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分散式侷限誘發療法於中風後忽略症患者之療效研究：運動學分析與臨床評估

Effects of Distributed Constraint-Induced Therapy in Stroke Survivors with Unilateral Neglect: Kinematic Analysis and Clinical Assessments

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中文摘要

背景: 半側忽略常見於右大腦損傷的中風患者，且會影響患者的日常生活功能與復健成效。患側空間的注意力缺損會導致患者於執行往對側空間之動作時出現障礙，亦會影響患側手(腦傷對側肢體)的動作復原。分散式侷限誘發療法為一新提倡適用於半側忽略症患者之介入方式，但其療效仍缺乏相關研究之探討。分散式侷限誘發療法可迫使患側手產生主動動作，並誘發患者增加對於患側空間的注意力，進而改善忽略症相關的動作缺損並促進動作之復原。本研究的目的為探討中風後忽略症患者接受分散式侷限誘發療法相較於控制療法於功能獨立，動作缺損及動作復原方面的改善程度。

方法: 本研究將 11 位中風後呈現半側忽略症之患者隨機分派至分散式侷限誘發療法組或控制治療組。分散式侷限誘發療法組患者從事每天 2 小時、每週 5 天的密集訓練，並每天侷限健側手 6 小時，為期 3 週；控制組則接受等量之傳統治療。成效評量採用運動學分析以探討患者往患側空間執行伸手及物的動作表現；臨床評估工具為功能性獨立測驗、傅格-梅爾動作復原評估量表、手臂動作研究測驗及動作活動日誌以評估患者生活功能及動作方面之改善程度。

結果: 隨機分派後，兩組參與研究之患者的特徵與前測時的動作表現皆無顯著差異。運動學分析結果顯示，分散式侷限誘發療法組相較於控制組於健側手執行跨中線往對側空間的伸手及物動作時，兩組之反應時間 (*P*=0.020)、動作時間 (*P*=0.017) 及尖峰速度 (*P*=0.013)，達統計顯著差異。接受分散式侷限誘發療法之患者呈現較好的動作控制策略，兩組於動作控制策略的表現差異接近顯著水平且達高度效果值(*P* =0.052; effect size η^2=0.334)。兩組患者於患側手執行伸手及物的動作表現上並無顯著差異，但接受分散式侷限誘發療法之患者於動作控制策略的改善仍呈現較好之趨勢，為中度至高度的效果值 (P =0.188; effect size η^2=0.113)。在臨床評估結果方面，兩組於功能性獨立測驗 (P=0.017) 及其動作分量表 (P=0.009) 達統計顯著差異。在動作活動日誌之次量表中，患側手使用量 (AOU of MAL, P=0.015) 與患側手使用品質 (QOM of MAL, P=0.023) 結果皆達顯著差異。雖然兩組於傅格-梅爾動作復原評估量表之改善並無顯著差異 (P=0.295; effect size η^2=0.044)，但分散式侷限誘發療法組的患者於動作復原的改善程度仍呈現較大的進步趨勢。兩組於手臂動作研究測驗的表現中亦未達顯著差異且效果值較小 (P =0.395; effect size η^2=0.011)。

結論: 經過為期 3 週的分散式侷限誘發療法，患者於功能性日常活動之獨立程度獲得顯著提升。健側手往患側空間的動作表現亦呈現顯著的改善，顯示患側手之主動動作可誘發往患側空間的注意力，進而降低其動作障礙。此外，分散式侷限誘發療法同時能促使患者增加對於患側手動作之注意力，使患者於日常生活活動中增加使用患側手的次數並改善動作品質。

關鍵字: 半側忽略，功能性獨立，運動學分析，伸手及物動作，中風

Abstract

Background: Unilateral neglect is a common disorder in right-hemisphere stroke patients and produced impact on reaching performances of both arms and on motor recovery of the more affected arm. Distributed constraint induced therapy (dCIT) has received much attention to become a new treatment of unilateral neglect. However the effects of dCIT in stroke patients with unilateral neglect remained uncertain. We proposed that dCIT could induce reduction of neglect and thus lead improvements in the related motor deficits. The objective of the present study was to investigate whether unilateral neglect patients would benefit more from dCIT, compared with controlled treatment.

Methods: 11 patients with unilateral neglect following stroke were recruited and were allocated randomly to dCIT group (2-hour practice in weekdays for 3 consecutive weeks and constraint of the less affected arm for 6 hours per day) and controlled treatment group (traditional rehabilitation for equivalent intensity and duration). We used kinematic analysis and clinical assessments (the Functional Independence Measure, the Fugl-Meyer Assessment, the Action Research Arm Test, and the Motor Activity Log) to investigate the outcomes of reaching movements towards contralesional space, and functional and motor improvements.

Results: There were no significant differences between the groups at pretreatment. Patients receiving dCIT showed significant improvements of the less affected arm in reaction time (*P*=0.020), movement time (*P*=0.017), and peak velocity (*P*=0.013) and showed greater improvement in preplanned motor control (p=0.052; effect size η^2=0.334). For the more affected arm, there were no significant differences in the kinematic variables, though the dCIT produced a moderate to large effect on better motor control strategy (P =0.188; effect size η^2=0.113). Patients after dCIT showed significant improvement in independence in daily functional tasks, especially in motor domain (FIM, P=0.017; FIM_motor, P=0.009) and improvement in functional use of the more affected arm (AOU of MAL, P=0.015; QOM of MAL, P=0.023). Though patients in dCIT group showed greater tendency in motor improvement measured by FMA, it failed to reach significant level (P =0.295; effect size η^2=0.044). The two groups showed a non significant and small effect of ARAT (P =0.395; effect size η^2=0.011).

Conclusions: After three-week dCIT intervention, compared with CT, patients presented much more independence in activities of daily living and had better motor performance while reaching with the less affected arm toward the contralesional space. Additionally, patients were facilitated to spontaneously use the more affected arm and perform better in functional activities.

Key words: Unilateral neglect, functional independence, kinematic analysis, reaching movement, stroke

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CHAPTER 1

Literature Review

Literature Review

Background

Stroke has been a leading cause of long-term disability. In addition to persistent motor impairment, perceptual and cognitive deficits were also important factors associated with limited daily living functions. Although clinical therapists often neglected its negative impact on motor function rehabilitation, unilateral neglect was a particularly important issue especially in right-hemisphere stroke survivors. The reported incidence in right hemisphere stroke patients ranged from 23% to 82% due to different evaluation methods or criteria used to select patients (Stone, Halligan, & Greenwood, 1993).

Unilateral neglect combined with hemiplegia may lead patients to show poor responses to rehabilitation and impact on the process of recovery (Denes, Semenza, Stoppa, & Lis, 1982). Evidences indicated that stroke patients with unilateral neglect needed much longer rehabilitation stays and presented much more dependence in activities of daily living than those without unilateral neglect (Katz, Hartman-Maeir, Ring, & Soroker, 1999; Pedersen, et al., 1996). Recent study showed that patients with neglect had a consistently worse prognosis of motor recovery than comparable patients without neglect (Gialanella, 1992). Furthermore, the grip strength was smaller in patients with neglect (Buxbaum, et al., 2004).

Since unilateral neglect has played an important role in recovery of motor function and independence in activities of daily living, unilateral neglect amelioration certainly should be taken into account when applying a stroke rehabilitation program.

Unilateral neglect

Unilateral neglect is characterized by a failure to report, response, or orient to stimuli presented to the space contralateral to a brain lesion, when this failure cannot be attributed to either sensory or motor deficits (Heilman & Valenstein, 1979a). Neglect may be spatial or personal. One may be inattentive to stimuli in space or on the person (attentional or sensory neglect), and one may fail to act in a portion of space, in a spatial direction, or to use a portion of body (intentional or motor neglect) (Heilman & Valenstein, 2003). Researchers (Na, et al., 1998) found that most patients with spatial neglect could be demonstrated to have both attentional and intentional biases, but attentional bias dominated in patients with temporal-parietal lesions, whereas intentional bias dominated in patients with frontal lesions (Heilman & Valenstein, 2003).

Inattention or sensory neglect. Inattention or sensory neglect refers to a deficit in awareness of stimuli contralateral to the lesion. Patients may fail to attend to visual, auditory, or tactile stimuli in space or on the body. If patients were able to detect stimuli in contralesional space but unable to detect the contralesional stimuli when bilateral stimuli presented simultaneously, it has been called extinction to double simultaneous stimulation. Personal neglect is defined as a failure to recognize their contralesional extremities. Patients may deny their limbs are their own and may fail to dress or groom the contralesional extremities (Bisiach, Perani, Vallar, & Berti, 1986; Heilman & Valenstein, 2003). Spatial neglect is defined that when patients are asked to perform a variety of tasks, they neglect the hemispace contralateral to their lesion, and is further divided into peripersonal neglect and extrapersonal neglect (Bisiach, et al., 1986; Halligan & Marshall, 1991). In terms of the reference coordinates, the neglected space may be body centered (egocentric neglect), object centered (allocentric neglect), or environment centered (Heilman & Valenstein, 2003).

Intentional or motor neglect. Motor neglect is defined as the failure to generate a movement response to a stimulus even though the person is aware of the stimulus (Heilman & Valenstein, 2003). Motor intentional hypothesis stated that patients fail to act on the stimuli because they have either a reduced ability to act in contralesional hemispace or they have an action-intentional bias to act rightward (Heilman & Valenstein, 2003). Motor deficits attributed to the neglect syndrome may simply divided into two broad categories; those that lead to a deficit in motor production of the contralesional limbs and those that describe a directional or spatial motor bias (Punt & Riddoch, 2006).

The motor deficits attributed to unilateral neglect

The effective control of behavior requires that just a subset of incoming sensory information be selected to guide subsequent action. The brain permits us to interact flexibly with our environment by selectively enhancing the processing of relevant information, while simultaneously inhibiting irrelevant inputs (Desimone & Duncan, 1995; Mattingley, et al., 1998). Thus patients with unilateral neglect may exhibit impaired goal-directed movements toward contralesional hemispace due to the deprivation of attentional resources.

It has been proposed that patients with unilateral neglect were slow to detect a visual target and slow to initiate a response to it in the neglected side, which termed as directional hypokinesia (Heilman, Bowers, Coslett, Whelan, & Watson, 1985). Previous study found that neglect patients showed prolonged movement initiation time and movement time while executing leftward movements, which were interpreted that neglect patients had difficulty disengaging their attention from the location of motor preparation for a shift toward the neglected side and neglect patients might fail to form a complete representation of the space where the movement oriented to (Coulthard, Parton, & Husain, 2006; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994; Mattingley, Bradshaw, & Phillips, 1992). Researchers later reported that the increased latencies for contralesional movements might be due to the non effective inhibition of the inappropriate motor programs toward ipsilesional events (Mattingley, et al., 1998). Additionally, studies reported that patients with unilateral neglect also showed lower peak velocity and departed from optimal bell-shaped velocity profiles (Mattingley, et al., 1994). The high proportion of total movement time spent in deceleration suggested an abnormal reliance on terminal visual guidance (Coulthard, et al., 2006;

Mattingley, et al., 1994). According to current findings, patients suffering from neglect may experience motor problems affecting spatial (position and orientation) and temporal (reaction and movement time) coordination among limb segments.

Limb activation

Researchers had found that active left limb movements in the left hemispace could significantly reduce visual neglect, compared with movements of right hand and movements of left hand performed in the right hemispace (Robertson & North, 1993; Robertson & North, 1994; Robertson, North, & Geggie, 1992). The left arm movements were referred as an endogenous cue to induce the shift of attention to the neglected side rather than a spatiomotor cueing, which passive movements did not produce the effect (Robertson & North, 1993). Thus the rehabilitation technique was developed on the basis of the premotor theory of attention. Limb activation is a bottom-up intervention with behavioral compensation and cognitive restoration (Luaute, Halligan, Rode, Rossetti, & Boisson, 2006). The underlying mechanism is to reduce the inter-hemispheric inhibitory process, and study had showed that the beneficial effects of the left limb activation in left hemispace would be eliminated if the right limb was simultaneously moved (Luaute, et al., 2006; Robertson & North, 1994).

Premotor theory of attention. The premotor theory of attention claimed that a higher attention network system interacts and is responsible for sensorimotor integration (Rizzolatti, Riggio, Dascola, & Umilta, 1987). Studies have evidenced that sensory attention and motor intention are closely linked and covert response preparation can trigger covert shifts of attention, regardless of which response modality is involved (Eimer, Van Velzen, Gherri, & Press, 2006; Rizzolatti, 1998). Therefore, motor intention (selection and planning of a specific movement) is accompanied by covert attention, and contrariwise, when one is attending to a spatial location, one is also prepared to act in that direction.

Constraint-induced therapy

Constraint-induced therapy (CIT) has received recent attention as a potential treatment of unilateral neglect (Freeman, 2001; Pierce & Buxbaum, 2002). Stroke patients with unilateral neglect may reduce the ability to attend to contralesional limbs resulting from damaged to lateralized attention systems (O'Neill & McMillan, 2004). Thus neglect patients may indeed develop learned non use phenomenon especially when they were right handed with left hemiplegia. CIT can constrain the less affected arm and force neglect patients to move the more affected arm. The constraint of the less affected arm can reduce sensory inputs form the ipsilesional space and the active movement of the left can induce attention to shift and engage into the contralesional space, thus the neglect syndrome can be ameliorated.

Background

CIT has been an evidence-based neuro-rehabilitation treatment for stroke patients, developed from basic science research and theoretical foundation (Wolf, Blanton, Baer, Breshears, & Butler, 2002). Early study showed that monkeys with somatosensory deafferention had learned not to use the paretic limb due to repeatedly unsuccessful use of the limb, and monkeys had continued not to use the limb after the somatosensory reafferention. This phenomenon was termed ‘learned non-use’ by Taub and his colleagues. Taub later suggested that the learned non-use phenomenon could occur in stroke patients, who used the less affected arm to compensate for activities of daily living due to positive reinforcement, and tended to not use the affected arm due to negative reinforcement (Taub & Morris, 2001; Wolf, et al., 2002). Taub suggested that combined constraint of the less affected arm with intensive task practice of the more affected arm could reduce learned non-use and increase spontaneous use of the affected arm, which developed into constraint-induced therapy (Taub, et al., 1993; Taub & Morris, 2001).

Possible mechanisms of CIT

The two primary mechanisms proposed were as follows: (1) overcoming learned non-use of the affected limb, or (2) producing use-dependent cortical reorganization (Wolf et al., 2002).

Patients often had persistent motor impairment after stroke, and the slow and clumsy movement of the more affected arm would discourage patients to use the paretic limb. Also, if patients were trained to use compensatory strategies, the phenomenon would be aggravated. Compared to traditional therapy, CIT seemed to be a better way to overcome learned non-use by restraint of less affected arm and restore the upper extremity function by massed practice of more affected limb (Taub & Morris, 2001; Wolf et al., 2002).

Central nervous system (CNS) has plasticity and can be facilitated. If patients learned not use the more affected arm after neurological injury, the motor cortex may atrophy, on the other hand, the massive and intensive use of the affected arm can facilitate activation of the area adjacent to lesion area, referred as use-dependent reorganization. CIT is thought to be a new approach that can facilitate treatment-induced brain plasticity and is proved by a volume of brain imaging evidences (Mark, Taub, Perkins, Gauthier, & Uswatte, 2008; Plummer, 2003; Taub & Morris, 2001; Wolf, et al., 2002).

Treatment strategy

CIT consists of three components. First, patients are encouraged to wear the mitt for 90% of their waking hours of a 2-week period, except for activities that are water-based or might compromise the patient’s safety or balance. Second, patients are required to engage in 6-hour activity sessions on 10 weekdays for the same 2 weeks. Third, therapist should provide functional tasks and utilize shaping skill, involved selecting functional tasks adapted to address the motor deficits of the more affected arm and making the task more difficult after the patients' motor improvement, dividing behavioral objective into small steps, and giving explicit feedback when patients showed improvement.

Because CIT has its limitations, such as safety consideration, lack of treatment resources, and compliance of patients, its clinical feasibility has been questioned. Page and colleagues brought up modified CIT (mCIT) protocol that reduced the therapy intensity and reduced time of constraint per day. The protocol could be adaptable for different patients (Page, Levine, & Leonard, 2005; Page, Sisto, & Levine, 2002).

Effects of CIT in patients with stroke

Mass studies have demonstrated that CIT and mCIT porduced positive effectiveness on upper extremity motor function in chronic, acute, and subacute stroke patients (Page, et al., 2005; Page, Sisto, Johnston, & Levine, 2002; Page, Sisto, & Levine, 2002; Wolf, et al., 2002). At motor impairment level, patients after receiving CIT/mCIT intervention showed significant improvement in Fugl-Meyer Assessment (FMA) (Dromerick, Edwards, & Hahn, 2000; Lin, Wu, & Liu, 2008; Page, et al., 2005; Wolf, et al., 2002), Action Research Arm Test (ARAT) (Dromerick, et al., 2000; Page, et al., 2005; Wolf, et al., 2002) and Wolf Motor Function Test (WMFT) (Tarkka, Pitkanen, & Sivenius, 2005). At the activity limitation level, patients also showed significant improvement, evaluated by Motor Activity Log (MAL) (Lin, et al., 2008; Tarkka, et al., 2005), Barthel Index (Dromerick, et al., 2000; Miltner, Bauder, Sommer, Dettmers, & Taub, 1999), or Functional Independence Measurement (FIM) (Dromerick, et al., 2000; Lin, et al., 2008). Clinical studies also reported that patients after CIT could perform more efficient and smoother movement and have better motor control strategy (Lin, Wu, Wei, Lee, & Liu, 2007; Wu, Chen, Tang, Lin, & Huang, 2007; Wu, Lin, Chen, Chen, & Hong, 2007).

Effects of CIT in patients with unilateral neglect after stroke

CIT involves constraint of the unaffected arm and massed practice of the affected arm, resulting in inducing patients to spontaneously use the paretic limb and in increasing sensory inputs (Taub et al., 1993). Effects of CIT in patients with unilateral neglect had been reported (van der Lee, et al., 1999). The authors recruited 66 chronic stroke patients and allocated them into the CIT or bimanual training group with equivalent intensity. After treatment for 2 consecutive weeks, 5 days a week, 6 hours a day and restraint the less affected arm at home during the 12 days, patients with sensory disorders in experimental group showed significant improvement in ARAT scores, compared with the patients in the reference group. A positive effect on amount of use (AOU) of the more affected arm in ADL measured by MAL was found in patients with hemineglect. Authors suggested that stroke patients with sensory disorders and hemineglect might tend not to use their more affected arm to perform motor task even they could, therefore, their upper extremity function might be more amendable through forced use. Furthermore, authors indicated that forced use probably had a positive effect on the awareness of sensory perception and could cause improvement if the sensory deficits ameliorated. However the author did not measure the neglect in a standard way and the effects of CIT on neglect symptoms awaited further investigated.

Eye patching

Background

Researcher (Sprague, 1966) reported that after unilateral cortical damaged, the contralesional superior colliculus might inhibit the activation of ipsilesional superior colliculus and resulted in attention imbalance. Thus, excising the contralesional superior colliculus might reorient attention to contralesional space. Superior colliculus is involved in controlling saccadic eye movement to the contralateral space. Researchers (Posner & Rafal, 1987) therefore postulated that patching the ipsilesional eye of patients with left visual neglect following right brain injury could cause contralateral deafferention of the superior colliculus by reducing input from the ipsilateral retina, and would reduce the tendency to bias eye movements to the ipsilesional side of space (Beis, Andre, Baumgarten, & Challier, 1999).

Possible mechanism

Hyperactive hypothesis (Kinsbourne, 1970) and hypoactive hypothesis ((Heilman & Valenstein, 1979b) attributed unilateral neglect to the damaged right-hemisphere dominant attention-shifting mechanisms, resulting in an ipsilesional attention bias. Therefore, activation of the right brain hemisphere by controlled sensory input from ipsilesional space and elimination of inhibition of contralesional superior colliculus might establish a balance between the hemispheres, and thus might ameliorate neglect (Lin, 1996).

Treatment strategy

Right half-field eye patching and monocular eye patching were proposed. For right half-field eye patching, the right side portion of each lens was blinded by an opaque tape. The vertical border line of this blinded zone was aligned with the vertical meridian of the patients' pupil while looking straight ahead. When patients wear the glasses, they have no visual information about the right hemispace (Zeloni, Farne, & Baccini, 2002).

Effects of eye patching on unilateral neglect

Compared with monocular eye patching, patients after right half-field eye patching showed greater improvement in functional independence and greater number of fixations in contralesional side (Beis, et al., 1999). Researchers had studied the effects of right half-field eye patching under test with line bisection, line cancellation, and figure copying tasks, and reported that four patients showed improvements, and the others showed no effects or deterioration (Arai, Ohi, Sasaki, Nobuto, & Tanaka, 1997). No data were reported enabling distinctions between patients who did or did not profit from the treatment (Pierce & Buxbaum, 2002). Another study by Beis et al (1999) focused on long term effects. Patients after 3-month eye patching intervention showed improvements in FIM scores and significant improvements in attention to the left visual field. Assessed by photo-oculography, patients showed longer duration and greater number of fixations in contralesional field.

Effects of motor training combined with eye patching on unilateral neglect

Recent study (Fong, et al., 2007) investigated the effects of combining voluntary trunk rotation and half-field eye patching to treat stroke patients with unilateral neglect. Patients received treatment for 1 hour 5 times a week for 30 days, but results showed no significant improvement in neglect and functional performance. The author suggested that the voluntary trunk rotation initiated by the ipsilesional (right) hand might abolish the advantage of left limb activation, and also therapists should notice patients’ responses to eye patching.

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CHAPTER 2

Effects of Distributed Constraint-Induced Therapy in Stroke Survivors with Unilateral Neglect: Kinematic Analysis and Clinical Assessments

Introduction

Unilateral neglect has been described as an attentional deficit that patients fail to report, response, or orient to sensory stimuli presented at the space contralateral to a brain lesion, when this failure cannot be attributed to either sensory or motor deficits (Heilman & Valenstein, 1979). The unilateral neglect syndrome included many features concerning different sites of lesions (Punt & Riddoch, 2006). Patients with unilateral neglect not only presented worse prognosis of motor and functional recovery (Gialanella, 1992), but also showed poor responses to rehabilitation (Denes, Semenza, Stoppa, & Lis, 1982; Katz, Hartman-Maeir, Ring, & Soroker, 1999; Pedersen, et al., 1996). Additionally, because lack of attention to one side might cause difficulties with many ADL tasks, patients with unilateral neglect following stroke showed more dependences in activities of daily living (ADL) (Freeman, 2001).

As spatial attention is important for us to prepare and organize a motor act, patients with unilateral neglect may fail to aware and register the presence of targets in the contralesional space, and fail to direct actions toward the contralesional space. Neglect patients showed a variety of impairments while reaching toward objects in the contralesional space (Coulthard, Parton, & Husain, 2006). The impaired movements directed to the contralesional space could be exhibited by the contralesional and ipsilesional limbs. Because patients with neglect often suffered from hemiplegia, to evaluate the performance of the less affected arm can investigate motor problems related to neglect syndrome (Pohl, Winstein, & Onla-or, 1997). Studies have indicated that patients with unilateral neglect showed impairments in temporal aspects of motor performance, including prolonged reaction time, prolonged movement time, lower peak velocity and higher proportion of total movement time spent in deceleration (Coulthard, et al., 2006; Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994).

The theory-based neglect rehabilitation technique “limb activation” proposed that active movement of the contralesional limb can lead patients to produce shifting of attention towards the contralesional space (Robertson & North, 1993; Robertson & North, 1994; Robertson, North, & Geggie, 1992). The movement of the contralesional limb would activate the right hemisphere, and thus would reduce the interhemispheric imbalance and lead attention balance to the left side (Kinsbourne, 1985). The essential factor underlying the technique has led a relatively new technique constraint -induced therapy to become a potential treatment of unilateral neglect because patients were both required to move their contralesional arms actively (Barrett, et al., 2006; Freeman, 2001; Pierce & Buxbaum, 2002).

Distributed constraint -induced therapy (dCIT) which involves 2 hours treatment per day during three weeks is a less intensive variant of the original CIT protocol (practice for 6 hours per day, 10-15 weekdays) (Page, Levine, & Leonard, 2005; Page, Sisto, & Levine, 2002; Wu, Lin, Chen, Chen, & Hong, 2007). CIT involves constraint of the less affected arm, massed practice of the more affected arm, and shaping skills which defined as progressively enhancing the difficulty of the task in accordance with patients' ability (Taub & Morris, 2001; van der Lee, et al., 1999; Wolf, Blanton, Baer, Breshears, & Butler, 2002). CIT has been a promising intervention to overcome learned non-use phenomenon, which developed from the unsuccessful use of the more affected arm and compensated use of the less affected arm (Page, et al., 2005; Page, et al., 2002; van der Lee, et al., 1999; Wolf, et al., 2002). Numerous studies have showed the effectiveness of CIT on motor improvements, motor control strategy and functional performances in acute, subacute and chronic patients (Dromerick, Edwards, & Hahn, 2000; Lin, Wu, & Liu, 2008; Lin, Wu, Wei, Lee, & Liu, 2007; Page, et al., 2002; Paolucci, et al., 1996; Wu, Chen, Tang, Lin, & Huang, 2007; Wu, Chen, Tsai, Lin, & Chou, 2007; Wu, Lin, et al., 2007).

In terms of the disengagement theory (Kinsbourne, 1985), reducing sensory inputs from the less affected side may improve neglect (Freeman, 2001). Thus dCIT which constrains the less affected arm may not only force the arm to move but also force the attention to shift. Additionally, patients with unilateral neglect may indeed have non-use of the more affected arm due to progressively not attend to the contralesional arm. Distributed CIT may improve neglect patients to aware the sensory perception in the more affected side, and increase the use of the more affected arm (Freeman, 2001; van der Lee, 1999). As in our knowledge no study has provided randomized controlled trial to investigate the effects of distributed CIT in unilateral neglect patients on neglect related deficits. We proposed that dCIT intervention can assist in neglect reduction and then improve motor performance of the less affected arm, and motor recovery of the more affected arm.

Purpose

The aim of this study was to provide a randomized controlled trial to investigate the effects of distributed CIT versus controlled treatment in unilateral neglect patients on improvement of functional performances and on amelioration of the deficits associated with neglect syndrome, which demonstrated by the less affected arm movement and the motor recovery of the more affected arm.

Hypotheses

We hypothesized that after three-week intervention, stroke patients with unilateral neglect treated with dCIT, would benefit more on functional and motor recovery and exhibit better motor control performances, compared with patients treated with controlled treatment (CT). Patients receiving dCIT would show better motor control performances, demonstrated by higher PV, higher PPV, shorter RT and shorter MT. Patients receiving dCIT would show more independence in daily activities measured by FIM and better motor recovery, measured by FMA, ARAT, and MAL.

Methods

Design

This experiment was a randomized-controlled trial, pretest-posttest design. Patients with right-hemisphere stroke and unilateral neglect were recruited and randomly allocated into one of the two groups, including distributed CIT or controlled treatment. All patients were blind to the study hypotheses. The outcome measures were administered within one week before and after the three-week intervention. All patients continued with other routine rehabilitation program, such as physiotherapy or speech therapy. See Figure 1.

Participants

We recruited 11 right-hemisphere stroke patients (8 men, 3 women; mean age, 61.20y; range, 38-73y; onset mean, 12.99 months) from medical centers and local hospitals in the north of Taiwan. Eligibility criteria were as following: first or recurrent unilateral stroke in right hemisphere (ischaemic or hemorrhagic) confirmed by clinical diagnosis, achieving the Brunnstrom's stage III or above, premorbidly right-handed evaluated by Edinburgh inventory (laterality quotient above 0.80), no significant cognitive impairments and able to follow instructions (MMSE ≧ 23), no excessive spasticity in the more affected arm (the mean score of the modified Ashworth Scale of Muscle Spasticity ≦ 2), and considerable non-use of the more affected arm (mean sore of amount of use of MAL < 2.5).

All patients presented left unilateral neglect after stroke, which was diagnosed by line bisection test (Lin, Cermak, Kinsbourne, & Trombly, 1996), the random shape cancellation test (Weintraub & Mesulam, 1985), the Random Chinese Word Cancellation test (Chen Sea, Henderson, & Cermak, 1993) and double simultaneous stimulation. Patients were recruited if unilateral neglect was presented on two of above tests. Patients were excluded if they had severe dysphasia, poor balance to threaten safety, significant impairments in visual acuity (Snellen acuity below 20/70 after remediation), or severe pain.

The data used in this study was collected from a large clinical trial and was shared in other articles.

Intervention

The experimental group and controlled group received the equivalent treatment dosage and intervention duration. The distributed CIT group received treatment for 2 hours per day, 5 weekdays, for consecutive 3 weeks. The patients received intensive practice with functional activities and also had to wear a mitt to constrain the less affected arm for at least 6 hours per day. Controlled treatment, including neurodevelopmental techniques, bilateral activity training, compensatory strategies for activities of daily living, was administered to the patients in the CT group for 2 hours per day, 5 days a week, for 3 weeks.

Materials and Instrumentation

Clinical evaluation

Screening measures

The line bisection test consisted of three different horizontal lines of 18 and 24 cm, each of them was separately presented twice with pseudo-random order. Each time patients had to bisect one horizontal line on a sheet of B4 paper, and then the bias index of each line was calculated (bias index = raw deviation score / half of the line length) (Lin, et al., 1996). Patients were diagnosed unilateral neglect if the average bias index were 0.055 or above. The diagnostic criteria of the two cancellation tests, the random shape cancellation test and the Random Chinese Word Cancellation test (Chen Sea, et al., 1993), included (1) the number of omissions reached five or more, and (2) the difference in number of omissions between left and right half page reached three or more (Lin, et al, 1996).

The Edinburgh Inventory (Oldfield, 1971) was used to examine brain laterality and dominant hand. The Mini-Mental State Examination (MMSE) was utilized as a cognition screening tool including orientation, attention, memory, and verbal ability dimensions. The higher score indicates better cognition. The modified Ashworth Scale of Muscle Spasticity (mASMS) was used to evaluate the muscle spasticity. It is a 6-point ordinal scale (0= no increase in muscle tone- 4= affected part is rigid), which is scored according to the resistance level given through the joint movement by passive stretch. This scale is with good inter-rater reliability (Bohannon & Smith, 1987).

Outcome measures

The upper-extremity subscale of the Fugl-Meyer Assessment (FMA) was used to evaluate motor impairment of the hemiparetic limb (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) with good validity (Gladstone, Danells, & Black, 2002), reliability and responsiveness (Duncan, Propst, & Nelson, 1983; Hsieh, et al., 2009). The 33 items of the FMA are based on the motor recovery level of the Brunnstrom stages. The upper-extremity subscale measures movement and reflexes of the shoulder/elbow/forearm, wrist, hand, and coordination and can be scored on a 3-point scale (0=cannot perform, 1= performs partially, 2= performs fully; maximum score, 66 points) (Fugl Meyer et al., 1975).

The Action Research Arm Test (ARAT) consists of 19 items grouped into grasp, grip, pinch, and gross movement subscales. The motor performance of each task was scored on a 4-point scale, ranging from 0 (perform no part of the task) to 3 (movement performed normally). The reliability, validity and responsiveness of the ARAT have been found in several studies (Dromerick, et al., 2000; Hsieh, et al., 2009; Van der Lee, et al., 2001).

The Motor Activity Log (MAL) is a semi-structured interview and was utilized to assess amount of use (AOU) and quality of movement (QOM) of the more affected arm in 30 specific activities of daily living. The scale ranges from 0 to 5. 0 means never use the affected and inability to use the affected arm for this activity, and 5 means always use the affected arm and ability to use the affected arm as well as before stroke. The mean score was obtained to evaluate the phenomenon of non-use and performance of the affected arm.

The Functional Independence Measure (FIM) contains six subscales divided into motor domain including self-care, sphincter control, transfer, and locomotion, and cognition domain including communication and social cognition ability (Kidd, et al., 1995). Maximum score is 126 for 18 items. Each item was scored 1~7 points based on the level of assistance required to perform basic activities of daily living.

Kinematic evaluation

Changes in motor control performances were evaluated using kinematic analysis. A seven-camera motion-analysis system (VICON MX; Oxford Metrics Inc., Oxford, UK) was used. The system in conjunction with a personal computer can capture the movement of markers during the task. Two channels of analog signals were collected simultaneously. Signal collection was linked to a desk bell provided for instruction of task start and a target bell used to determine movement offset. Movements were recorded at 120 Hz and digitally low-pass filtered at 5 Hz using a second-order Butterworth filter with forward and backward pass.

Testing procedure

During the unilateral task, the patient sat on a height-adjustable chair with seat height adjusted to 100% of the lower leg length, measured from the lateral knee joint to the floor with patient standing. Adjacent to the chair was a table with a height adjusted to 5 cm below elbow. The patient rested the arm on the edge of the table as a starting position. See Figure 2. Reference marker was attached on the nail of the index finger of the reaching arm. The task bell was located in the contralesional space with distance of patient's functional arm length from the medial border of the axilla to the distal wrist crease (Wu, Chen, Tang, et al., 2007). The patient was instructed to reach and press the task bell (3 cm^2 in square and 0.5 cm in height) in the contralesional space as quickly as possible with the index finger of the more affected or less affected arm. See Figure 2.

The patient could start to move when the start bell rang. For the unilateral task, a rise of tangential wrist velocity above 5% of its peak value was indicated as the movement onset. Movement offset was defined as the time when patient pressed down the task bell.

Data reduction for kinematic variables

An analysis program coded by LabVIEW (National Instruments, Inc.) language was used to process kinematic data. Kinematic variables for reaching included reaction time (RT) (sec.), normalized movement time (nMT) (sec.), peak velocity (PV) (mm/sec.), and the percentage of movement time where peak velocity occurs (PPV) (%).

Reaction time (RT) is the interval from the start signal to movement onset, and refers to the time to initiate the movement. *Normalized movement time* (nMT) is the interval between movement onset and movement completion which was normalized by the direct distance of arm and target in each patient, and indicates the efficiency of movement execution (Lin, et al., 2007; Wu, Chen, Tang, et al., 2007). *Peak velocity* (PV) indicates force or impulse at movement initiation. Higher PV represents greater force (Wu et al., 2007). *The percentage of movement time where peak velocity occurs* (PPV) reflects the percentage of movement time for acceleration phase. The acceleration phase is proposed to be the major preplanned aspect of the movement and a longer acceleration phase suggests that the movement is performed primarily based on feedforward control (Lin et al., 2007).

Statistics

Analysis of covariance (ANCOVA) was used to test the differences between the groups for each variable. Because the means of the onset months showed great differences, we used the onset months and pretest scores as covariates for controlling pretreatment differences. For each analysis, pretest performance and onset months were covariates, group was the independent variable, and posttest performance was the dependent variable. One-tailed test was used with α level set at .05. The effect size $\eta^2 = SS_b/SS_{total}$ was calculated for each outcome variable to index the magnitude of group differences in performance. A large effect is represented by a η^2 of at least 0.138, a moderate effect by a η^2 of 0.059, and a small effect by a η^2 of 0.011 (Cohen, 1988).

Results

Characteristics of study patients

11 patients were recruited (mean age, 61.20 in years; male/female, 8/3), and who were assigned randomly to one of the two groups. The demographic and clinical characteristics were presented in Table 1. The baseline characteristics of patients were comparable. There were no significant differences between these two groups in age, gender and months after stroke, extinction, visual field deficit and the syndrome of neglect. Table 1 also showed that there were no significant differences in cognition level and motor impairments by the scores of the MMSE and FMA.

Effects of distributed CIT on kinematics

The dCIT group showed significant improvements in the reach movement performances with the less affected arm after three-week intervention. The ANCOVAs results of dCIT versus CT were presented in Table 2. The performances on kinematic measure of PV, RT and nMT variables showed large effects at posttest and reached level of significant differences. The inferential statistics results showed as following, PV ($F_{(1, 7)}=7.848$, $P=0.013$, $\eta^2=0.529$), RT ($F_{(1, 7)}=6.314$, $P=0.020$, $\eta^2=0.474$), and nMT ($F_{(1, 7)}=6.895$, $P=0.017$, $\eta^2=0.496$). The performance on reach movement control strategy measured by PPV was presented a large effect though almost reached the significant level ($F_{(1, 7)}=3.506$, $P=0.052$, $\eta^2=0.334$).

For the more affected arm after three-week treatment, the results of the ANCOVAs that tested the effects of dCIT versus CT were displayed in Table 3. The kinematic variables showed no significant differences between groups, but the performance on the kinematic measure of PPV showed a non-significant and moderate to large effect in the patients receiving dCIT ($\mathrm{F}_{(1, 7)}= 0.896$, $P=0.188$, $\eta^2=0.113$). The small-to-moderate and non significant effects were found for the kinematic variables of PV ($F_{(1, 7)}=0.396$, $P=0.275$, $\eta^2=0.054$), RT ($F_{(1, 7)}= 0.085$, $P=0.390$, $\eta^2=0.012$), and nMT ($F_{(1, 7)}=0.125$, $P=0.367$, $\eta^2=0.018$).

Effects of distributed CIT on clinical measures

The ANCOVA results of the clinical outcome measures that tested the effects on functional and motor improvements after intervention were presented in Table 4. The patients receiving dCIT showed much more independences in activities of daily living, measured by FIM ($F_{(1, 7)}= 6.940$, $P= 0.017$, $\eta^2=0.498$), especially in the motor domain ($F_{(1, 7)}= 9.440$, $P= 0.009$, $\eta^2 =0.574$). The dCIT group showed the tendency to have greater improvement than CT group in FMA at posttest, but the level of effect size was small to moderate and failed to reach level of significant differences ($F_{(1, 7)}= 0.318$, $P= 0.295$, $\eta^2= 0.044$). The dCIT group also showed the tendency to greater improvement than CT group in ARAT, but the effect size was small and failed to reach level of significant differences ($F_{(1, 7)}= 0.077$, $P= 0.395$, $\eta^2=$

0.011). The dCIT group showed significant differences between CT group and presented a large effect in the amount of use of the more affected arm, measured by AOU subscale of MAL ($F_{(1,\ 7)}$ =7.432, P =0.015, η^2 =0.515). The dCIT group also showed a large and significant effect in the quality of use of the more affected arm, measured by the QOM subscale of MAL ($F_{(1,\ 7)}$ =5.956, P =0.023, η^2=0.460).

Discussion

In this study, we provided the experimental data addressing the changes that occurred in reaching movement control of the more and less affected arms, and motor and functional performances in unilateral neglect patients following stroke after three-week distributed CIT. The results were consistent in part with the prior hypotheses. We found dCIT induced significant greater positive effects in stroke patients with unilateral neglect on the reaching movement towards the contralesional space with the less affected arm than patients in CT group, demonstrated by kinematic variables of higher peak velocity, shorter reaction time and better efficiency of movement execution (shorter nMT). Patients in dCIT group also showed a greater tendency toward more feedforward control (a higher percentage of movement time where peak velocity occured). Additionally, dCIT produced significantly much more independences, especially in motor aspects of activities in daily living and better functional performance of the more affected arm and greater tendency to improve motor impairment.

According to the premotor theory of attention (Rizzolatti, 1998), spatial attention and motor planning are closely linked, when planning and executing an active movement, attention may simultaneously shift to where the motor prepared, and vice versa. The intention of the contralesional arm might activate the right hemisphere to reduce the imbalance of orientation tendencies (Lin, 1996). Thus the intensive and extensive forced use of the more affected arm could produce massed endogenous cue to induce the attention shift to the contralesional space. The reduction of the left attention deficit in unilateral neglect patients following stroke could lead to improve the motor deficits of the less affected arm, especially in the temporal aspects of motor performances. The results of the kinematic measure of reaching movement to the contralesional space with the less affected arm suggested that the motor deficits attributed to the neglect syndrome could be significantly ameliorated through dCIT. The effectiveness of dCIT supported that the active motor output in the contralesional space might be an essential factor for attention shifting, and that the bilateral arm movement might recede the effects (Robertson & North, 1994).

The dCIT could restore the interaction between perceptual and motor systems. While reaching with the less affected arm across midline to the contralesional space, patients receiving dCIT could disengage and shift the spatial attention more quickly and had better ability to localize the target and register the perceptions in the contralesional space. The sufficient information could assist in forming a complete representation of the space where a motion intended to act (Mattingley, et al., 1994). While preparing a movement, patients could have better ability to computer the motor commands to the target, such as the distance between hand position and target location, and to predict the consequences of the planned motor program (Coulthard, et al., 2006). Additionally, the attention bias correction could lead patients to attend to process the sensory perception input from the contralesional space and select information to integrate into the ongoing motor commands. Thus patients could reduce hesitated motions, and produce quicker response and enhance the efficiency of movement execution. As patients could execute more preplanned movement, the path to adjust movement relied on feedbacks decreased (Weintraub & Mesulam, 1985; Winstein & Pohl, 1995). For the reaching movement with the more affected arm, dCIT provided massed opportunities for patients to practice a motor skill, and might lead patients to use the massive feedbacks to develop an internal model for feedforward control of movement, which also caused patients receiving dCIT to show greater tendency to perform more preplanned reaching movements (Lin, et al., 2007).

Patients after dCIT intervention showed much more independences in functional activities. The result might be due to the decreased impact of neglect syndrome on motor deficits and functional performances. The significant motor improvements might reduced the limitations in many motor function tasks. The results of the use of the more affected arm were consistent with the previous studies on the effectiveness of dCIT or modified CIT (Lin, et al., 2008; Tarkka, Pitkanen, & Sivenius, 2005). The intensive training of the more affected arm in functional tasks might provide sufficient proprioceptive inputs, thus patients might increase the awareness to use the more affected arm and improve the performances in activities of daily living. Though the patients in dCIT group showed great tendency to improve in FMA, the effects of dCIT on motor recovery measured by FMA and ARAT were not consistent with previous studies, and the results needed further study. Previous study of forced use therapy in stroke patients with neglect induced improvement on ARAT involved treatment for two consecutive weeks, five days a week, six hours a day (van der Lee., 1999). The unilateral neglect patients might have less efficiency of rehabilitation and motor learning than those patients without unilateral neglect (Denes, et al., 1982), and comparing to previous findings of CIT (van der Lee, 1999), patients with neglect might need more intensive and massed practice to induce the same large effects as in patients without neglect on motor recovery, but it remained further investigation.

Limitations and future study

The sample size was small and might be insufficient to generate significant differences between the groups in the large effect variables. The heterogeneity of patients recruited in the study should be controlled more precisely, such as onset months. Additionally, it's difficult to dissociate the neglect types of patients because neglect is a heterogeneous disorder and as well as that patients might comprise more than one symptom. The future study can provide outcome measures on quality of life.

Conclusion

The results supported that distributed CIT was an optimal treatment for patients with unilateral neglect. The dCIT produced a significant efficacy on functional independence and reduced the impact of neglect on motor performances. The dCIT was a promising treatment in reducing the motor deficits attributed to neglect syndrome demonstrated by the less affected arm, especially in the time characteristics of motor performances. The dCIT might induce neglect reduction and thus produced improvements in functional independences in daily motor tasks. The motor deficits of the less affected arm improvements might be one of factors for enhancing the functional independence in patients with unilateral neglect, because many ADL tasks required the cross midline movements towards the contralesional space, especially for stroke patients who may need to compensate some tasks by the less affected arm. Additionally, patients with unilateral neglect in dCIT group presented better and more spontaneously use of the more affected arm, representing the massed movements of the more affected arm increased the sensory perceptions of the arm to overcome the non-use. The neglect syndrome might produce less efficiency of motor rehabilitation in the unilateral neglect patients than others without neglect, so to increase the intensity of training or reduce the impact of neglect on motor learning might facilitate the motor recovery of the more affected arm.

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Table 1. Demographic and clinical characteristics of the participants

Characteristics	dCIT (n=6)	CT (n=5)	Statistic	P^a
Gender	4/2	4/1		0.576
Age (years)	63 ± 9.94	59.41 ± 3.13	0.269	0.617
Onset (m)	7.17 ± 5.64	18.8 ± 17.63	2.370	0.158
Diagnosis (infarction/hemorrhage)	4/2	2/3		0.392
MMSE scores	25.33 ±5.92	24.6 ± 4.72	0.050	0.828
FMA scores	30.83 ± 10.53	38.8 ± 21.09	0.759	0.406
Extinction	5 (83%)	4 (80%)		0.455
Visual field deficit	1 (17%)	2 (40%)		0.424
Line bisection bias index	0.07 ± 0.04	0.04 ± 0.03	1.350	0.275
RSCT				
Number of omissions in right field	5.17 ± 5.04	1.8 ± 3.49	1.584	0.240
Number of omissions in left field	13.67 ± 12.83	6.2 ± 5.89	1.422	0.264
RCWCT				
Number of omissions in right field	6.5 ± 6.92	3.6 ± 4.62	0.636	0.446
Number of omissions in left field	16 ± 15.06	6.4 ± 6.77	1.717	0.222

Note: dCIT, distributed constraint-induced therapy; CT, controlled treatment; values are mean± standard deviation; MMSE, Mini-Mental State Examination; FMA, upper extremity subtest of Fugl-Meyer assessment; RSCT, randomized shape cancellation test; RCWCT, randomized Chinese word cancellation test. ^{a}P is associated with Fisher’s exact test for categorical variables, one-way analysis of variance for continuous variables.

Table 2. Descriptive and inferential statistics for analysis of reaching kinematics with the less affected arm

	dCIT (n=6)		CT (n=5)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1, 7)}$	P	η^2
PV	1186.15 ± 449.87	1278.29 ± 179.17	1073.21 ± 179.61	1160.43 ± 298.17	7.848	0.013*	0.529
		(1359.49 ± 59.99)		(1081.91 ± 66.59)			
PPV	43.58 ± 10.57	44.37 ± 4.83	37.17 ± 11.88	38.93 ± 5.94	3.506	0.052	0.334
		(43.62 ± 3.06)		(37.15 ± 3.42)			
RT	0.54 ± 0.4	0.36 ± 0.13	0.450 ± 0.094	0.42 ± 0.13	6.314	0.020*	0.474
		(0.34 ± 0.03)		(0.46 ± 0.04)			
nMT	0.03 ± 0.04	0.01 ± 0.002	0.02 ± 0.01	0.02 ± 0.008	6.895	0.017*	0.496
		(0.01 ± 0.002)		(0.02 ± 0.002)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.

Abbreviation: dCIT, distributed constraint-induced therapy; CT, controlled treatment; PV, peak velocity; PPV, the percentage of movement time to peak velocity; RT, reaction time; nMT, normalized movement time.

*$P < .05$.

Table 3. Descriptive and inferential statistics for analysis of reaching kinematics with the more affected arm

	dCIT (n=6)		CT (n=5)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1,7)}$	P	η^2
PV	401.45 ± 186.26	548.95 ± 172.48	489.25 ± 227.21	654.50 ± 151.78	0.396	0.275	0.054
		(562.95 ± 74.70)		(637.70 ± 82.83)			
PPV	34.34 ± 15.21	43.12 ± 28.73	44.7 ± 16.18	44.25 ± 22.7	0.896	0.188	0.113
		(48.96 ± 7.84)		(37.23 ± 8.69)			
RT	0.53 ± 0.24	0.444 ± 0.130	0.52 ± 0.20	0.43 ± 0.10	0.085	0.390	0.012
		(0.434 ± 0.026)		(0.45 ± 0.03)			
nMT	0.11 ± 0.04	0.06 ± 0.02	0.09 ± 0.04	0.04 ± 0.02	0.125	0.367	0.018
		(0.05 ± 0.01)		(0.05 ± 0.01)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.

Abbreviation: dCIT, distributed constraint-induced therapy; CT, controlled treatment; PV, peak velocity; PPV, the percentage of movement time to peak velocity; RT, reaction time; nMT, normalized movement time.

Table 4. Descriptive and inferential statistics for analysis of clinical outcome measures

	dCIT (n=6)		CT (n=5)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1,7)}$	P	η^2
FIM	86.83 ± 21.27	95.67 ± 22.91	86.40 ± 22.81	89.40 ± 22.43	6.940	0.017^*	0.498
		(95.51 ± 1.41)		(89.60 ± 1.57)			
FIM_motor	61.83 ± 15.08	69.17 ± 15.96	60.80 ± 18.55	63.40 ± 17.78	9.440	0.009^*	0.574
		(68.88 ± 1.05)		(63.74 ± 1.17)			
FIM_cognition	25.00 ± 15.08	26.50 ± 7.18	25.60 ± 5.68	26.00 ± 6.04	1.158	0.159	0.142
		(26.67 ± 0.51)		(25.80 ± 0.56)			
FMA	30.83 ± 10.53	38 ±12.82	38.8 ± 21.09	40 ±19.98	0.318	0.295	0.044
		(40.54 ± 3.25)		(36.95 ± 3.77)			
ARAT	32.83 ± 24.31	40.83 ±20.18	31.4 ± 26.21	33.00 ± 25.43	0.077	0.395	0.011
		(38.09 ± 3.85)		(36.29 ± 4.31)			
MAL_AOU	0.44 ± 0.40	1.47 ± 0.98	1.08 ± 1.2	0.93 ± 1.17	7.432	0.015^*	0.515
		(1.74 ± 0.24)		(0.61 ± 0.27)			
MAL_QOM	0.50 ± 0.47	1.69 ±1.36	1.11 ± 1.32	1.03 ± 1.49	5.956	0.023^*	0.460
		(1.96 ± 0.30)		(0.71 ± 0.34)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.
Abbreviation: dCIT, distributed constraint-induced therapy; CT, controlled treatment; FIM, Functional Independence Measure.
FMA, upper extremity subtest of Fugl-Meyer assessment; ARAT, Action Research Arm Test; MAL: Motor Activity Log;
AOU: Amount of Use; QOM: Quality of Movement. $^*P < .05$.

Figure 1. Flow diagram of the randomization procedure.

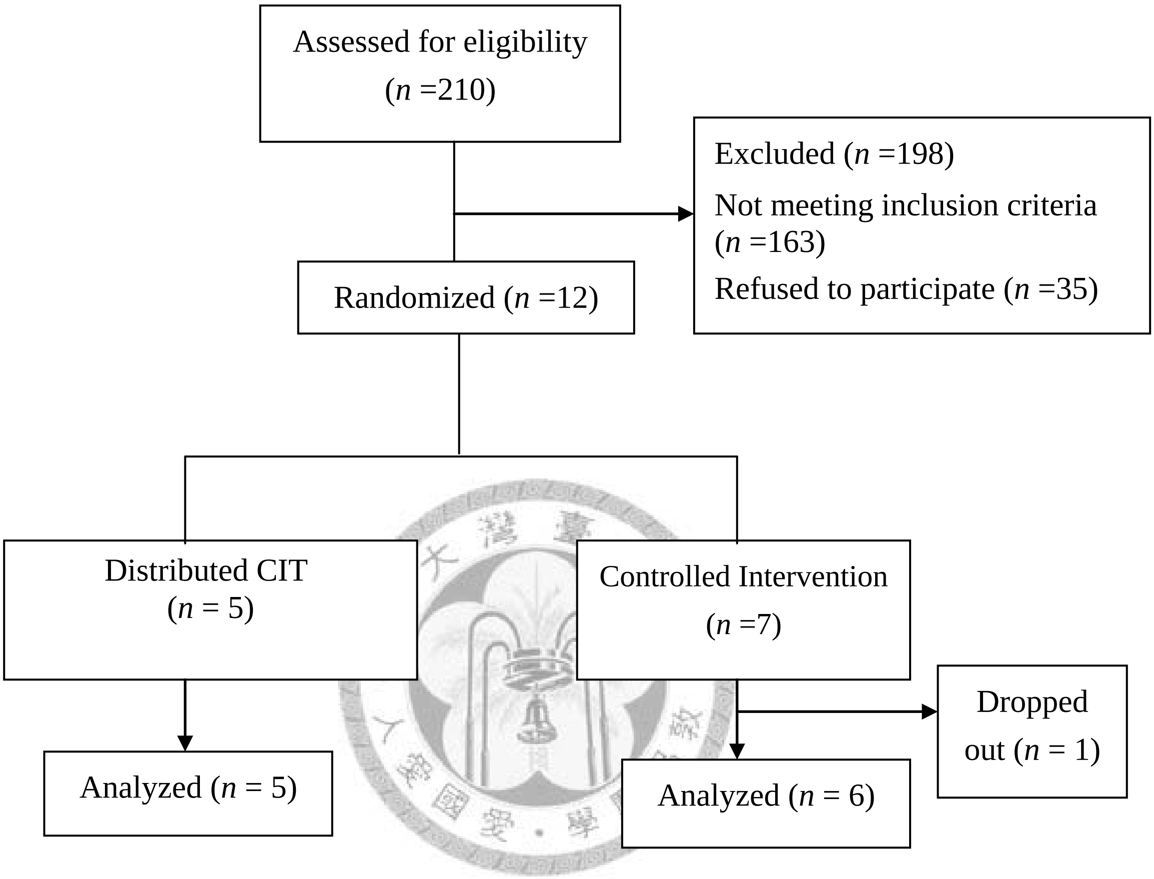
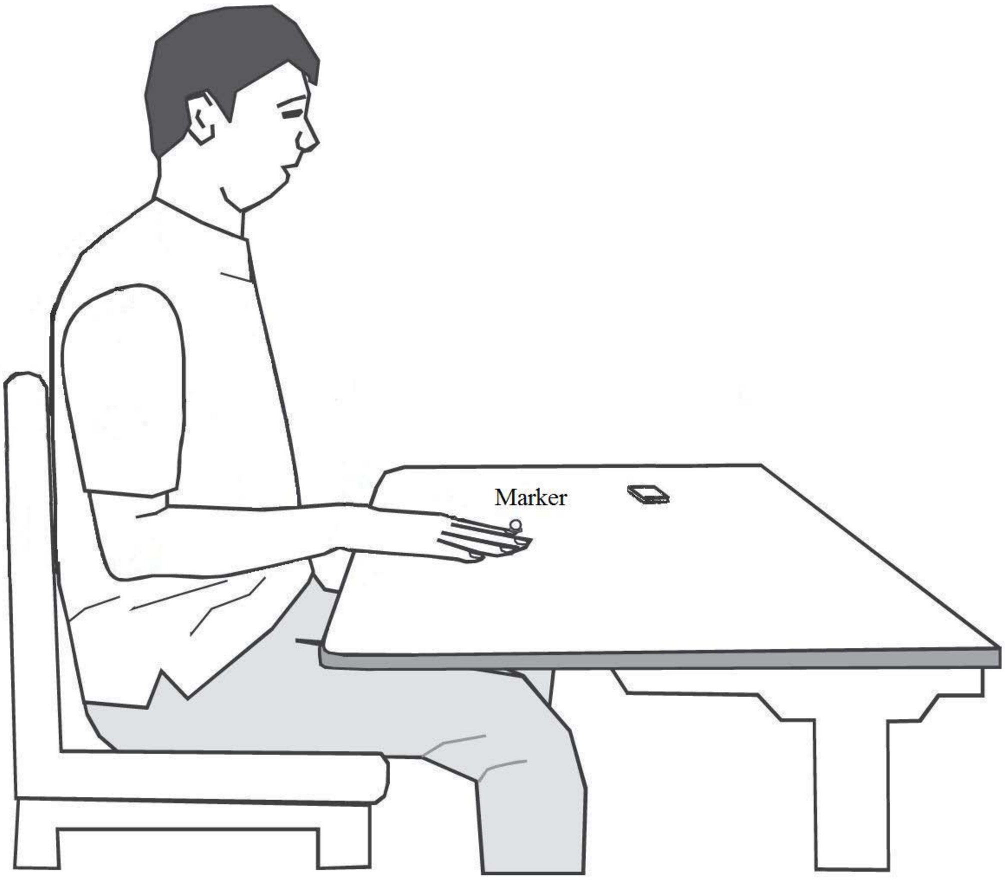


Figure 2. Marker set and starting position for the kinematic measure.



Note: Marker was attached on the nail of index finger.

CHAPTER 3

Effects of Distributed Constraint-Induced Therapy Combined with Eye Patching in Stroke Survivors with Unilateral Neglect: Kinematic Analysis and Clinical Assessments

Introduction

Stroke is a leading cause of long-term disability. In addition to the motor sequela, perceptual and cognitive deficits are also important factors associated with the outcomes of recovery. Unilateral neglect is often described as a deficit that patients fail to report, response, or orient to sensory stimuli presented at the space contralateral to a brain lesion, when this failure cannot be attributed to either sensory or motor deficits (Heilman & Valenstein, 1979). The presence of the neglect syndrome has been demonstrated as a predictor of poor responses to rehabilitation program, and which might impact on the process of motor recovery (Denes, Semenza, Stoppa, & Lis, 1982).

Additionally, the attention deficit might disrupt the interaction between perceptual and motor systems. Studies reported that patients with unilateral neglect showed impairments in temporal aspects of motor performance, including prolonged reaction time, prolonged movement time, lower peak velocity and higher proportion of total movement time spent in deceleration (Coulthard, Parton, & Husain, 2006; Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Mattingley, Bradshaw, & Phillips, 1992). Though distributed constraint -induced therapy (dCIT) has been a promising intervention for motor and functional improvements (Lin, Wu, Wei, Lee, & Liu, 2007; Wu, Chen, Tang, Lin, & Huang, 2007; Wu, Chen, Tsai, Lin, & Chou, 2007; Wu, Lin, Chen, Chen, & Hong, 2007), it also has been a potential treatment of unilateral neglect (Freeman, 2001; Pierce & Buxbaum, 2002). Based on the underlying theory basis of limb activation intervention (Robertson & North, 1993; Robertson & North, 1994; Robertson, North, & Geggie, 1992), the active movement of the more affected arm could induce patients to shift attention toward the space where motor performed. In addition to dCIT which involved constraint of the less affected arm, eye patching was also a treatment of reducing sensory input from the ipsilesional side. Eye patching which activated right superior colliculus might induce reflex eye movement, as well as shifting the visual attention, to the contralesional side, rather than passively inducing the attention shifting (Posner & Rafal, 1987; Sprague, 1966).

Distributed CIT combined with eye patching may reinforce the attention shift and engagement into the contralesional space, and then the reduction of unilateral neglect may improve the motor deficits attributed to the neglect syndrome and enhance efficiency of the motor recovery process.

Purpose

The purpose of the study was to investigate the effects of distributed CIT combined with eye patching in patients with unilateral neglect following stroke on motor improvements of the less affected arm evaluated by kinematics, and motor recovery of the more affected arm evaluated by clinical and kinematic measures.

Hypotheses

We hypothesized that after three-week intervention, patients treated with distributed CIT combined with eye patching would exhibit better motor control performance and benefit more on motor recovery, compared with patients treated with distributed CIT alone.

Methods

Design

The experiment was a randomized-controlled trial, pretest-posttest design. Patients with right-hemisphere stroke and unilateral neglect were recruited and randomly allocated into one of the two groups, including dCIT combined with eye patching group (dCIT+EP) and dCIT group. See Figure 1. All patients were blind to the study hypotheses. The outcome measures were administered within one week before and after the three-week intervention. All patients continued with other routine rehabilitation program, such as physiotherapy or speech therapy.

Participants

We recruited 11 right-hemisphere stroke patients (8 men; mean age, 61.45y; onset mean, 10.48 months) from medical centers and local hospitals in the north of Taiwan. Eligibility criteria for including patients were as following: (1) first or recurrent unilateral stroke in right hemisphere (ischaemic or hemorrhagic) confirmed by clinical diagnosis, (2) achieving the Brunnstrom’s stage III or above, (3) right handed before stroke evaluated by Edinburgh inventory (laterality quotient above 0.80), (4) no significant cognitive impairments and able to follow instructions (MMSE ≧ 23), (5) no excessive spasticity in the more affected arm (the mean score of the modified Ashworth Scale of Muscle Spasticity ≦ 2), (6) considerable non-use of the more affected arm (the mean score of amount of use of MAL < 2.5). All patients presented left unilateral neglect after stroke. Unilateral neglect was diagnosed by line bisection test (Lin, Cermak, Kinsbourne, & Trombly, 1996), the random shape cancellation test (Weintraub & Mesulam, 1985), the Random Chinese Word Cancellation test (Chen Sea, Henderson, & Cermak, 1993) and double simultaneous stimulation. Patients were recruited if unilateral neglect was presented in two of above tests. Patients were excluded if they had severe dysphasia, poor balance to threaten safety, significant impairments in visual acuity (Snellen acuity below 20/70 after remediation), or severe pain.

The data used in this study was collected from a large clinical trial and was shared in other articles.

Intervention

Patients in the experimental group received the distributed CIT combined with right half-field eye patching for 2 hours per day, 5 days a week, for 3 weeks. Based on distributed CIT program, the less-affected hand was constrained by a mitt for at least 6 hours per day during the 21-day treatment period. The therapist had to provide functional tasks for motor practice and use skills to shape the behavior we expected. For right half-field eye patching intervention, opaque 3M tape was used to partially occlude the nasal side of left eye and the temporal side of right eye. The half-field eye-patching glasses were applied to patients in the combined group during treatment. The distributed CIT group received treatment with equivalent dosage. The patients in dCIT group also had to wear a mitt for at least 6 hours per day and received intensive practice with functional motor activities.

Materials and Instrumentation

Clinical assessments

The line bisection test consisted of three different horizontal lines of 12, 18, and 24 cm, each of them was separately presented twice with pseudo-random order. Each time patients had to bisect one horizontal line on a sheet of B4 paper, and then the bias index of each line was calculated (bias index = raw deviation score / half of the line length) (Lin, et al., 1996). Patients were diagnosed unilateral neglect if the average bias index were 0.055 or above. The diagnostic criteria of the random shape cancellation test included (1) the number of omissions reached five or more, and (2) the difference in number of omissions between left and right half page reached three or more. Similarly, patients were considered to present unilateral neglect on Random Chinese Word Cancellation test if there were five or more omissions, and if the difference in number of omissions between left and right half page reached three or more (Chen Sea, et al., 1993).

The Edinburgh Inventory (Oldfield, 1971) was used to examine brain laterality and dominant hand. The Mini-Mental State Examination (MMSE) was utilized as a cognition screening tool including orientation, attention, memory, and verbal ability dimensions. The higher score indicates better cognition. The modified Ashworth Scale of Muscle Spasticity (mASMS) is a 6-point ordinal scale (0= no increase in muscle tone – 4= affected part is rigid), which is scored according to the resistance level given through the joint movement by passive stretch. This scale is with good inter-rater reliability (Bohannon & Smith, 1987).

The upper-extremity subscale of the Fugl-Meyer Assessment (FMA) was used to evaluate level of motor impairment of the hemiparetic limb (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) with good validity, reliability and responsiveness (Duncan, Propst, & Nelson, 1983; Hsieh, et al., 2009). The 33 items of the FMA were developed based on the motor recovery level of the Brunnstrom stages. The upper-extremity subscale measures movement and reflexes of the shoulder/elbow/forearm, wrist, hand, and coordination and can be scored on a 3-point scale.

The Motor Activity Log (MAL) is a semi-structured interview and is utilized to assess amount of use (AOU) and quality of movement (QOM) of the more affected arm in 30 specific activities of daily living. The scale ranges from 0 to 5. 0 means never use of the more affected arm and inability to use the affected arm for this activity, and 5 means always use of the more affected arm and ability to use the more affected arm as well as before stroke. The mean score was obtained to evaluate the phenomenon of non-use and performance of the more affected arm.

The Catherine Bergego Scale (CBS) is used to assess neglect behavior by observation of patients' functional performance in ten daily activities, such as eating, dressing, and walking. It's a 4-point scale, ranging from 0 (no neglect) to 3 (severe neglect). Higher total score represents severer neglect that patients explore the left space less frequently (Azouvi, et al., 2003).

Kinematic Measure

Changes in motor control were evaluated by kinematic analysis. A seven-camera motion-analysis system (VICON MX; Oxford Metrics Inc., Oxford, UK) was used. The system in conjunction with a personal computer can capture the movement of markers during the task. Two channels of analog signals were collected simultaneously. Signal collection was linked to a desk bell provided for instruction of task start and a target bell used to determine movement offset. Movements were recorded at 120 Hz and digitally low-pass filtered at 5 Hz using a second-order Butterworth filter with forward and backward pass.

Testing procedure

Reference marker was attached on the nail of index finger in order to analyze endpoint control performance of reaching movement. During the task, the patient sat on a chair with seat height adjusted to 100% of the lower leg length, measured from the lateral knee joint to the floor with patient standing. Adjacent to the chair was a table with a height adjusted to 5 cm below elbow. The patient rested the arm performed reaching on the edge of the table as a starting position. See Figure 2.

The patients were instructed to perform an unrestraint unilateral reaching task with the less and more affected arm alternatively. The task bell was located in the contralesional space with distance of patient's functional arm length from the medial border of the axilla to the distal wrist crease (Wu, Chen, Tang, Lin, & Huang, 2007). The patient was instructed to reach and press the task bell (3 cm^2 in square and 0.5 cm in height) in the contralesional space as quickly as possible with the index finger of the more affected arm or less affected arm. The patient can start to move when the start bell ring. For the unilateral task, a rise of tangential wrist velocity above 5% of its peak value was indicated as the movement onset. Movement offset was defined as the time when patient pressed down the task bell.

Data reduction for kinematic variables

An analysis program coded by LabVIEW (National Instruments, Inc.) language was used to process kinematic data. Kinematic variables for reaching included reaction time (RT), normalized movement time (nMT), peak velocity (PV), and the percentage of movement time where peak velocity occurs (PPV).

Reaction time (RT sec.) is the interval from the start signal to movement onset, and refers to the time to initiate the movement. Normalized movement time (nMT sec.) is the interval between movement onset and movement completion which was normalized by the direct distance of arm and target in each patient, and indicates the efficiency of movement execution (Lin, et al., 2007; Wu, Chen, Tang, et al., 2007). Peak velocity (PV mm/sec.) indicates force or impulse at movement initiation. Higher PV represents greater force generated (Wu, Chen, Tang, et al., 2007). The percentage of movement time where peak velocity occurs (PPV %) reflects the percentage of movement time for acceleration phase. The acceleration phase is proposed to be the major preplanned aspect of the movement and a longer acceleration phase suggests that the movement is performed primarily based on feedforward control (Lin et al., 2007).

Statistics

Analysis of covariance (ANCOVA), controlling for pretreatment differences, was used to test the differences between the two groups at posttest for each variable. For each analysis, pretest performance and onset months were covariates, group was the independent variable, and posttest performance was the dependent variable. One-tailed test was used with α level set at .05. The effect size $\eta^2 = SS_b/SS_{total}$ was calculated for each outcome variable to index the magnitude of group differences in performance. A large effect is represented by a η^2 of at least 0.138, a moderate effect by a η^2 of 0.059, and a small effect by a η^2 of 0.011 (Cohen, 1988).

Results

Characteristics of study patients

11 patients were recruited (mean age, 61.45y; male/female, 8/3). The demographic and clinical characteristics were presented in Table 1. The baseline characteristics of patients were comparable. There were no significant differences between the groups in age, gender and months after stroke. Table 1 also showed that there were no significant differences in cognition level, motor impairments, and neglect syndrome.

Effects of distributed CIT combined with eye patching on kinematics

For the less affected arm after three-week treatment, the results of the ANCOVAs that tested the effects of dCIT+EP versus dCIT were displayed in Table 2. The kinematic variables showed no significant differences between groups, but performance on the kinematic measure of PPV showed a large effect in dCIT+EP group ($F_{(1, 7)}$ =1.479, P =0.132, η^2 =0.174). Moderate to large effects were found for the kinematic variables of PV ($F_{(1, 7)}$ =0.496, P =0.252, η^2 = 0.066), RT ($F_{(1, 7)}$ =0.500, P =0.251, η^2 =0.067), and nMT ($F_{(1, 7)}$ =0.443, P =0.264, η^2 =0.060). For the more affected arm, the descriptive and inferential statistics for the dependent variables were presented in Table 3. There were no significant differences between the groups at posttest, but a large effect was found on PPV ($F_{(1, 7)}$ =2.611, P = 0.080, η^2 =0.272). Moderate to large effects were found for the kinematic variables of RT ($F_{(1, 7)}$

=1.103, P =0.164, η^2 =0.136) and nMT ($F_{(1, 7)}$ =0.841, P =0.390, η^2 =0.107). The kinematic variable of PV showed a small effect ($F_{(1, 7)}$ =0.020, P =0.446, η^2 =0.003).

Effects of distributed CIT combined with eye patching on clinical measures

The ANCOVA results of the clinical outcome measures that tested the effects on functional and motor improvements were presented in Table 4. There were no significant differences between the groups, but we focused on the effect size η^2 for each variable. The dCIT+EP induced a large effect on CBS ($F_{(1, 7)}$ =2.615, P =0.075, η^2 =0.272). The dCIT produced a large effect on scores of the upper-extremity subscale of FMA ($F_{(1, 7)}$ =1.677, P =0.118, η^2 =0.193). A large though non-significant effect was found in the dCIT+EP group for QOM of MAL ($F_{(1, 7)}$=1.394, P =0.138, η^2 =0.166). A small to moderate effect was found in the dCIT+EP group for AOU of MAL ($F_{(1, 7)}$ =0.344, P =0.288, η^2 =0.047).

Discussion

In the present study, we proposed a new treatment approach, which combined distributed CIT with right half-field eye patching based on the perceptual-motor integration model. The findings were partially consistent with prior hypotheses. Though all the variables of outcomes showed no significant differences between the groups which might be due to the small sample size, we found dCIT+EP produced large effects on better motor control strategy, improvement of neglect behavior and better functional use of the more affected arm. The dCIT produced a large effect on the motor improvements measured by FMA.

Both dCIT and eye patching were “forced therapy”. In terms of the premotor theory of attention, which claimed that sensory attention and motor intention (selection and planning of a specific movement) are closely linked, and when one is attending to a spatial location, one is also prepared to act in that direction, and vice versa (Eimer, Van Velzen, Gherri, & Press, 2006; Rizzolatti, 1998). Both the active movement induced by dCIT and reflex eye movement induced by eye patching could cause effects on facilitating attention shift. Adding eye patching to dCIT might enhance the amelioration of attention bias and thus improve the motor deficits related to lack of attention resources. The dCIT combined with eye patching might induce a large and positive effect than dCIT alone on attending to process the sensory perception in the contralesional space while executing the reaching movement toward contralesional side with the less affected arm, and thus the patients could have sufficient information to perform more preplanned movements. Patients in the dCIT+EP group also showed a large effect on improvement in motor control strategy when reaching with the more affected arm. The eye patching might induce reflex attention shift to the more affected arm and facilitate the intention of left arm movement, resulting in the engagement of attention consequently. The dCIT led patients to generate an internal model of feedforward control through extensive practice of motor tasks, and which might accompany consecutive attention shift. The dCIT combined with eye patching might lead patients to execute more preplanned movements and decrease the reliance on feedbacks through the integration of attention shift and motor practice (Lin, et al., 2007; Winstein & Pohl, 1995).

The dCIT combined with eye patching showed great potential to improve the neglect related behavior, which suggested that the dCIT+EP might induce more shifts of attention and improve the neglect syndrome, and thus enhanced better functional performances of ADL which required attention to interact with the motor behaviors. The result of FMA was not consistent with our hypothesis that we proposed that dCIT combined with eye patching might reduce the impact on motor recovery. The possible interpretation was that patients wearing the eye patching glasses during treatment might feel uncomfortable and might compensate by head rotation to try to see the patched right-half field (Fong, et al., 2007). The negative responses might interfere with the process of motor learning and thus patients might not have opportunities to accomplish adequate massive practice (Kwakkel, Kollen, & Wagenaar, 1999).

There was no significant difference between groups in the amount of use of the more affected arm, and it might be due to that patients in both groups were required to constrain the less affected arm and use the more affected arm in ADL. Patients in the dCIT+EP group might pay more attention to the movement of the more affected arm via the attention shift induced by active movement and reflex attention shift, and thus patients might more attend to the changes of motor improvements, suggested by the quality of movement of MAL.

Limitations and future study

The sample size was small and might be insufficient to generate significant differences between the groups in some variables with a large effect size. Additionally, it’s difficult to dissociate the neglect types of patients because neglect is a heterogeneous disorder and as well as that patients might comprise more than one symptom. We suggested that future study can include a larger sample size to accomplish a more powerful inference, and classify patients into subgroups in order to define what kinds of patients are most likely to profit from this combined therapy, or to modify the components of the combined therapy. Furthermore, the underlying interaction of dCIT and eye patching remained uncertain and the effects of combining right half-field eye patching needed further investigation according to the inconsistent results of the previous studies of eye patching on neglect treatment (Pierce & Buxbaum, 2002).

Conclusion

The techniques of distributed CIT and eye patching were easily integrated into the clinical rehabilitation program. Though the outcome variables showed no significant differences between groups but large effects were found for some variables. The dCIT combined with eye patching induced more attention shifts and presented a great potential to reduce the impact of neglect on ADL execution and thus patients showed better functional performances. The dCIT combined with eye patching also improved the motor control strategy through extensive motor practice and more attention resources, and enhanced the positive use of the more affected arm. Additionally, therapists should monitor patients' responses to eye patching and the combined therapy needed further study to clarify if patients with unilateral neglect could enhance the efficiency of motor learning via sufficient attention engagements.

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Table 1. Demographic and clinical characteristics of the participants

Characteristics	dCIT+EP (n=5)	dCIT (n=6)	$F_{(1,9)}$	P^a
Gender	4/1	4/2		0.576
Age (years)	59.60 ±15.04	63 ± 9.94	0.203	0.663
Onset (m)	13.80 ±16.43	7.17 ±5.64	0.872	0.375
Diagnosis (infarction/hemorrhage)	4/1	4/2		0.576
MMSE scores	26.60 ±1.14	25.33 ± 5.92	0.218	0.652
FMA scores	37.80 ±16.02	30.17 ± 11.23	2.516	0.147
Extinction	4 (80%)	5 (83%)		0.455
Visual field deficit	3 (60%)	1 (17%)		0.197
Line bisection bias index	0.095±0.037	0.067 ± 0.035	1.719	0.222
RSCT				
Number of omissions in right field	1.80 ± 2.95	5.17 ± 5.04	1.721	0.222
Number of omissions in left field	8.20 ± 8.23	13.67 ± 12.83	0.670	0.434
RCWCT				
Number of omissions in right field	5.40 ± 6.73	6.50 ± 6.92	0.071	0.796
Number of omissions in left field	7.60 ±5.73	16.00 ±15.06	1.369	0.272

Note: dCIT, distributed constraint-induced therapy; dCIT, distributed constraint-induced therapy; EP, eye patching; values are mean ± standard deviation; MMSE, Mini-Mental State Examination; FMA, upper extremity subtest of Fugl-Meyer assessment; RSCT, randomized shape cancellation test; RCWCT, randomized Chinese word cancellation test. ^{a}P is associated with Fisher's exact test for categorical variables, and one-way analysis of variance for continuous variables

Table 2. Descriptive and inferential statistics for analysis of reaching kinematics with the less affected arm

	dCIT+EP (n=5)		dCIT (n=6)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1,7)}$	P	η^2
PV	1224.73 ± 479.60	1362.97 ± 285.1	1174.34 ± 445.41	1291.46 ± 185.57	0.496	0.252	0.066
		(1364.88 ± 76.62)		(1289.86 ± 69.56)			
PPV	42.53 ± 9.69	46.37 ± 10.51	43.58 ± 14.34	44.37 ± 4.18	1.479	0.132	0.174
		(47.60 ± 4.02)		(40.85 ± 3.65)			
RT	0.388 ± 0.050	0.355 ± 0.066	0.525 ± 0.406	0.377 ± 0.173	0.500	0.251	0.067
		(0.379 ± 0.021)		(0.358 ± 0.019)			
nMT	0.019 ± 0.012	0.013 ± 0.005	0.03 2 ± 0.042	0.014 ± 0.002	0.443	0.264	0.060
		(0.013 ± 0.001)		(0.014 ± 0.001)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.

Abbreviation: dCIT, distributed constraint-induced therapy; dCIT, distributed constraint-induced therapy; EP, eye patching; PV, peak velocity; PPV, the percentage of movement time to peak velocity; RT, reaction time; nMT, normalized movement time.

Table 3. Descriptive and inferential statistics for analysis of reaching kinematics with the more affected arm

	dCIT+EP (n=5)		dCIT (n=6)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1,7)}$	P	η^2
PV	655.73 ± 291.13	608.80 ± 166.31	401.45 ± 186.26	548.95 ± 172.48	0.020	0.446	0.003
		(585.21 ± 82.01)		(568.61 ± 73.85)			
PPV	24.49 ± 19.32	46.64 ± 22.65	34.34 ± 15.21	43.12 ± 28.73	2.611	0.080	0.272
		(54.10 ± 7.62)		(36.90 ± 6.91)			
RT	0.545 ± 0.140	0.399 ± 0.065	0.534 ± 0.237	0.444 ± 0.130	1.103	0.164	0.136
		(0.396 ± 0.035)		(0.446 ± 0.031)			
nMT	0.112 ± 0.089	0.056 ± 0.045	0.107 ± 0.038	0.055 ± 0.021	0.841	0.390	0.107
		(0.048 ± 0.011)		(0.062 ± 0.010)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.

Abbreviation: dCIT, distributed constraint-induced therapy; dCIT, distributed constraint-induced therapy; EP, eye patching; PV, peak velocity; PPV, the percentage of movement time to peak velocity; RT, reaction time; nMT, normalized movement time.

Table 4. Descriptive and inferential statistics for analysis of clinical outcome measures

	dCIT+EP (n=5)		dCIT (n=6)		ANCOVA		
	Pretest	Posttest	Pretest	Posttest	$F_{(1,7)}$	P	η^2
CBS	15.80 ± 3.77	9.60 ± 3.51	14.33 ± 5.47	10.67 ± 4.68	2.615	0.075	0.272
		(8.95 ± 1.01)		(11.21 ± 0.92)			
FMA	37.80 ± 16.02	41.80 ± 20.24	30.83 ± 10.53	38.00 ± 12.82	1.677	0.118	0.193
		(36.93 ± 2.79)		(42.06 ± 2.53)			
MAL_AOU	0.240 ± 0.470	1.12 ± 1.30	0.440 ± 0.400	1.47 ± 0.978	0.344	0.288	0.047
		(1.50 ± 0.440)		(1.14±0.397)			
MAL_QOM	0.190 ± 0.310	1.36 ± 1.70	0.500 ± 0.470	1.69 ± 1.36	1.394	0.138	0.166
		(2.02 ± 0.519)		(1.14 ± 0.468)			

Note: Values are mean ± standard deviation. Values in bracket are means adjusted for covariate in the ANCOVA model.

Abbreviation: dCIT, distributed constraint-induced therapy; dCIT, distributed constraint-induced therapy; EP, eye patching; CBS, Catherine Bergego Scale; FMA, upper extremity subtest of Fugl-Meyer assessment; MAL, Motor Activity Log; AOU, amount of Use; QOM, quality of movement.

Figure 1. Flow diagram of the randomization procedure.

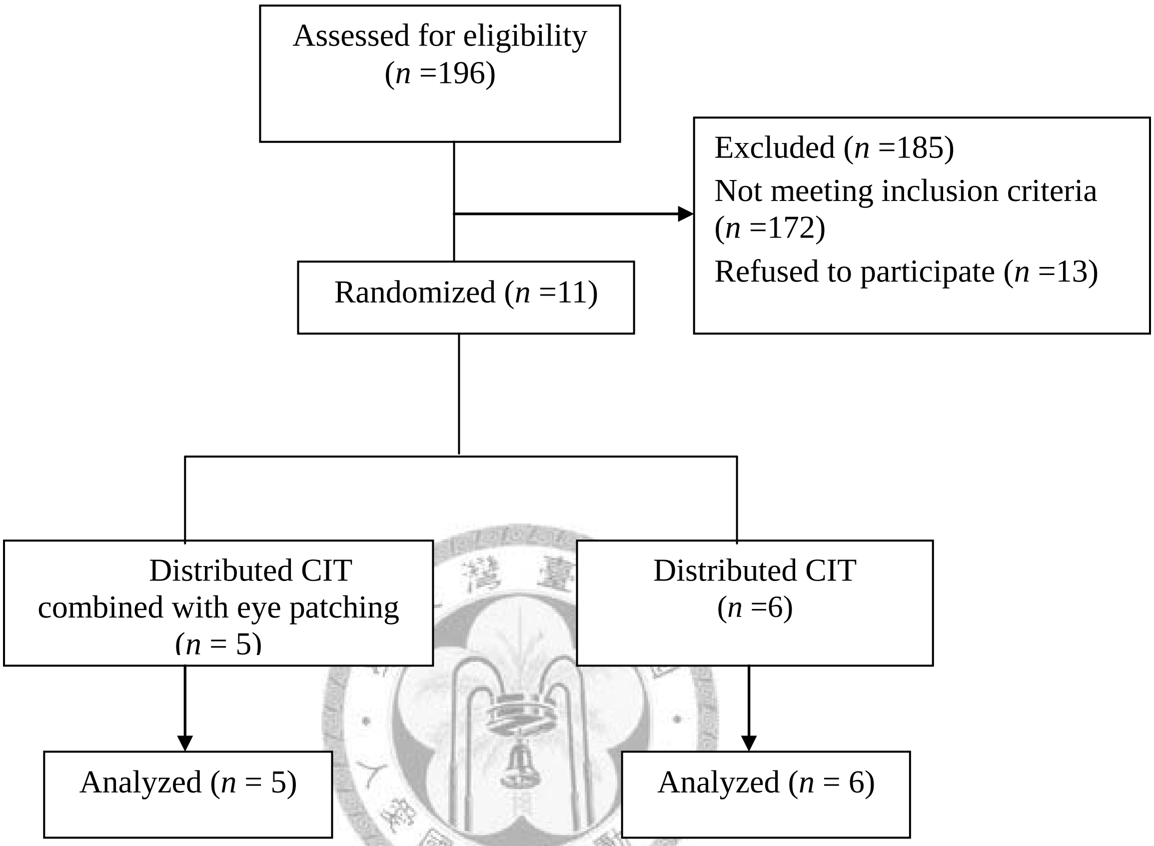
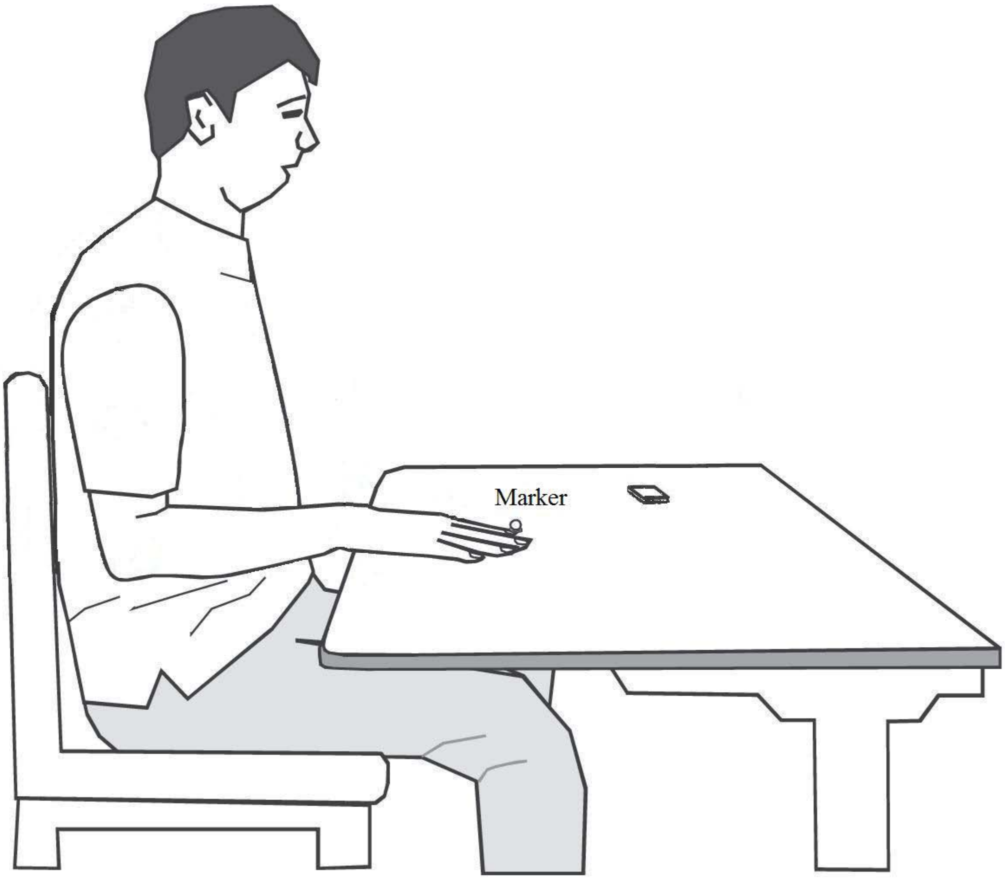


Figure 2. Marker set and starting position for the kinematic measure.



Note: Marker was attached on the nail of index finger.