對下肢原地踏步動作的學習，參與此實驗並不會剝奪或影響您現正接受的治療權益。除此之外，我們也會在實驗結束之後根據您的動作表現狀況給予您物理治療諮詢，並將您在實驗中的表現情形讓您的主治醫師了解。

(七)試驗/研究預期效益：

1. 評估聽覺提示合併步態訓練的效果，以發展由聽覺提示作為下肢動作訓練的基礎。
2. 探討聽覺提示訓練的神經生理改變及可能機轉，以協助開拓臨床復健的應用及更合理有效地應用治療策略。

(八)試驗/研究進行中受試者之禁忌、限制與應配合之事項：

1. 您必須意識清晰，在實驗過程中保持清醒，不要睡著。
2. 實驗進行其間您若有任何不適，可隨時要求實驗人員暫停或終止實驗。
3. 需請您配合的是，為減低巴金森氏症之藥物對本研究造成的影響，會請您在非藥效時期進行實驗(即OFF期)，即於進行本實驗前8小時停藥，在每次實驗評估結束之後會請您立即服藥；但若您有個人因素之考慮，本研究並不強求。唯請您務必配合的是，在進行第二次實驗時，與前次實驗的相同時間點服藥，並與前次實驗的相同時間點進行實驗，以確保兩次實驗中藥效作用為一致。

(九)受試者個人資料之保密：

台大醫院將依法把任何可辨識您的身分之記錄與您的個人隱私資料視為機密來處理，不會公開。研究人員將以一個研究代碼代表您的身分，此代碼不會顯示您的姓名、國民身分證統一編號、住址等可識別資料。如果發表試驗/研究結果，您的身分仍將保密。您亦瞭解若簽署同意書即同意您的原始醫療紀錄可直接受監測者、稽核者、研究倫理委員會及主管機關檢閱，以確保臨床試驗/研究過程與數據符合相關法律及法規要求，上述人員並承諾絕不違反您的身分之機密性。除了上述機構依法有權檢視外，我們會小心維護您的隱私。

(十)試驗/研究之退出與中止：

您可自由決定是否參加本試驗/研究；試驗/研究過程中也可隨時撤銷或中止同意，退出試驗/研究，不需任何理由，且不會引起任何不愉快或影響其日後醫師對您的醫療照顧。為了您的安全，當發生以下情形時，您必須退出試驗/研究：

1. 癲癇
2. 頭昏、頭痛、嘔吐
3. 嚴重脖子痛

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病歷號：
姓　名：
生　日：西元　　年　月

國立臺灣大學醫學院附設醫院
National Taiwan University Hospital

臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201802068RINC

請詳細閱讀內容，待主持人或其授權人員向您說明後，再簽署同意書　　第 8 頁

4. 刺激部位發癢、刺痛、發紅、或任何不適

當試驗/研究執行中有重要的新資訊(指和您的權益相關或是影響您繼續參與意願)，會通知您並進一步說明，請您重新思考是否繼續參加，您可自由決定，不會引起任何不愉快或影響其日後醫師對您的醫療照顧。

計畫主持人亦可能於必要時中止整個試驗/研究之進行。

當您退出本試驗/研究或主持人判斷您不適合繼續參與本試驗/研究時，在退出前已得到的資料將被保留，不會移除。在退出後您可決定是否同意試驗主持人繼續收集您的資料。

*退出後讓試驗主持人繼續收集我的資料，例如經由我的病歷記載取得後續醫療過程、實驗室檢查結果。繼續收集資料期間，仍會維護您的隱私和個人資料的機密性。

□同意收集。

□不同意本試驗/研究繼續收集或檢視我的資料，但可經由公共資料庫查詢之紀錄不在此限。

(十一) 損害補償與保險：

試驗/研究一定有風險，為確保因為參與試驗/研究發生不良反應致造成您的損害時所可能獲得之保障，請您務必詳閱本項說明內容：

1. 如依本研究所訂臨床試驗/研究計畫，因發生不良反應造成損害，由國立臺灣大學醫學院附設醫院負補償責任。但本受試者同意書上所記載之可預期不良反應，不予補償。
2. 如依本研究所訂臨床試驗/研究計畫，因而發生不良反應或損害，本醫院願意提供專業醫療照顧及醫療諮詢。您不必負擔治療不良反應或損害之必要醫療費用。
3. 除前二項補償及醫療照顧外，本研究不提供其他形式之補償。若您不願意接受這樣的風險，請勿參加試驗/研究。
4. 您不會因為簽署本同意書，而喪失在法律上的任何權利。
5. 本研究未投保人體試驗責任保險。

(十二) 受試者之檢體(含其衍生物)、個人資料之保存、使用與再利用

1. 檢體及剩餘檢體之保存與使用

本試驗/研究不收取檢體

2. 個人資料

在試驗/研究期間，依據計畫類型與您所授權的內容，我們將會蒐集與您有關的病歷資料、醫療紀錄、量表、問卷、神經生理數據、步態表現等資料與資訊，並以一個編號來代替您的名字及相關個人資料。前述資料若為紙本型式，將會與本同意書分開存放於研究機構之上鎖櫃中；若為電子方式儲存或建檔以供統計與分析之用，將會存放於設有密碼與適當防毒軟體之專屬電腦內。這些研究資料與資訊將會保存10年。

(十三) 受試者權益：

1. 如果您在試驗/研究過程中對試驗/研究工作性質產生疑問，對身為患者之權利有意見或懷疑因參與研究而受害時，可與研究倫理委員會聯絡請求諮詢，電話號碼為：(02)2312-

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3456轉63155。

2. 試驗/研究過程中，與您的健康或是疾病有關，可能影響您繼續接受臨床試驗/研究意願的任何重大發現，都將即時提供給您。如果您決定退出，醫師會安排您繼續接受醫療照護。如果您決定繼續參加試驗/研究，可能需要簽署一份更新版的同意書。
3. 為進行試驗/研究工作，在試驗事項上您必須接受計畫主持人或協同主持人：陸哲駒助理教授的照顧。如果您現在或於試驗/研究期間有任何問題或狀況，請不必客氣，可與在台大物理治療研究所的高珮容研究生聯絡 (24小時聯繫電話：0961-160-629)。
4. 本同意書一式2份，試驗主持人或其授權人員已將1份已簽名的同意書交給您，並已完整說明本研究之性質與目的。計畫主持人或協同主持人：陸哲駒助理教授已回答您有關試驗/研究的問題。
5. 參加試驗研究計畫之補助：本研究會提供您來參與實驗之車馬費，並會提供您物理治療諮詢與建議。車馬費為每次500元，會在您接受兩次實驗後給予。
6. 若試驗結束後2年內，發現有非預期且直接影響您的安全疑慮，亦將通知您。

（十四）本研究預期可能衍生之商業利益：

本研究預期不會衍生專利權或其他商業利益。

（十五）簽名：

1. 試驗主持人、或協同主持人或其授權人員已詳細解釋有關本研究計畫中上述研究方法的性質與目的，及可能產生的危險與利益。

   試驗主持人/協同主持人簽名：_____

   日期：_____年____月____日

   在取得同意過程中其他參與解說及討論之研究人員簽名：_____

   日期：_____年____月____日

2. 經由說明後本人已詳細瞭解上述研究方法及可能產生的危險與利益，有關本試驗/研究計畫的疑問，亦獲得詳細解釋。本人同意接受並自願參與本研究，且將持有已簽名的同意書。

   受試者簽名：　　日期：_____年____月____日

   出生年月日：_____年____月____日　電話：

   國民身分證統一編號：　　性別：

   通訊地址：

   法定代理人/有同意權之人簽名：　　日期：_____年____月____日

   與受試者關係（請圈選）：配偶、父、母、兒、女、其他：_____

   出生年月日：_____年____月____日　電話：

版本/日期： 3.0/2018.04.15

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病歷號：
姓　名：
生　日：西元　　年　月

國立臺灣大學醫學院附設醫院
National Taiwan University Hospital

臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201802068RINC

請詳細閱讀內容，待主持人或其授權人員向您說明後，再簽署同意書　　第 10 頁

國民身分證統一編號：

通訊地址：

*適用醫療法第 79 條第 1 項但書或人體研究法第 12 條第 1 項但書情形者，其同意權之行使分別依醫療法第 79 條第 2 項、人體試驗管理辦法第 5 條或人體研究法第 12 條第 3、4 項規定辦理：

*受試者為**無行為能力者**(未滿七歲之未成年人者或受監護宣告之人)，由法定代理人簽名；受監護宣告之人，由監護人擔任其法定代理人。

* 受試者為**限制行為能力者**(滿七歲以上之未成年人或因精神障礙、其他心智缺陷，致其為意思表示、受意思表示、辨識其意思表示效果之能力，顯有不足，而受法院之輔助宣告者)，應得其本人及法定代理人或輔助人之同意。

* 受試者雖非無行為能力或限制行為能力者，但因**意識混亂或有精神與智能障礙，而無法進行有效溝通和判斷時**，由有同意權之人簽名。有同意權人順序如下：

1. 屬新藥、新醫療器材、新醫療技術之人體試驗(人體試驗管理辦法第 5 條)：
(1)配偶。(2) 父母。(3) 同居之成年子女。(4)與受試者同居之祖父母。(5)與受試者同居之兄弟姊妹。(6) 最近一年有同居事實之其他親屬。

2. 屬人體研究（人體研究法第 12 條）：
(1)配偶。(2)成年子女。(3)父母。(4)兄弟姊妹。(5)祖父母。

依前項關係人所為之書面同意，其書面同意，得以一人行之；關係人意思表示不一致時，依前項各款先後定其順序。前項同一順序之人，以親等近者為先，親等同者，以同居親屬為先，無同居親屬者，以年長者為先。

見證人簽名：_____日期：_____年____月____日

* 受試者、法定代理人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意之討論。並確定受試者、法定代理人或有同意權之人之同意完全出於其自由意願後，應於受試者同意書簽名並載明日期。試驗/研究相關人員不得為見證人。

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Appendix C. Safety questionnaire of Transcranial Magnetic Stimulation (TMS)

Version: 1.0 Date: 20180116

試驗編號：_____ 參與日期：_____

經顱磁刺激安全問卷

非常感謝您參加我們的經顱磁刺激研究(Transcranial magnetic stimulation, TMS)。以下您的回覆僅會用於本研究用以評估您是否適合接受經顱磁刺激。本研究其他細節已詳述於受試者同意書中。為了確保您在接受經顱磁刺激的安全性，煩請圈選下列問題。若有任何疑問可立即提出由檢測者為您回答。

是	否	1. 您年紀是否小於 18 歲？
是	否	2. 您是否有裝設心臟節律器或是心內導線？
是	否	3. 您是否有裝設人工電子耳？
是	否	4. 您是否有裝設脊椎或是腦室引流管？
是	否	5. 除了牙套或牙齒填充物，您的頭部或是體內是否有移植任何金屬/電/磁場裝置(如：深腦刺激器) ？
是	否	6. 您目前是否懷孕/可能懷孕？
是	否	7. 您或您的直系親屬 (祖父母、父母、兄弟姊妹、叔叔阿姨輩、子女、自己) 是否有癲癇病史?若有，煩請圈選括號中有癲癇病史之親屬。
是	否	8. 您是否有任何現行之重大疾病或是不穩定之疾病情況？
是	否	9. 您是否有任何神經系統或是精神相關的疾病病史？
是	否	10. 您是否曾頭部受傷過或是接受過頭部、脊椎手術？
是	否	11. 您是否有未控制得宜之偏頭痛或是耳鳴？
是	否	12. 您是否曾未預期昏倒、感受到輕微頭痛或是突然視覺受限? 若有，請敘述在何種場合發生？_____
是	否	13. 您是否有固定服藥？ 若有，煩請詳列於:_____
是	否	14. 您在過去 12 小時內是否有服用任何藥物？(避孕藥物除外)
是	否	15. 您在過去 12 小時內是否有服用或使用酒精、尼古丁或其他藥物？
是	否	16. 您對於本實驗是否有任何擔心或是疑問？若有，可向施測者表達您的疑問或是擔心。
是	否	17. 身上是否有任何金屬物 (如：手錶、珠寶、髮飾或髮夾、眼鏡、耳環或舌環、鼻環、錢包、鑰匙、手機)？如果有，請移除放置於遠離身體處。
是	否	18. 您過去是否接受過經顱磁刺激或是核磁共振？若有，煩請圈選項目。

我已經閱讀理解以上相關問題。我已正確並完整回答本問卷所有問題，並簽名表示回答正確無誤。

■ 受試者簽名:_____ 日期: _____

■ 研究者簽名:_____ 日期: _____

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