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巴金森氏症病患於聽覺提示下執行節律性動作之依頻大腦皮質興奮性

Frequency-Dependent Cortical Excitability in Rhythmic Movement with Auditory Cues in Parkinson's Disease

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本論文係洪郁婷君(R02428011)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104年7月24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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誌謝

當初選擇繼續升學，或多或少都是為自己的長不大找理由，擔心脫離習慣的學生生活，也對於社會一無所知而惶恐。「飛快」是碩班兩年的其一註解，而如此的字眼通常十分不負責任，不需要回想或分享有關學習、收穫、人際、任何心情。

有限的篇幅，只能單純的記下一些名字，卻有無限感激。感謝我的指導教授團：陸哲駒老師、張雅如老師與黃英儒醫師、口試委員：黃正雅老師與周立偉老師、林口長庚神經內科：陳柔賢醫師與陸清松醫師、林素絹小姐、協調受試者的護理師們、臺大的夥伴們：張嘉容、張甯雅、游舒涵、李穎軒與陳慈慧、各個時期的好友們：楊宜儒、許憶婷、邱寶儀、李依臻、劉子瑛、蕭茗榕、楊翊君。不論實驗、撰寫論文、或茶餘飯後，你們給予的是我當下真正需要的協助、支持與娛樂，是你們搖滾了我的生活。最後，吳若媽以及我的父母、妹妹，除了論文中的這一頁，在人生的扉頁裡，你們依然舉足輕重，是我身心靈最堅強的後援部隊。我愛你們。

做研究、寫論文，有趣不有趣，無聊也不無聊，想到未來 Google 學術可能會出現這篇研究，都已經開始傻笑了。我的青春不酣觴賦詩，我的青春寫論文。

中文摘要

背景：外在提示 (External cue) 被廣泛運用於巴金森氏症 (Parkinson's disease) 之動作功能訓練。前驅研究發現，巴金森氏症病患於 2 赫茲聽覺提示下執行手指敲擊 (Finger tapping) 訓練後，除了動作表現進步外，亦可能調節大腦動作皮質的活性。然而，患者並不侷限於單一的動作頻率，且物理治療師會依病患狀況給予不同頻率的外在提示。根據以往研究，不同頻率的聽覺提示會影響巴金森氏症患者的動作表現，而大腦動作皮質活性是否能顯現不同頻率間的差異，目前仍未清楚。**目的：**本研究採用同步化的 1 赫茲或 3 赫茲的聽覺提示，對照無同步化的聽覺提示，並要求巴金森氏症病患執行節律性手指動作，觀察其動作表現，且利用經顱磁刺激 (Transcranial magnetic stimulation, TMS) 評估訓練前後大腦皮質興奮性改變情況，是否與 2 赫茲有所差異。以研究巴金森氏症於不同頻率之聽覺提示訓練時神經生理的改變及可能機轉。**方法：**此為隨機交叉研究 (Cross-over study)，收取 25 位侯葉分期 (Modified Hoehn & Yahr Stage) 為 I 至 III 期原發性巴金森氏症候群患者，其中 12 位 (年齡為 64.2 ± 8.0 歲) 分配至 1 赫茲組，13 位 (年齡為 61.4 ± 9.4 歲) 則分配至 3 赫茲組。而兩組受試者皆需接受兩次相隔一星期之介入，外在提示為同步化的聽覺提示下進行手指節律動作，而自我導引則於無聽覺提示下進行。**結果：**外在提示練習後，只有 2 赫茲組快速手指動作的變異度顯著減少 (p= .032)，三組大腦皮質內的抑制強度 (Short intracortical inhibition, SICI) 顯著增加 (1 赫茲：p= .002；2 赫茲：p< .001；3 赫茲：p< .001)，且與自我引導練習後有顯著差別 (1 赫茲：p< .001；2 赫茲：p= .005；3 赫茲：p= .011)，而大腦皮質內促進強度 (Intracortical facilitation, ICF) 則顯著降低 (1 赫茲：p= .006；3 赫茲：p= .002)。三組間比較發現，大腦皮質內促進強度於 1 赫茲與 3 赫茲相對 2 赫茲有顯著差異 (1 赫茲與 2 赫茲間：p= .001；2 赫茲與 3 赫茲間：p= .008)。**結論：**僅 2 赫茲同步化聽覺提示能顯著增加節律性動作表現，雖然三者頻率皆能調節大腦皮質內興奮性，但並未能完整地解釋運動皮質興奮性之改變與運動表現的

相互關係。

關鍵字：聽覺提示、巴金森氏症、頻率、動作表現、大腦皮質興奮性

ABSTRACT

Background: External cues are widely applied on training motor functions in movement disorder such as Parkinson's disease (PD). In our previous study, changes in the motor cortex excitability were shown the 2 Hz finger tapping with auditory cue might modulate the cortical activity in PD patients. However, movements of human subjects are not restricted to a specific rhythm, and physical therapists use external cues across different frequencies depending on patients' status in rehabilitation. Frequency-dependent movement activities were reported in present studies. It is still unclear whether motor cortex activity reveals a frequency-dependent pattern at different rates in PD. **Objective**：The performance and motor cortex excitability of frequency-dependent finger movements with auditory cue in patients with PD were investigated in this study. To explore the mechanism underlying the auditory cued training across different frequencies, changes of motor cortex excitability were obtained by using transcranial magnetic stimulation (TMS). **Methods:** This study was a cross-over study. A total of twenty-five patients (H & Y stage I-III) were randomly assigned to 1 Hz (12 patients, 64.2 ± 8.0 years) or 3 Hz (13 patients, 61.4 ± 9.4 years) group. All participants received two sessions of experiment in random order, one was external-triggered condition which received auditory cue while performed movements, and self-initiated condition which performed movement after listened to required

rhythm. **Results:** After training with auditory cues, CV of fast tapping only significantly decreased in 2 Hz condition (p= .032). There were significant increase of short intracortical inhibition (SICI) (1 Hz: p= .002; 2 Hz: p< .001; 3Hz: p< .001) and significant difference between ET and SI conditions (1 Hz: p< .001; 2 Hz: p= .005; 3Hz: p= .011). Significant post-training decrease of intracortical facilitation (ICF) in 1 Hz and 3 Hz groups (1 Hz: p= .006; 3Hz: p= .002). Additionally, ICF was significantly different between 1 Hz and 2 Hz conditions (p= .001), 2 Hz and 3 Hz conditions (p= .008). **Conclusions:** Only 2 Hz auditory cues had significant benefit in rhythmic movements. Though 1 Hz, 2 Hz and 3 Hz cues were able to modulate the cortical excitability in the motor cortex, the mechanisms involved in the application of auditory cues still needed more studies.

Keywords: Auditory cue, Parkinson's disease, frequency, motor performance, motor cortex excitability

LIST of ABBREVIATIONS

CV	coefficient of variation
DBS	deep brain stimulation
EMG	Electromyogram
FDI	first dorsal interosseus
fMRI	functional magnetic resonance imaging
FOGQ	Freezing of gait Questionnaire
GPi	globus pallidus interna
ICF	intracortical facilitation
ISI	interstimulus intervals
M1	primary motor cortex
MEPs	motor evoked potentials
MT	motor threshold
PET	Positron emission tomography
PD	Parkinson's disease
rCBF	regional cerebral blood flow
SICI	short intracortical inhibition
SMA	supplementary motor area

STN	subthalamic nucleus
TMS	transcranial magnetic stimulation

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Chapter 1 Introduction

1.1 Background

Basal ganglia mediate internal timing operations,[1] so people suffering from Parkinson's disease (PD) lose their ability to maintain movements at a constant rhythm.[2] Such disturbed timekeeping is a possible basis of freezing of gait (FOG),[3,4] motor blocks during performing finger tapping, or difficulties in executing self-initiated movements.[5]

Visual or auditory guidance is often used by physical therapists to facilitate movement in PD patients. Mounting evidence has revealed that external cues can enhance balance, gait and upper extremities functions.[6-8] Meanwhile, auditory cues provide more promises on improvement in rhythmic movement and benefit in clinical use. However, few studies investigated neurophysiological mechanism underlying the use of external cues.[9,10] Motor training with visual cues rather than auditory cues improved motor cortex excitability.

To further assess changes of the motor cortex excitability due to auditory cues, our laboratory previously investigated PD patients with or without auditory finger-tapping task at 2 Hz and observed modulated short intracortical inhibition (SICI) effect. However, restricted cueing patterns such as frequency represented limitation of the study Impairment in rhythmic movements of the upper extremity in PD patients

may be frequency dependent. Patients tend to tap at higher rates than asked for.[11] In addition, variability of tapping rhythms is greater than healthy subjects.[12]

Frequency-dependent neural activation in brain regions has been the focus of a few studies, but it is still ambiguous.[13,14] An increase of neural activity at higher frequency in cortical and cerebellar areas has been observed both in healthy subjects and PD. In contrast to healthy subjects, the lack of frequency-dependent neural activity in the basal ganglia was observed in patients.[1]

1.2 Purpose and Significance

The aims of this study were (1) to investigate performance and motor cortex excitability of frequency-dependent finger movements in patients with PD, (2) to explore the mechanism underlying the auditory cued training across different frequencies (1 Hz, 2 Hz, and 3 Hz).

Understanding specific neural activity pattern can inform further clinical application of various components of auditory cues to maximize motor improvement.

1.3 Hypotheses

Study question 1: Are there any behavior changes* after finger tapping with auditory cues?

Null hypothesis: After finger tapping with auditory cues, there are no significant changes in all of the behavior measurements*.

Alternating hypothesis: After finger tapping with auditory cues, there are significant changes at least one of the behavior measurements*.

Study question 2: Are there any neurophysiological changes* after finger tapping with auditory cues?

Null hypothesis: After finger tapping with auditory cues, there are no significant changes in all of the neurophysiological measurements**.

Alternating hypothesis: After finger tapping with auditory cues, there are significant changes at least one of the neurophysiological measurements**.

Study question 3: Are there any differences of neurophysiological measurements** among three groups after auditory finger tapping?

Null hypothesis: There are no significant differences in neurophysiological measurements** among three groups after auditory finger tapping.

Alternating hypothesis: There are significant differences in neurophysiological measurements** among three groups after auditory finger tapping.

Study question 4: Are there any differences of behavior measurements* among three groups after auditory finger tapping?

Null hypothesis: There are no significant differences in all of the behavior

measurements* among three groups after auditory finger tapping

Alternating hypothesis: There are significant differences in at least one of the behavior measurements* among three groups after auditory finger tapping.

*Behavior measurements: Coefficient of variance (CV) and mean duration of inter-tap interval (ITI)

**Neurophysiological measurements: motor evoked potentials (MEPs), short intracortical inhibition (SICI) and intracortcial facilitation (ICF)

Chapter 2 Literature Review

2.1 Introduction of Parkinson's disease

2.1.1 Functions of Basal Ganglia

Basal ganglia are one of major subcortical structures that form multisynaptic loops with the cerebral cortex via ventrolateral thalamus. Two important circuits in the basal ganglia are direct and indirect pathways. These circuits modulate movement by facilitation and inhibition. The direct pathway is responsible for triggering the movement and for activating the neurons in the thalamocortical route. The indirect pathway inhibits the neurons in the path from the thalamus to the cortex.[16]

One of the major functions of the basal ganglia is temporal information processing.[17, 18] It might refer to various functions such as processing of the duration of stimuli or their temporal order. The role of the basal ganglia in timing was examined by Harrington and Haaland.[1] 24 normal controls and 34 PD patients were studied in tow conditions of a motor-timing and a duration perception task. The finding that timing operations were regulated by the basal ganglia was consistent with other studies.

2.1.2 Definition and Symptoms

The pathologic features of Parkinson's disease (PD) were explained initially in the

early 20th century and are highlighted by degeneration of dopamine-secreting cells in the substantia nigra pars compacta (SNc).[19] It's named in honor of James Parkinson, who provided a description of the disorder in his famous manuscript 'An Essay on the Shaking Palsy' in 1817. Clinically, the disease is characterized by a series of cardinal symptoms which include resting tremor, rigidity, bradykinesia, and gait impairment with postural instability.[20]

Basal ganglia mediate internal timing operations, so people suffering from Parkinson's disease (PD) lose their ability to maintain movements at a constantrhythm.[2] Such disturbed timekeeping is a possible basis of freezing of gait (FOG),[3,4] motor blocks during performing rhythmic finger tapping, or difficulties in executing self-initiated movements.[5] An unbalance between the direct and indirect pathways ultimately influences cortical activity, and, in particular, the primary motor cortex (M1), prefrontal cortex and supplementary motor area (SMA).[21-23]

Patients tend to display not only motor symptoms mentioned above, but non-motor symptoms involve higher order functions. Brown and colleagues found that greater activity in frontal lobe by functional magnetic resonance imaging (fMRI) during planning and preparation states before movement.[24] Affected people will develop cognitive disturbances, behavior changes, and poor execution functions, these symptoms may attributed to pathologies in prefrontal cortex and basal ganglia circuits.

2.1.3 Prevalence

PD is a common age-related neurodegenerative disorder, second only to Alzheimer's disease (AD).[25] Approximately four million people worldwide are affected by PD. The median onset age is 60 year-old, and around 10% of patients are younger than 45 years. The prevalence of PD is about 1% in the population older than 65 years, and rising to 3% among persons who are older than 80 years.[26] In general, aging is the greatest factor for PD. In Taiwan, the prevalence is 0.63% and it is similar to other countries.[27]

2.1.4 Current Management

The treatment options for PD continue to expand. And the current management is mainly focus on pharmacotherapies. As the disease progresses, neurosurgery may be considered for some patients.

Drugs are symptomatic treatment which aims at controlling motor symptoms and preventing motor complications.[28] Since the symptoms of PD are consequence of dopamine depletion in the basal ganglia, dopaminergic therapies are reasoned by modulating dopamine level. Levodopa is a dopamine-replacement drug which has been highly success in improving motor symptoms. Other medicine, such as dopamine agonists, COMT inhibitors, monoamine oxidase isoenzyme type B (MAO-B) inhibitor

are common drugs for PD.

However, there are side effects of drugs. Motor complications such as motor fluctuations and dyskinesia occur after long term use. Patients experience reduced drugs effect. The duration of improvement after taking drugs decreased, it is called wearing-off phenomenon. The motor symptoms may reappear, the motor performance becomes fluctuated. Dyskinesia involves involuntary movement, it may occur at peak-dose level.

Invasive surgery may be applied to some patients who may have motor complications and poor response to the medicine. Two common surgical treatments are pallidotomy and deep brain stimulation (DBS).[29] Pallidotomy is to destroy some cells in globus pallidus by a tiny electrical probe. It causes irreversible lesion, it sometimes requires reoperation because of inadequate lesion volume. DBS has become the most frequent surgical procedure in recent year. The mechanism of the DBS is to stimulate brain cells rather than destroy them. The stimulation probe of DBS is implanted inside the two most common sites, the subthalamic nucleus (STN) or the globus pallidus interna (Gpi), stimulation of STN is highly recommended because there are more evidences about its effect. The parameters of DBS stimulation can be adjusted after the implant. However, these invasive techniques are expensive and usually recommended only for patients who have failed in conventional treatment.

Both surgical options are considered as efficacious and clinically useful for the treatment of motor symptoms. There are still potential risks of infarction, intracerebral bleeding and seizures. Dysfunction of device may happen because of infection or inadequate position of the device.

2.2 External Cue as Rehabilitative Technique

2.2.1 Effects of External Cue on Motor Performance

External cue refers to use a temporal or spatial stimulus to facilitate initiation and continuation of movement, and is delivered in auditory or visual forms.[30] Cueing is a major component in rehabilitation and widely applied in different population. Visual cues can be set by laser pointers or lines marked on the floor. Auditory cues may include strategies which use counting, music or metronome to produce rhythmic beat. Recent studies supported that cueing can have a significant effect on motor performance in PD patients.[6-8, 31, 32]

Gait deficits in people with PD are characterized by reduced velocity and stride length, increased cadence, and freezing of gait. Spaulding and colleagues conducted a meta-analysis which focused on the use of external cues to improve gait in PD.[7] 718 individuals from the 28 studies were included, all studies provided objective kinematic gait parameters. The findings inferred that auditory cues could decrease cadence,

increase stride length and gait velocity; whereas visual cues were only effective in improving stride length in patients.

Freezing of gait is considered to be associated with an increased risk of falls.[33] Thus, it is important in rehabilitation to normalize the movements during gait. 153 PD experienced gait freezing were tested by Nieuwboer and colleagues.[6] Subjects received 3-week home auditory or visual cued training (cue type was chosen by the subjects). In agreement with other studies, showing that gait velocity, stride length, and cadence were all improved. In addition, a reduction of freezing severity was found after intervention.

Further investigation about the effect of cueing on upper limbs movement was done by Vercruysse and colleagues.[8] A total of 23 PD subjects and 11 controls performed repetitive index finger movements in cued or non-cued mode. The results showed the mean and variation of movement frequency are comparable between the groups under the presence of auditory cues, the variation of frequency significant increased 13.47% in PD group after withdrawing the auditory cues (p= .0028).

Over all, optimal external cue strategy is efficacious in rehabilitation for motor improvements in affected people. Moreover, auditory cues other than visual cues appear to provide larger effect on rhythmic and repetitive movement.

2.2.2 Effects of External Cue on Cortical Excitability

Motor training with external cues enhances motor functions and benefits in clinical use. However, there are scarce evidences about effects on neurophysiological changes. Sawy and colleagues explored the effect of verbal auditory cues on motor cortex excitability in 17 PD patients and 18 controls.[10] The subjects performed repetitive thumb abduction-adduction at preferred rates and verbal auditory cues. Compared with performance without cue, MEP has not changed among patients in cued-condition.

Changes in motor cortex function were observed by Chuma and colleagues.[34] 12 PD patients and 9 controls were measured by TMS-induced movement after 15-min thumb extension training with and without 1 Hz rhythmic sound. After 15 minutes cued training, the TMS-evoked movement amplitude increased in PD patients and revealed no significant difference compared to normal controls. They concluded the process of motor reorganization in patients was the same as normal subjects.

Mak and Hallett examined the changes of motor cortex excitability with TMS after training under visual cues in eight PD patients.[9] Patients received two sessions of 30-min pinch grip training with or without visual cues. The visual cue was given in form of an arrow which indicated the required force level was showed in monitor. There were significant increases in the motor evoked potential (MEP) peak, and

tapping speed after the practice under the cued conditions, but not for the non-cued conditions. It proved that practice with external cue may significant enhanced motor cortex excitability.

Previous research in our laboratory investigated the motor cortex excitability with TMS after auditory finger-tapping practice at 2 Hz and observed modulated short intracortical inhibition (SICI) effect. Neurophysiological changes such as motor cortex excitability are valuable to understand more about the external cue, especially for the auditory cues because of its importance of clinical application.

2.2.3 Potential Mechanisms of External Cue

Visual or auditory guidance is often applied to facilitate movement in PD patients. However, the neurophysiological mechanism underlying the use of external cues has yet to be established. But the common hypothesis is external cues may be a compensatory way bypassing the deficient basal ganglia-thalamo-motor (BGTM) pathway and utilize the cerebro-cerebellar (CC) pathway.[35, 36, 39]

The internal and external loops of motor control were proposed by Goldberg in 1985.[37] Basal ganglia and the supplementary motor area (SMA) play important roles in internally generated movements, involved in the internal loop. On the other hand, the external loop is considered to include the cerebellum, parietal cortex, and lateral

premotor cortex (PMC).

Regional cerebral blood flow was made in six healthy men in Jenkins' s study.[38] The subjects were asked to tap their right index finger rhythmically with Positron emission tomography (PET) scan under three conditions: at rest, during self-initiated and external-triggered movements. Bilateral putamen was found significant increased rCBF during the SI and ET movement than resting, but the rCBF was higher under SI condition than ET. Similar study was investigated by Cunnington and colleagues, 12 healthy subjects participated. The subjects executed movements freely with irregular time interval between taps. FMRI analysis revealed significant increased neural activity within bilateral putamen during the SI movement, but not during the ET movement.

Pathologies in PD include depletion of nigral dopaminergic neurons projecting to the dorsal putamen, and then to the SMA. SMA is responsible for the reproduction of rhythms, in the absence of an auditory cue to guide performance.[40] Rao and colleagues found that right index finger tapping activated right cerebellum and left sensorimotor cortex during the synchronization (SYNT) and continuation tasks (CONT).[41] The CONT made greater demands on an internal timekeeping system including SMA, putamen (basal ganglia) and vetrolateral thalamus.

Cerebellum is another major structure in motor control. Although the basal

ganglia and cerebellum are organized into two discrete loops, they all project to the thalamus, and communicate with each other.[42,43] Moreover, there is high consensus that both structures involve in motor-timing operations so that it is believed that cerebellum play compensation role for the basal ganglia to execute rhythmic or repetitive movement.[35, 36]

Taniwaki and colleagues investigated the connectivity within the BGTM and CC circuits in 12 PD and controls under SI and ET conditions.[36] All participants were right handed and they performed the movement with the left hand. FMRI showed that predominantly activities located in BGTM circuit during the SI movement, while predominantly activities were in CC circuit during the ET movement in the control group. However, there was disrupted connectivity in the BGTM circuit in PD subjects. Compared with the controls, the PD patients showed hypoactivation in bilateral putamen, right SMA, hyperactivation in right PMC and cerebellum. During the ST movement, the activities in BGTM circuit were significantly lower in the PD group than controls; during the ET movement the activities in CC circuit were significantly higher. It implicated that the use of external use can bypass the disrupted motor circuit (BGTM circuit) so that another circuit (CC circuit) complete the movement goals.

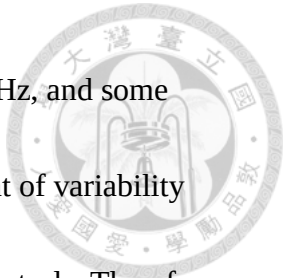
2.3 Finger Tapping Test

2.3.1 Introduction of Finger Tapping Test

The finger tapping test (FT) is a commonly used tool for evaluating rhythmic movement patterns and for clinically assessing neurophysiological changes in human. It is also frequently used to quantitatively detect alternative performances in elderly, PD and other neuropathologies.[12,44]

The task usually referred to periodic tapping, the interval between each tap should be the same. It can be performed at fastest rate, comfortable rate or externally paced movement.

Subjects were reminded to tap as fast as possible in fast tapping condition mode, it was advocated by Shimoyama in 1990 for people with different ages and other pathologies.[45] However, some studies reported that decreased tapping rate after a few seconds due to fatigue or central rhythm formation impairment. Arias and colleagues evaluated the validity of tapping task to assess rhythm formation in PD, elderly healthy (HE) and young healthy controls (HY).[12] All subjects executed two condition modes including fastest and comfortable rates, 3 sets of 50 taps in each mode. They found that only young subjects significantly decreased their tapping rate in the fastest mode. It suggested that repeated sets of 50 fast taps did not affect the tapping rate in PD and HE groups.



Comfortable tapping rate for normal healthy subjects is about 2 Hz, and some studies stated similar results in the PD patients.[46] However, coefficient of variability (CV) of inter-tap interval is larger in patients with PD than healthy controls. Therefore, 2 Hz is the most common frequency used in researches and CV is more sensitive markers for detecting alteration of movement.

2.3.2 Synchronization-continuation Paradigm

Tapping in synchrony with and external pacing rhythms is called synchronization. Both the action and the external event are periodic, so human beings have the ability to predict it and turn it into internal rhythm. In general, there is a certain range (200-2000ms) of the interval between every cue for normal subjects.[47] It represents the maximum frequency the effecter can generate and the predictability of the rhythm. So, tapping with 1-3 Hz is also reasonable for the case of synchronization.

Synchronization-continuation is a special tapping paradigm.[48] It required the subject to synchronize the tapping with the external pacing stimulus at the beginning, then followed by an unpaced phase in which subject is required to continue tapping at the same rate for further 30 to 50 taps. In other words, this design includes external triggered and internal generated phases. The continuation part can provide value assessments about the self-initiated movement with standard required rhythm, so it is a

widely applied test for PD.

2.4 Frequency-dependent Movement Control

Earlier observations of Freeman and colleagues for finger tapping with auditory signals of target frequencies (range 1-5 Hz) and sustained required rhythms following absent of auditory cues.[11] PD patients' tapping rates increased for low intermediate frequencies (1-3 Hz) and decreased for high target frequencies (4-5 Hz) under these conditions. And the patients exhibited a greater reliance on auditory cues.

The disturbed internal clock influences the execution of normal motor rhythm. Yahalom and colleagues assessed the rhythmic hand movements in 51 PD and 36 controls and in parkinsonian subtypes.[49] Patients were classified into: tremor predominant (TP), freezing predominant (FP), akinetic-rigid (AR) and an unclassified group (UC), and asked to tap at a target rhythm of different frequencies (range 2-5 Hz). Only TP subgroup showed hastening when tapped at 2.5 Hz and greater variation in external pacing frequency of 4, 4.5 and 5 Hz. Specific PD subtypes might be associated with differences in rhythm generation.

Neural correlates of frequency dependent movement control are thought to be restricted to specific areas. Previous study investigated healthy subjects with an auditory finger tapping across six frequencies (range 2-6 Hz) and demonstrated a

negative relationship between movement rates and hemodynamic response within the basal ganglia. Moreover, an increase of the activations in cortical regions (SMC and SMA) was parallel to increasing movement frequency.[14] Wurster and colleagues studied ten healthy subjects and ten PD patients using an acoustically finger tapping task under three frequencies (1, 2.5, and 4 Hz).[15] FMRI analysis revealed a frequency dependent activation within the supplemental motor area, primary sensorimotor cortex, thalamus and cerebellum with higher activation at higher frequency in both groups. The basal ganglia (putamen/pallidum) displayed an inverse activation pattern in healthy subjects, whereas this observation was not evident in PD. It implicated that the basal ganglia dysfunctions in frequency-dependent requirements.

2.5 Transcranial Magnetic Stimulation

2.5.1 Basic Principles of Transcranial Magnetic Stimulation

In 1980, Merton and Morton developed a high-voltage electrical stimulator to elicit a muscle response by stimulating the primary motor cortex (M1) through the scalp. But a problem with transcranial electrical stimulation (TES) was pain. Transcranial magnetic stimulation (TMS) provided, introduced by Anthony Barker in 1985, a non-invasive pain-free method of activating the motor areas and examining the functional integrity of the corticomotor pathways. It has now come into wide use in

clinical and research settings. Then its modulation of cortical excitability was noticed by scientists and was also being developed as a therapeutic tool.[50-53] We focus on the diagnostic use here.

The other important base of TMS design is the famous Faraday's Law. It was a principle of electromagnetic induction which discovered in 1831.A TMS device consist of high voltage (400V-3kV) and high current (4kA-20kA) discharge systems. Magnetic coil is placed over the scalp, a pulse of high current pass through the coil and generate a magnetic field (1-2.5T) and typically lasts for about 100μs, and further induces secondary current inside the intracranial tissue. The secondary current with opposite current direction to the origin current runs in parallel to the plane of coil. It usually focuses on the primary motor cortex (M1) and results in action potentials in cortical axons, the excitation travels along the corticospinal tract and peripheral motor nerve, then the responding muscle will be activated and can be recorded by surface electromyogram. The size and shape of the waveform of EMG represents the TMS results.

2.5.2 Assessment of Cortical Excitability

Using TMS, the functional integrity of the corticomotor tract can be detected, and the brain can be briefly facilitated or inhibited. However, the application of TMS is

limited to deep brain structures such as the basal ganglia or thalamus. The information comes from the motor cortex implies much information about other brain structure.

The diagnostic measurements of TMS can be divided into two modes: single pulse TMS and paired pulse TMS. The following review focus on the parameters used in this study.

Single pulse TMS

Motor Evoked Potentials (MEPs)

Motor evoked potentials (MEPs) can be recorded through surface EMG of the target muscle which is contralateral to the stimulation site of brain area.

The presence of intact MEPs not only indicates integrity of the pyramidal tract, but represents the excitability of the motor cortex, nerve roots and the conduction along the peripheral motor pathway to the muscles.

Motor threshold (MT)

Motor threshold (MT) refers to the minimum TMS intensity required to produce small MEPs (50-100μV) in the target muscle, in at least 50% of consecutive trials. MT reflects membrane excitability of corticospinal neurons, interneurons and motor neurons in the spinal cord, neurotransmitter junctions and muscles**.**

Paired pulse TMS

Paired pulse TMS combines of a subthreshold conditioning stimulus with a

suprathreshold test stimulus at different inter-stimulus intervals (ISI) of 1-20ms. The modulation effect depends on the intensity of the conditioning stimulus and the ISI. Effects of inhibition and facilitation appear to interact in a roughly linear manner.

Short intracortical inhibition (SICI)

Inhibitory effects are found at short ISI of 1-5ms and conditioning stimuli of 60-80% of the resting motor threshold (RMT). It induces about 20-40% decrease of test MEPs.50 SICI might be mediated through GABAergic effect, specifically GABA-A.[54]

Intracortical facilitation (ICF)

Facilitatory effects are found at longer ISI of 8-20ms. The amount of facilitation can be start form 120-300% of test MEPs.[50] In addition, these intracortical mechanisms are similar across different motor representations. The paired pulse technique can be used to investigate the effects of drugs and motor training on the motor cortex.

2.5.3 Application in Patients with Parkinson's Disease

The degeneration of dopaminergic pathways in PD results in functional disturbances of motor cortex. These disturbances can be revealed by the abnormalities of cortical excitability and be assessed by TMS. Imaging studies such as fMRI, PET and single-photon emission computed tomography (SPECT) attempted to investigate

the changes of cortical activity by accessing the regional cerebral blood flow, it cannot differentiation between excitatory or inhibitory synaptic activity. In contrast, the advantages of using TMS can detect whether excitatory or inhibitory changes in motor cortex by using paired pulse design.

Abnormalities of cortical excitability in PD

Although there is diversity of PD with different stage of the disease, rather consistent results reported for cortical excitability. Two of reviews conducted by Cantello and colleagues and other studies revealed that when patients with reduced MTs and enhanced MEP than controls at rest.[55,56] Decreased SICI and ICF was also found, it indicated that PD patients had less modulation ability than controls. However, the results of SICI remains controversy, some studies shown no changes of SICI in PD patients. Because the ISI of short-interval intracortical facilitation (SICF) is less than 5ms, there is an overlap to SICI. Ni and colleagues suggested not to overestimate the amount of decreased inhibition because some portion of SICI may cancelled by SICF, but they still supported dysfunction of inhibition in PD patients.[57] Taken together, the cortical excitability in PD revealed an excessive corticospinal output at rest, resulting from reduced ICI and reduced MT. These disturbances are corresponding to the clinical pictures about tremor and rigidity of PD patients.

Medications normalized the abnormalities of cortical excitability

The effect of dopaminergic medication normalized the excitability of PD, and can balance the inhibitory and excitatory mechanisms of motor cortex. Lou and colleagues noticed that MT and MEPs of PD in OFF state was significant lower (p= .02) and larger (p=.0006) than the control, respectively.[58] The MEPs was significant smaller in the ON than in the OFF state.

Riddling and colleagues evaluated 11 PD patients both at ON and OFF state, 10 age-matched controls were also recruited.[59] They discovered that PD-OFF group had significant decreased inhibition relative to the controls, but it was not significant after taking L-dopa.

Chapter 3 Methodology

3.1 Study Design

The study was a randomized cross-over design. First, patients were randomly assigned to 1 Hz or 3 Hz group. And each group included external-triggered (ET) condition which received auditory cues while performed movement, and self-initiated (SI) condition which executed movement after listened to required rhythm. All participants were in both conditions in different time (one week wash-out period) in random order.

3.2 Subjects

Subjects who aged between 40 and 80 years and diagnosed as idiopathic Parkinsonism were recruited through the Movement Disorders Clinics at Chang Gung Memorial Hospital. Prior to the experiment, all participants were informed of the purpose and process of the study and provided their consent forms. The study was approved by the Chang Gung Medical Foundation Institutional Review Board (Appendix 1). No patients felt any ill-effects throughout and after the experiments.

Exclusion criteria

Subjects were excluded from the study if any of the following were found: (1) diagnosis of neurological diseases other than PD, (2) dementia (Mini Mental State

Examination score less than 24/30), (3) inadequate language function to understand study-related instructions due to cognitive dysfunction, (4) potential contraindications to TMS: history of epilepsy, intracranial metal implant, pace-maker, or electrical neurostimulators, (5) subjects who had brain injury, stroke or brain surgery, (6) syncope of unknown reason or intermittent headache.

3.3 Experimental Assessment

The assessment of this study included three aspects: basic data collection, behavior measurements of finger tapping test and TMS recording.

Basic data collection

Basic data included age, gender, disease duration, dominant hand, medication conditions, modified Hoehn & Yahr stage, scores on Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Examination (MMSE). The information was retrieved from medical chart or taken by the researcher.

UPDRS was developed by Fahn and colleagues in 1987. We used part III to assess motor functions in PD patients. Higher scores correspond to more severe disease. MMSE is a tool to exclude severe cognitive deterioration (Appendix 2 and 3).

Behavior measurements of finger tapping test

Cyclic index finger flexion-extension movements were executed in comfortable,

fastest and synchronization-continuation modes for pre- and post-motor practice assessments.

(1) Comfortable tapping task: Subjects started to execute finger movements at their comfortable speed for 50 taps at the beginning of the experiment.

(2) Fastest tapping task: Subjects were asked to tap at their fastest rate for 50 taps. 3 runs were tested to minimize intra-session variation. 30-s rest between repetitions was set to prevent fatigue.

(3) Synchronization-continuation task: Each run began with computer generated tones at 1or 3 Hz. Subjects were asked to tap synchrony to the tones for 50 taps (synchronization). After the tones stopped, they continued to tap at the same pace for further 50 taps (continuation). It repeated 3 runs and 30-s rest was set between repetitions.

During motor practice, programs were set in different ways in ET and SI conditions. For ET condition, participants were instructed to tap synchronously to reach the same rhythm (1 or 3 Hz) generated by computer. Subjects had to repeat this action 10 runs, and a 60-s rest was given between each run. The SI condition listened to 50 tones (1 Hz or 3 Hz) without finger movements, they made 50 taps at the required rhythm after listening, and repeated 10 runs. A 10 or 43-s rest was given between repetitions in 1 Hz or 3 Hz group. After rest, subjects in SI condition would

listen to another 1 Hz or 3 Hz tones for 50 beats, it took 50 or 17 seconds, so it was the same as the ET condition that 60 seconds (1 Hz: 50s + 10s, 3 Hz: 17s + 43s) in total without finger movements.

Behavior measurements included mean duration and coefficient of variance (CV) of the inter-tap intervals (ITI). When movement occurs to synchrony with an external beat or settle to into continuation rhythm, it generally takes 3-5 taps. Therefore, the first 3 taps were discarded in both synchronization and continuation phases to avoid transition periods. It ITI fell outside of ± 50% the inter-tones interval were recognized as error taps.

TMS recording

TMS was delivered through a hand-held figure-of-eight coil connected to Magstim 200 stimulator (TMS, Magstim Company, Whitland, UK). The coil was held tangentially on the skull and aligned in the sagittal plane with the handle pointing backwards and laterally at 45 degrees. Electromyographic recordings (EMG) were obtained from surface electrodes placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) muscle of task performing hand. EMG was amplified 5000 and 1000 times by D360 EMG device (D360 8 channel Digitimer, Hertfordshire, UK) with band-pass filtering between 10 and 2000 Hz. Amplified EMG were recorded using CED Power 1401 AD converter (Cambridge Electronic Design Ltd, Cambridge,

UK). Signal v3.03 (Cambridge Electronic Design Ltd, Cambridge, UK) and NuCursor software (J. Rothwell, Institute of Neurology, University College of London, UK) were used for later off-line analysis. TMS elicited a single pulse at a 5s inter-trial interval to the hemisphere contralateral to behaving FDI. The following measurements were included in this study.

(1) Resting motor threshold (rMT): rMT was measured by single pulse TMS. It was defined as the minimum stimulation intensity that could produce MEPs at rest with at least 50μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials.

(2) Motor evoked potentials (MEPs): The MEP size represents corticospinal excitability. TMS was applied at 120% RMT for ten times in each measurement. MEP amplitude was measured as peak-to-peak of the elicited wave.

(3) Short intracortical inhibition (SICI) and intracortical facilitation (ICF): SICI and ICF were measured by paired-pulse technique. The conditioning stimulus was set at 70% RMT and following by 120% RMT testing stimulus. SICI indicates suppression of a testing MEP by a conditioning stimulus 1-5ms earlier. And ICF represents facilitation of a testing MEP by a conditioning stimulus 10-15ms earlier. Different inter-stimulus intervals (ISI) of 2ms, 3ms, 7ms, 10ms, 15ms were delivered in random order. Ten stimuli were delivered for each ISI. SICI and ICF

were divided mean MEP amplitude which induced by testing stimulus. Therefore, SICI and ICF were expressed as a percentage of MEP.

3.4 Experimental Procedure

The PD patients were assessed after overnight withdraw of their antiparkinsonian medication. If there were difficulties for them to execute, the time interval between the medication taking time and the experiment starting time should be the same in both two test sessions. They were allocated and determined the order of two sessions in the experiment. Basic data were collected before the experiment started (Figure 1).

Behavioral and electrophysiological tests were done prior to and immediately after motor practice (Figure 2). During TMS assessment, the head and forearm of each subject were well supported by the back and arm of a chair to prevent any movement artifact in the experiment. They needed to place dominant hand on keyboard with index finger to execute tests and motor practice. Only if patients showed obvious unilateral symptoms, the hand with less neurological deficit was tested.

3.5 Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social

Science Version 17.0 (SPSS Inc., Chicago, IL, USA). Outcome measurements were expressed by mean and standard error mean (mean ± SEM).

Basic data were expressed by descriptive statistic. The Shapiro-Wilk's test and Levene's test were conducted to check normality of outcome variables and assumption of homogeneous of variance. Independent t test was used to compare basic data between groups.

For continuous variables such as the mean duration and CV of ITI, the peak MEP amplitude, SICI and ICF, 3x2x2 three-way mixed measure analysis of variance (ANOVA) was carried out for the analysis. Independent factors were groups (1Hz, 2Hz and 3Hz) or cued conditions (ET and SI) whereas repeated factors were time (pre- tests and post-tests). When a significant interaction was detected, post-hoc analyses and a compensatory α adjustment procedure might be applied (Bonferroni).

A criterion of $p < .05$ was used in all tests for statistical significance. Intention-to-treat analysis was used when there was missing data.

Chapter 4 Results

4.1 Demographic and Clinical Data

Twelve patients (3 female, averaged 64.2 ± 8.0 years, disease duration 6.9 ± 5.5 years, Hoehn and Yahr stage I-III) in 1 Hz group and thirteen patients (4 female, averaged 61.4 ± 9.4 years, disease duration 6.2 ± 5.0 years, Hoehn and Yahr stage I-III) in 3 Hz group were referred from outpatient clinic for movement disorders, Department of Neurology, Chang Gung Memorial Hospital. The demographic and clinical characteristics of all subjects are listed in Table 1.

4.2 Finger Tapping Test

All participants completed finger tapping test. Behavior measurements of finger tapping test is shown in Figure 3 and 4, including coefficient of variance (CV) of inter-tap interval in three groups.

4.2.1 Comfortable Tapping Task

For each participant, the average comfortable tapping frequency was determined initially. And patients moved at a mean rate of 2.41 ± 0.27 Hz. It indicated that 2 Hz was considered to be an optimal frequency for the PD patients.

4.2.2 Fast Tapping Task

In all three groups, CV was no significant difference in the baseline between ET and SI conditions. Compared to the mean duration, CV was a more sensitive index to investigate behavior changes in fast tapping task. We found a time effect for CV ($F_{(1,32)}$= 11.027, p= .002). Post hoc analysis demonstrated that the CV decreased significantly in ET condition in 2 Hz group (p= .032) (Figure 3). Trends of reduce decrease CV was investigated after cued training in 1 Hz and 3 Hz groups, but there were no significance (p= .16 and p= .094, respectively). CV in SI condition in three groups remained no significant change (1 Hz: p= .592; 2 Hz: p= .226; 3 Hz: p= .965). Therefore, patients experienced more improvement after 2 Hz cued training.

4.2.3 Synchronization-continuation Task

CV was no significant difference between ET and SI conditions in 1 Hz or 3 Hz group. The results showed significant interactions among group, cued condition and time ($F_{(2,32)}$= 4.399, p= .02). CV obtained during continuation phase of synchronization-continuation task detected significant decline after acoustic motor practice in 3 Hz group (p= .006). However, no decreasing of CV was observed at the end of the external-triggered mode in 1 Hz and 2 Hz groups (p= .191 and p= .511, respectively) (Figure 4).

4.3 Transcranial Magnetic Stimulation

4.3.1 Resting Motor Threshold (rMT)

The conditioning and testing stimulus were determined by the resting motor threshold. There was no significant difference in resting motor threshold between two sessions of the experiment, so the stimulus intensity was similar throughout two sessions in all conditions.

4.3.2 Motor Evoked Potentials (MEPs)

Percentage change in MEP amplitude ([(post-pre)/pre]*100%) was used in analysis. 2x2 two-way independent ANOVA was conducted for factors group and cued condition. No significant main effects of group and cued condition for MEP changes were detected ($F_{(2,61)}$= .792, p= .457; $F_{(1,61)}$= 3.502, p= .066).

4.3.3 Intracortical Inhibition (ICI) and Facilitation (ICF)

Figure 5 and 6 provides post-training $SICI_{(2ms, 3ms)}$ and $ICF_{(10ms, 15ms)}$ for each of the groups. The baseline data showed that there were no significant differences between ET and SI conditions in three groups. And there were no significant differences in SICI and ICF among three groups before cued training or non-cued training.

In our study, main effects of cued condition and time for SICI were found ($F_{(1,61)}$= 13.368, p= .001; $F_{(1,61)}$= 16.420, p< .001, respectively). There was also significant interactions between cued conditioned and time ($F_{(1,61)}$= 36.066, p< .001). Finger movements with 1 Hz, 2 Hz or 3 Hz auditory cues resulted in significantly increased SICI in FDI muscle (1 Hz: p= .002; 2 Hz: p< .001 3 Hz: p< .001). It demonstrated that there was significant increasing of inhibitory effect. Additionally, significant decrease for SICI was observed after non-cued training in 1 Hz group *(*p= .03). After followed three alternating frequencies, following different training programs, patients showed significant differences in SICI (1 Hz: p< .001; 2 Hz: p=.005 3 Hz: p= .011).

The analysis reflected main effects of group and time for ICF ($F_{(2,61)}$= 7.424, p= .001; $F_{(1,61)}$= 14.749, p< .001, respectively), and significant interactions between group and time ($F_{(2,61)}$= 3.210, p= .048). Immediately evaluate after cued training, ICF values had dropped significantly for FDI muscle in two groups (1 Hz: p= .006; 3 Hz: p= .002) were not consistent with 2 Hz group (p= .979). Post non-cued training ICF declined significantly in 3 Hz group (p= .012), whereas no significance in other two groups (1 Hz: p= .317; 2 Hz: p= .628). Looking into different frequencies, there were significant decreased ICF after following 1 Hz and 3 Hz external cues, compared to 2 Hz (1 Hz vs. 2 Hz: p< .001; 2 Hz vs. 3 Hz: p= .008). Besides, significantly different ICF was found in SI condition between 2 Hz and 3 Hz groups (p= .002).

Chapter 5 Discussion

5.1 Motor Performance in Different Cue Frequencies

The finger tapping test was a common method for assessing rhythmic movement patterns. The test was also a sensitive marker to detect changes in rhythm formation because of aging or neurological degeneration.[60-65] In people suffering from PD, an internal timekeeping system generated by the basal ganglia is disturbed. They experienced difficulty in executing repetitive voluntary movements.[74]

Results proved that the frequency performed by PD patients in comfortable tapping task was near 2 Hz (2.41 ± 0.27 Hz). In the present studies, self-paced finger tapping in the absence of auditory cues in human spontaneously concentrated at around 2 Hz.[75] And performance of finger tapping in response to auditory cues at 2 Hz had the lowest variation. As to PD patient's ability to execute repetitive tapping, it had similar comfortable rate of 2 Hz to elderly healthy and young healthy subjects.[63]

In our previous study, CV obtained by fast tapping task significantly declined after training with 2 Hz auditory cues. The CV after motor practice was about 15%, whereas it was about 10% in healthy controls according to previous study.[63] Although patients had no similar improved pattern of CV to health, decrease of variability indicated that the PD subjects had better timing control.

To further specify alterations of motor performance due to various movement

rates, slower (1 Hz) and faster frequency (3 Hz) than 2 Hz were chosen in this study. In contrast to 2 Hz, no significant CV decline after training with 1 Hz or 3 Hz cue was found. According to our results, PD tended to tap comfortably near 2 Hz. It suggested that rhythmic movements at 2 Hz might be not so difficult. When an external stimulus was applied, patients could maintain the required rhythms much better and also had the potential for sustained improvement in retention test (fast tapping task). However, abnormal tapping performance such as hesitation and hypokinesia among PD was demonstrated at lower and higher frequencies.[11] Yahalom et al revealed that the PD group had significant lower CV at 2.5 Hz following two different cue frequencies (1 Hz and 2.5 Hz).[49] Movements were synchronized with an auditory cues (1 Hz to 3 Hz), Stegemöller et al suggested a deficit in movement performance above 2 Hz. Thus, patients might lose their ability to maintain a lower or higher frequency than 2 Hz. Considering same sessions of motor practice in three groups, it might take much time and more efforts to correct to reach a constant rhythm at 1 Hz and 3 Hz. It was probably no decrease of CV in fast tapping task after 1 Hz and 3 Hz cued training.

5.2 Motor Cortex Excitability in Different Cue Frequencies

Rhythmic movement has been investigated to be controlled by several brain areas, including the primary motor cortex, premotor cortex, supplemental area, cerebellum

and basal ganglia. And there were functional links between audition and these motor systems. Chuma et al. found that after cued and non-cued finger movements, PD patients could be produced more force by TMS stimulation, it implicated that higher MEP was produced by constant TMS.[62] Floel et al. also found that increased MEP size of FDI muscle while listening to linguistic sounds even without performing any motor task.[70] Enlarged MEPs after listened to verbal and non-verbal sounds were also investigated.[71] Our results showed post-training MEPs increased, but it did not reach the significance.

In our study, we observed an increase of SICI after performed acoustically paced motor task in 1 Hz or 3 Hz groups. This seemed to agree with pervious work by Lam et al. who showed an inhibitory effect after training with 2 Hz cue. SICI was thought to be mediated by intracortical γ-aminobutyric acid type A (GABAα).[67] And the common SICI in normal subjects is 20-40% of the unconditioned MEP.[47] Reduced SICI was detected in resting state of our PD sample, and its amount was similar to previous studies.[68-69, 72-73] Therefore, SICI could also be modulated by external cues to a normal level as dopaminergic drugs and DBS did.[69, 72] We suspected that motor performance improved by external cues might be related to normalization of SICI. However, we failed to investigate frequency-dependent adjustments of intracortical inhibition in the PD patients.

Dissociated cortical circuitries under SICI and ICF were supported by previous study.[51] ICF was believed to measure NMDA circuit activity. NMDA was more related to long-term potentiation (LTP) increasing strength of synaptic transmission. Nevertheless, lack of evidence regarding to the role of ICF in repetitive motor training induced brain plasticity. Post-training ICF declined when compared to baseline values. This was more pronounced in 1 Hz and 3 Hz groups. Though not consistently, our previous study have observed no ICF change after 2 Hz training. Furthermore, we also found there was significant difference in post-training ICF between 1 Hz and 2 Hz, 2 Hz and 3 Hz groups. There was a possible explanation for the investigation. It was difficult for patients to reach an unoptimal frequency of 1 Hz or 3 Hz. To increase performance accuracy, SICI might be strengthen and suppress ICF in the motor cortex. Nevertheless, the mechanisms involved in change of ICF need further studies.

5.3 Study Limitation and Future Study

There are some limitations in this study. We could not fully explain the connection between motor performance and motor cortex excitability. This study only showed immediate effect of auditory cues. The future study should investigate whether there is a long term effect of auditory cues and how long does it last. In addition, we did not compare our PD sample to aged-matched healthy controls. So there was no reference

supported our results about intracortical excitability.

The mechanisms underlying the application of auditory cues still need further investigation. External cues might bypass the impaired basal ganglia-thalamo-motor circuit so that cerebro-cerebellar circuit can reach the movement goals. Thus, we may find out the mechanisms through cerebro-cerebellar assessment. Moreover, different types of external cues such as visual and verbal cues may also lead to different results. To understand more about auditory cues can drive us into more efficient clinical practice.

Chapter 6 Conclusion and Clinical Relevance

In conclusion, we have demonstrated alteration of corticomotor excitability following repetitive finger movements executed at 1 Hz, 2 Hz and 3 Hz auditory cues in PD patients, with improvement in behavior measurements. These findings suggested a modulated motor cortex excitability response to repetitive movements with auditory cues. Auditory cues may change both GABAnergic and NMDA activities. However, the mechanisms underlying the application of auditory cues still needed further research. The present study could be an important step to apply auditory cues at comfortable rates to rehabilitative training in PD patients (finger tapping at 2 Hz).

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FIGURES

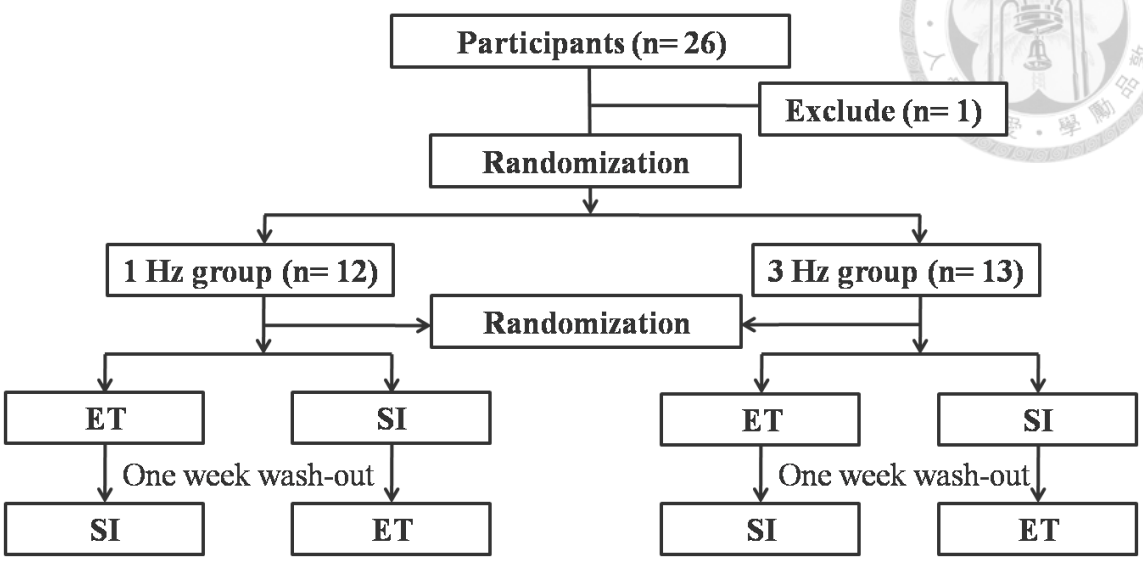

Figure 1. Randomized cross-over designed in this study. Subjects were randomized into two groups (1 Hz or 3 Hz). Subjects received another experimental session with one week interval. (ET: external triggered; SI: self-initiated)

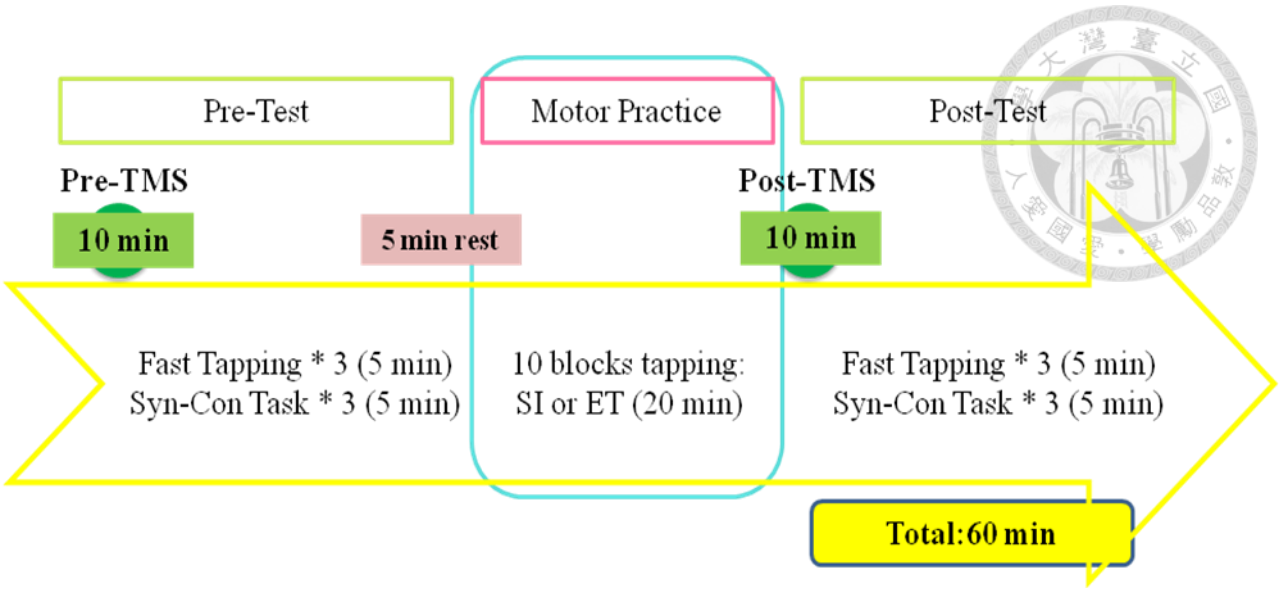

Figure 2. Experiment procedure.

(Syn-con: synchronization-continuation; TMS: transcranial magnetic stimulation)

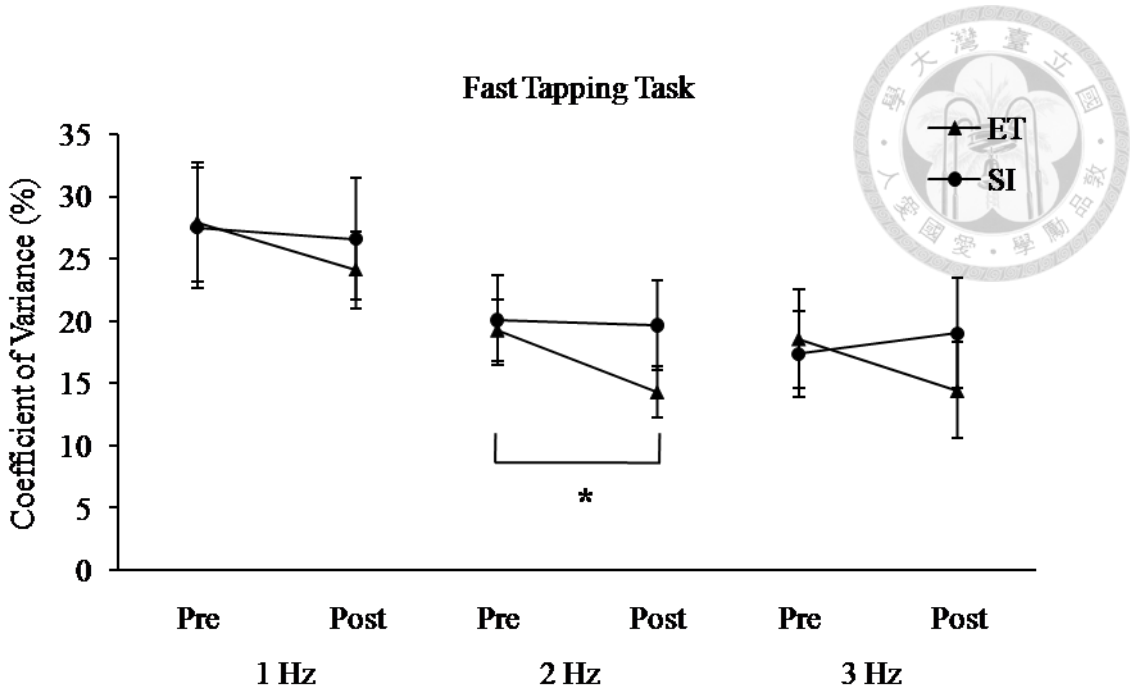

Figure 3. Changes in CV of fast tapping task in three groups.

The CV significantly decreased after motor practice with auditory cues (ET) in 2 Hz group (p= .032*). No siginificant decrease of CV was detected in 1 Hz and 3 Hz groups.

*p< .05

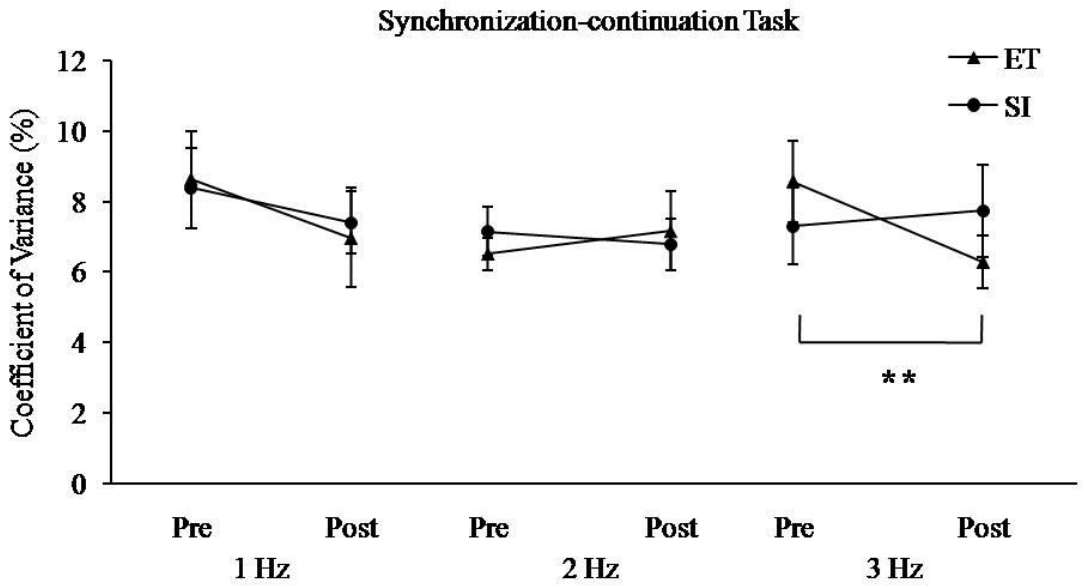

Figure 4. Changes in CV of synchronization-continuation task in three groups.

The CV significantly decreased after motor practice with auditory cues (ET) in 3 Hz group (p= .006**). No significant decrease of CV was found in 1 Hz and 2 Hz groups.

**p< .01

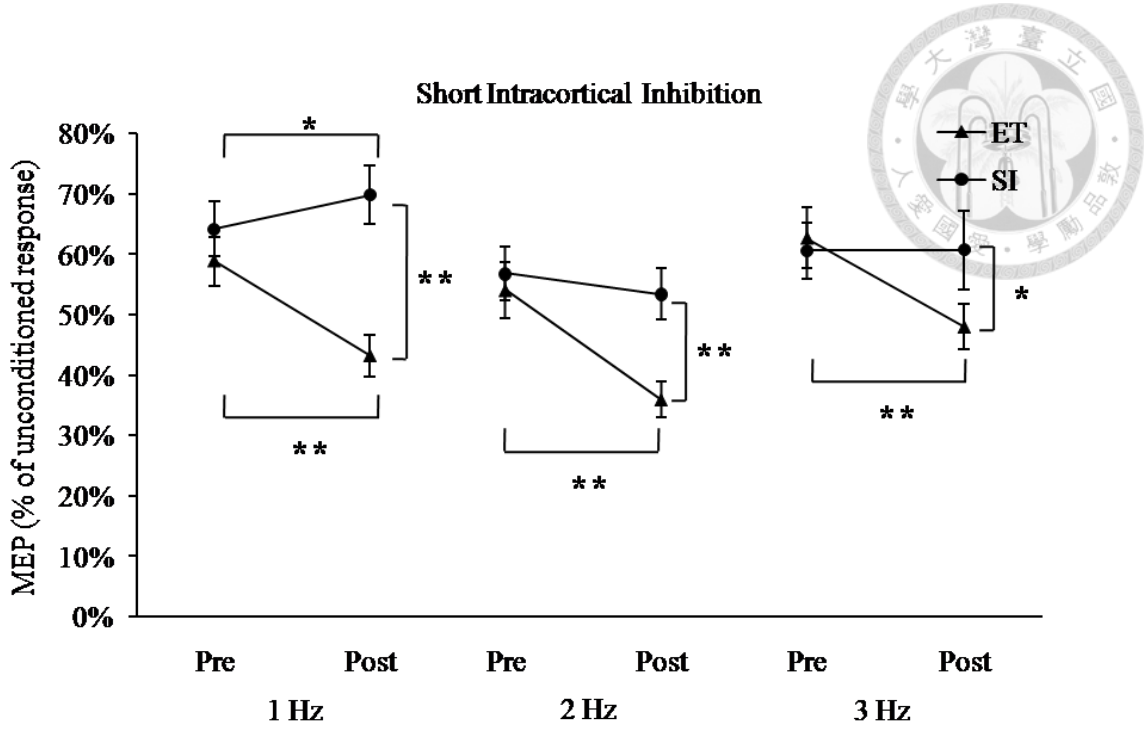

Figure 5. Cued and non cued training induced changes in SICI.

Post cued training SICI revealed significant increased in all groups (1 Hz: p= .002**; 2 Hz: p< .001**; 3 Hz: p< .001**). There were significant differences between ET and SI conditions after motor practice (1 Hz: p< .001**; 2 Hz: p= .005**; 3 Hz: p= .011*).

*p< .05; **p< .01

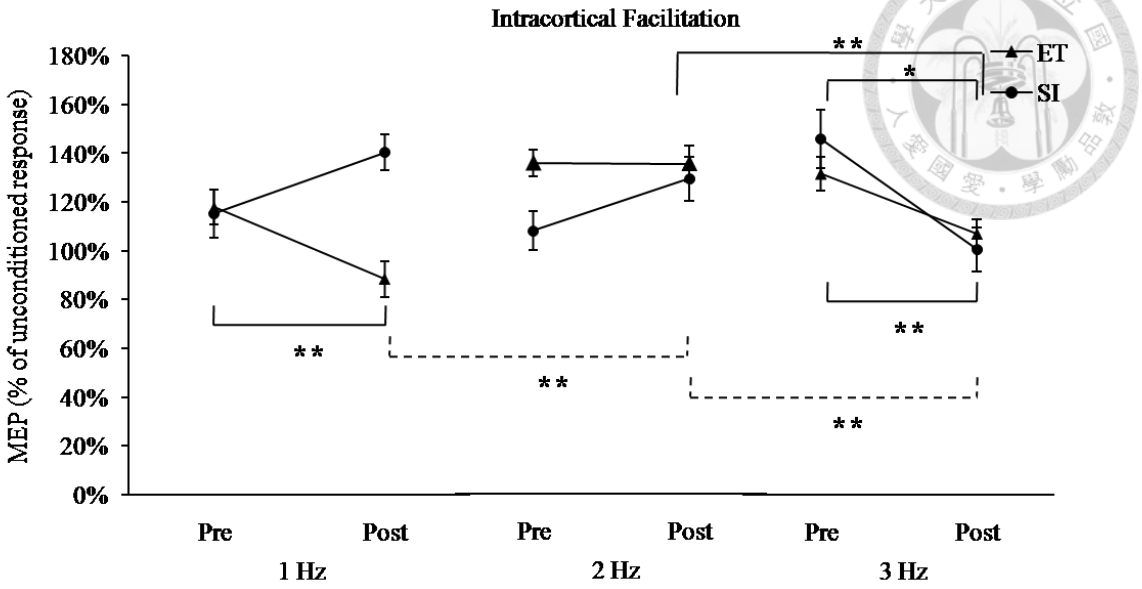

Figure 6. Cued and non cued training induced changes in ICF.

Post cued training ICF showed significant decreased in 1 Hz and 3 Hz groups (1 Hz: p= .006**; 3 Hz: p= .002**). ICF also decreased significantly after non cued training in 3 Hz group (p= .012*). As for comparison among three groups, there were significant differences between 1 Hz and 2 Hz (p< .001**), 2 Hz and 3 Hz (p= .008**) after training with auditory cues (dashed line). Significant difference between 2 Hz and 3 Hz (p= .002**) was investigated during post assessment in SI condition (solid line). *p< .05; **p< .01

TABLES

Table 1. Baseline characteristics of the participants in 1 Hz and 3 Hz groups

	1 Hz	3 Hz
Age, yrs	64.2 ± 8.0	61.4 ± 9.4
Gender, M/F	3/9	4/9
Disease Duration, yrs	6.9 ± 5.5	6.2 ± 5.0
Hoehn&Yahr total	1.9 ± 0.8	1.75 ± 0.51
MMSE	28 ± 2.90	28.86 ± 1.41
UPDRS-III	20.3 ± 8.8	17.0 ± 4.2

Note:

Values are expressed as mean ± SD

APPENDIICES

Appendix 1 The IRB Approval Letter

長庚醫療財團法人人體試驗倫理委員會
臨床試驗同意證明書

地　址：333 桃園縣龜山鄉舊路村頂湖路123
傳　真：03-3494549
聯絡人及電話： 黃庭筠 03-3196200 ext. 3713
電子郵件信箱： b9409033@cgmh.org.tw

試驗名稱： 巴金森氏症病患於聽覺提示下執行節律性動作之依頻大腦皮質興奮性
本院案號： 103-5379A3
試驗期間： 103年12月09日起至104年08月07日止
主持人： 林口物理治療學系張雅如教授
協同主持人： 陸哲駒、黃英儒
執行機構： 長庚大學
同意計畫書版本： 2014年11月5日 第二版
同意之受試者同意書版本： 2014年11月26日 第三版
通過日期： 103年12月09日
通過會期： 103年11月19日
※請於到期前二個月繳交期中報告以利本會進行審查※

長庚醫療財團法人
人體試驗倫理委員會謝燦堂主席

中　華　民　國　103　年　12　月　11　日

Appendix 2 Mini Mental State Examination (MMSE)

MMSE™

Date of examination_____/_____/_____ Examiner_____

Name_____ Age_____ Years of School Completed_____

說明：必須將粗體文字清楚並緩慢地大聲向受試者說出。括弧內顯示的是替代項目。測試時必須以受試者的主要語言在私下進行。若答錯則圈選 0，答對則圈選 1。一開始時詢問下列兩個問題：

您有記憶力上的任何問題嗎？ **我可以問您一些有關您記憶力的問題嗎？**

與時間相關的問題		回答	得分（圈選其中之一）	
現在是...	**民國幾年？**		0	1
	什麼季節？		0	1
	一年中的幾月？		0	1
	一週的星期幾？		0	1
	什麼日期？		0	1

與地點相關的問題*

您現在在哪裡？是在...

哪一省？		0	1
哪一縣？		0	1
哪一市（或城市的哪一區/鄰里）**？**		0	1
哪棟大樓（名稱或類型）**？**		0	1
大樓的幾樓（房間號碼或地址）**？**		0	1

*若有其他恰當的描述，或有更準確有關地點的字眼時，可以取代後並加以註明。

熟記*

仔細聽好，我將說出三個名詞。您必須在我說完後把它們再說出來。準備好了嗎？

開始了... 蘋果 [*暫停*]、**硬幣** [*暫停*]、**桌子** [*暫停*]。**現在請對我重複說出這幾個名詞。**

[*重複測試最多 5 次，但僅記錄首次嘗試的得分。*]

蘋果		0	1
硬幣		0	1
桌子		0	1

現在請記住這些名詞。幾分鐘後我會請您將它們再說一遍。

*在重新測試受試者時，可以利用替代字眼組合（例如：小馬、玫瑰、柳丁）來取代，並加以註明。

注意力和計算能力 [*連續減 7*]*

現在我要您從 100 減去 7，然後將每個答案再繼續減 7，直到我告訴您停下來爲止。

100 減去 7 等於多少？	[93]		0	1
*必要時，說：***繼續。**	[86]		0	1
*必要時，說：***繼續。**	[79]		0	1
*必要時，說：***繼續。**	[72]		0	1
*必要時，說：***繼續。**	[65]		0	1

*只在受試者拒絕進行「連續減 7」項目時才能進行替代項目（以倒著順序唸出「今日好天氣」）。 →

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MMSE - Taiwan/Mandarin - Version of 31 Jul 08 - Mapi Research Institute.
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Sent Via Email: g79013@gmail.com

May 29, 2015

Yu-Ting Hung
School and Graduate Institute of Physical Therapy
College of Medicine, National Taiwan Univ
No. 17, Xuzhou Rd., Zhongzheng District
Taipei 100
Taiwan

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Sincerely,

Vicki M. McFadden
Permissions Specialist
vmark@parinc.com

ACCEPTED AND AGREED:

BY: Yu Ting Hung
YU-TING HUNG

DATE: 2015. 6. 1

ACCEPTED AND AGREED:

BY: Vicki M McFadd
VICKI M. MCFADDEN

DATE: June 2, 2015

PAYMENT RECEIVED: VISA
PAR CUSTOMER No.: 185933 * S01

SIGNATURE OF PROFESSOR REQUIRED:

I hereby agree to supervise this student's use of these materials. I also certify that I am qualified to use and interpret the results of these tests as recommended in the *Standards for Educational and Psychological Testing*, and I assume full responsibility for the proper use of all materials used per this Agreement.

BY: Jer-Junn Luh

Printed Name: Jer - Junn Luh

MMSE Hung Chinese with Sample Items - 5-29-2015

Appendix 4 Unified Parkinson's Disease Rating Scale (UPDRS)

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.