Multi-sensory feedback therapy combined with task-oriented training on the hemiparetic upper limb in chronic stroke: study protocol for a pilot randomized controlled trial

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Study Protocol

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Abstract

Background An important reason for the difficulty in recovering sensorimotor dysfunction of the upper extremity in chronic stroke survivors, is the lack of sensory function, such as tactile and proprioception feedback. In clinical practice, single sensory training is only for the restoration of sensory function. Increasing evidence suggests that use of task-oriented training (TOT) is a useful approach to hand motor rehabilitation. However, neither approach is optimal since both methods are trained only for specific functional recovery. Our hypothesis is that multi-sensory feedback therapy (MSFT) combined with TOT has the potential to provide stimulating tasks to restore both sensory and motor functions. The objective of the trial is to investigate whether novel MSFT is more effective in improving arm sensorimotor function in chronic stroke phase than single TOT.

Methods/Design: The study will be conducted as a multicenter, randomized, double blind controlled trial. Participants (n = 90) will be randomised into three groups to compare the effect of the multi-sensory feedback therapy group against task-oriented training group and conventional group. Participants will receive treatment at the same intensity (60 min, 5 days a week, 4 weeks, 20 hours total). Primary outcome measures for assessment of sensory function are the Semmes Weinstein monofilaments examination (SWME),two-point discrimination test (2PD) test. Secondary measures are the Action Research Arm Test (ARAT)、Nine-Hole Peg Test (NHPT), Wolf Motor Function Test (WMFT), Box and Blocks Test (BBT), Modified Barthel Index (MBI), Instrumental activities of daily living (IADL) and Generalized Anxiety Disorder 7-Item Scale (GAD-7). Outcome mearsures will be evaluated at baseline, post treatment, and two months follow-up. All assessments will be conducted by trained assessors blinded to treatment allocation.

Discussion This study will determine the acceptability and efficacy of the intervention on the hemiparetic upper limb, it may be promising tools for sensorimotor functional recovery after stroke.

Background

Stroke is a major cause of serious long-term disability in chronic stroke [1, 2]. In China alone, the age-standardized prevalence, incidence, and mortality rates were approximately 1114.8/100 000 people, 246.8 and 114.8/100 000 person-years, respectively [3]. More than two thirds of all patients experience impaired function in the upper extremity [4, 5], and many of chronic stroke patients require continued rehabilitation for hand disability from hospitals. Sensory impairments of all modalities are thought to be common during the chronic stage of stroke [6].

Although tactile loss is more frequent than proprioceptive dysfunction, especially in the hand. Approximately 80% of chronic stroke patients experience tactile loss, over 69% without proprioceptive discriminations [7]. Somatosensory deficits are associated with the degree of weakness and stroke severity, and they are also related to mobility, mental health, independence in activities of daily living, and recovery [8]. Sensory function is an important composition of widely used physiotherapy approaches

such as Bobath (known as Neurodevelopment Therapy in the United States) and Brunnstrom, and it is considered a precursor to the recovery of movement and functional activities of daily living in patients with stroke [9]. Poor motor function is associated with reduced sensory experience and processing after stroke [10, 11]. Joint position sensation of the upper extremity is closely related to motor ability due to stroke-related reduced discrimination in proprioception [9], it causes disturbances in the arm movement trajectory. The relation between sensory and motor dysfunction is unsurprising since biomechanics and motor control of human movement require bidirectional interaction between cortex and periphery [12].

Sensory disorders include light touch, temperature, joint position, two-point discrimination, object discrimination, spatial orientation [5]. Different types of sensory disorders have different inefficiencies to perform daily activities and social participation [12]. Thermohypesthesia is the reason leading to scalding and freezing injury [6]. Scalding injuries often occur as the result of spilled food or beverages. They are also unable to feel pain, which means that they can’t retract arms and hands actively. In addition, bleeding often happens after touching acupuncture or sharp objects. Stroke is also a major global mental health problem. The sensory impairment has negative implications to explore environment, and lower the effect of rehabilitation outcomes. Anxiety, depressive symptoms, general psychological distress and social isolation are prevalent if chronic patients have sensory disorders [13]. Psychosocial difficulties may impact significantly on long-term functioning and quality of life [14, 15], and it reduces the effects of rehabilitation services and bring about higher mortality rates [16].

The purpose of this study is to determine whether multi-sensory feedback therapy (MSFT) can promote upper limb motor function, daily life activities, social participation and help to relieve anxiety in patients with chronic stroke.

Study Objectives And Hypotheses

The primary aim of this trial is to determine whether multi-sensory feedback therapy (MSFT) group promotes sensory function, motor abilities and social participation among chronic stroke survivors with sensory deficits, compared to task-related training (TOT) group and basic group of hand rehabilitation. We will test the following hypotheses:

1.
Primary outcome: Stroke survivors with sensory loss in the MSFT group will experience significantly higher levels of sensory function (measured by SWME, 2PD), than stroke survivors in the TOT group and basic group at 1 and 2 months after intervention.

2. Secondary outcomes: Stroke survivors with sensory loss in the MSFT group will experience significantly higher levels of motor function (measured by ARAT, NHPT, WMFT, BBT), social participation (measured by MBI, IADL), and lower levels of depressive symptoms and anxiety (measured by GAD-7) than stroke survivors in the TOT and basic group at 1 and 2 months after intervention. The secondary aim of this trial is to understand the effect of the three groups, such as the patients' responsiveness to the

intervention, motivation to achieve rehabilitation expectancy, confidence in their ability to perform rehabilitation exercises, and adherence to rehabilitation therapy.

Methods

Setting and study design

This study is a prospective multicenter, double-blind, randomized controlled trial (RCT) conducted in Shanghai Province, China. The study centres include Shanghai Jing An District Central Hospital, Huashan Hospital affiliated to Fudan University, Shanghai Third rehabilitation Hospital. All study settings are governmental hospitals. The trial consists of three groups, namely the multi-sensory feedback therapy (MSFT) group, the task-oriented training (TOT)group, and basic group of hand rehabilitation. The allocation ratio is 1:1:1, patients who meet the inclusion criteria will be recruited, and randomly assigned to one of them. Three groups will be given 5 days per week for 4 weeks. The evaluators will assess the effectiveness of the three groups on the hemiparetic upper limb in chronic stroke for persons with sensory impairments. Outcome mearsures will be assessed at baseline, post treatment, and two months follow-up. Data will be managed by statisticians and blind evaluators during this trial. All patients will be asked to sign the Consent Form before the screening. Ethics approval was granted by the Shanghai Jing An District Central Hospital Institutional Review Board on 30 October (2019-34). The study was registered in the Chinese Clinical Trial Registry on 4 December 2019 (ChiCTR1900027914). We plan to submit the results to a peer-reviewed journal and present them at conferences, rehabilitation forums and to the general public. This research program was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [17]. The trial flow diagram is presented in the following (Fig. 1).

Fig. 1 Flow chart of the study design

Sample size calculations

The G Power software package was used to prospectively calculate the adequate sample size for this trial. The calculation of sample size was based on the change of the Semmes Weinstein monofilaments examination (SWME) score. The repeated analysis of variance (ANOVA) was carried out. Setting a power of 0.80 and a two-sided type-I error of 0.05, with an effect size of 0.27 [18-21], this predicted a total sample size of 74. Accounting for roughly a 20% drop-out rate, so we estimated that 90 participants (30×3groups) would be sufficient to minimise the risk of type 1 or type 2 errors. According to previous studies, 30 patients in each group has a more stable statistical power. We anticipate that results from this pilot trial will yield data for a sample size calculation for a future definitive RCT.

Participants

Inclusion criteria

This RCT study includes stroke survivors meeting the following inclusion criteria [22-24]:

1. Being adults over 18 years of age; male or female
2. Inpatients for ischemic or hemorrhagic stroke
3. Diagnosed with unilateral stroke by CT or MRI
4. Patients on the hemiparetic upper limb in chronic phase (≥6 months)
5. Medically stable, sufficient cognitive functioning to participate (MMSE score ≥ 24/30 [25], assessed by their physician/stroke team)
6. Able to understand and complete the scale evaluations
7. interested in participating, and able to give informed consent.
8. Agree with the investigation and sign the written informed consent form

Exclusion criteria

Participants meeting any one of the following exclusion criteria will be excluded:

1. Patients who are assessed as moderate to severe cognitive dysfunction (MMSE≤24/30), serious psychiatric or somatic disease
2. Any other recent neurological deficit that affects arm and hands function;
3. Patients with haemorrhagic disease or a bleeding tendency
4. patients who experienced trauma, fever, or allergic his tory in the recent 2 weeks
5. Patients who have contagious disease, mental illness, cardiovascular diseases, or primary diseases of the liver, kidney, and haematopoietic and endocrine systems
6. Severe illness with life expectancy less than 3 months
7. Patients who are participating in other clinical trials concurrently.
8. The patient is unwilling or unable to comply with the protocol or can not/ will not cooperate fully with the investigator or study personnel.

Study procedures

Recruitment and consent

Through hospital-based advertisements, all participants will be recruited in the three hospitals mentioned above. Once the patients are willing to participate in this trial, they will be assessed according to the stated inclusion and exclusion criteria following the recruitment protocol of the study. The trained clinical staff will identify participants specifically in the participating units. Eligible patients will be asked to sign the written informed consent form before the rehabilitation starts, then they will receive assessments and rehabilitation intervention at these hospitals. Baseline data analysis will be collected and analyzed during the first days of treatment. Shanghai Jing An District Central hospital is the initiator of this study. The institutional review committee of Shanghai Jing An District Central hospital will receive the study report during the entire study, and supervise the implementation of the study and data collection.

Randomization

The randomization schedule and all assignments will be computer generated using a basic, random number generator by an independent researcher. Participants will be randomly allocated in a 1:1:1 ratio into the MSFT group, the TOT group and the basic group. Random allocation will be performed for the participants who meet all selection standards, then they will sign the Consent Form. Participant identification codes will be allotted by the research coordinator who should record the codes in the Case Report Forms. A total of 90 participants, admitted at the above hospitals in Shanghai, will receive the rehabilitation therapy.

Blinding

The coordinator will send group allocation and the study number to rehabilitation therapists via Email. The trial records of the therapists will be stored in a locked briefcase that will be available for cooperative researchers and the therapists. Only the therapists and the coordinators will know the group assignment of each subject. The therapists and researchers will not discuss related in formation with the participants.

The participants who are informed to participate in the study will be treated separately, without knowing their allocation in the entire intervention. Since participants in the three groups will receive different rehabilitation strategies, these patients will not be treated at the same space after random allocation. To minimize the chance of acquaintance between the three groups of patients as much as possible, the rehabilitation therapists will inform the patients about the independent treatment room number before each treatment session. All research personnel responsible for assessing outcome indicator will be blinded to the patients' allocation. The research therapists and assessors will have separate telephones, offices, and document-storage facilities, they must avoid discussion about patients in front of the assessor. Everything should follow the guidelines recommended by Siemonsma and Walker [26]. The trial coordinator will make the appointment for the assessment by telephone, and will remind the patients not

to discuss the details of the accepted treatment to the assessors through this opportunity. The data will be recorded immediately after the evaluator's assessments. In order to identify whether the assessors know or have guessed each patient's group, they will be informed to fill
in questionnaires or take interviews after their involvement at the end of the trial.

These recorded data will be compared with the actual randomized grouping to determine the success of the blinding, which is recommended by Minnowe et al. [27]. Blinding method will be monitored and assessed by independent statisticians and and the Ethics Commit tee of the study centre who are responsible for data monitoring. Unblinding is permissible when the therapists determine that they should terminate the study, or the participants decide to withdraw from the experiment at their own discretion. With permission from the supervisors, the therapists may disclose specific interventions to the participants associated with withdrawal from this randomized trial.

Interventions

The allocation sequence will be based on a computer-generated random number table. Patients will be randomly assigned to one of the two groups: multi-channel sensory feedback (MCSF), and task-oriented training (TOT). During their hospitalisation, a 60 min per day training session will be delivered in the entire study. Patients randomized to multi-sensory feedback therapy (MSFT) or task-oriented training (TOT) will receive an intensive program consisting of 5 days a week, lasting for 4 weeks (20 sessions) and 8-week follow-up. The 20 sessions will be scheduled in a flexible manner as long as all sessions are completed within the 4 weeks. In addition, all inpatients will also received muscle stretch, massage, physical therapy on the upper limbs upon tolerance for 60 min. All of these interventions will be in addition to their routine hospital treatments (2 hours per day).

Multi-sensory feedback therapy (MSFT)

The definition of sensory training has been defined as: “the gradual and progressive process of reprogramming the brain through the use of cognitive learning techniques such as visualization and verbalization, the use of alternate senses such as vision or hearing and the use of graded tactile stimuli designed to maintain and restore sensory areas affected by nerve disorder to improvetactile gnosis” [25,26]. The design program of sensory training is influenced by Carey et al., Rosénand Lundborg, Guttman, Yekutiel [28-30]. However, delayed sensory feedback is closely related to behavior [31-38]. Few studies have reported the effects of multiple sensory training on upper limb function in stroke patients. Therefore, we designed multi-sensory feedback therapy program for different sensory disorders, including touch discrimination, proprioceptive training, auditory and visual feedback therapy (Fig. 2). The following are specific types of operational items (Step 2 in fig. 2):

1. 10-min sessions of touch discrimination to identify different materials, textures, weights. Tactile training to explore different surfaces and shapes (triangle, circle, square, rectangle). Also, the therapist asks patients to describe the shape as accurately as possible.
2. 10-min sessions of proprioceptive discrimination to identify motion of joint position sensation and direction of joint motion on proprioception.
3. Under the alternations of visual openness and visual masking, patients were trained to identify objects for 5min each. Tactile object recognition to examine and identify different objects, such as nuts, eggs, peanuts, apples, bananas and other physical objects or models.
4. Different shape and size balls will be applied for 10 min to provide sensorial stimulus, patients will hold a bumpy or smooth ball with the injured side hand to train.

All steps for 60 min, that are combined with somatosensory relearning, auditory and visual feedback, will be based on the sensory training equipment. The equipment provides a visual converter that controls by the footswitch, where patients can see sensory stimulus (walnuts, peanuts, objects with different textures, sizes, shapes, and weights) and the orientation of the motion in the upper limbs. Sensory stimulation in all patients will be conducted in two states, visual shielding and visual exposure (Step 2 in fig. 2). The rehabilitation therapists inform the patients about specific multi-sensory training and occupational therapy training.

After a 10-min break, patients will continue with 20-min of task-oriented training (Step 3 in fig. 2), including (1) gross motor and fine movements of the hands, such as functional grip, hand motor control, knitting, tying shoelaces, tying shoelaces, using cutlery, etc; (2) hand-eye coordination exercises, such as chain pulling, reaching objects for height, etc; (3) daily activities training, such as doing housework, pouring water for a drink, etc; (4) TOT and cognitive training, such as brushing, dealing, flipping, playing board games, etc. We will focus on the effects of task-oriented training with multisensory input on the sensory function of the upper limbs and the improvement of daily life activities.

Fig. 2 The multi-sensory feedback therapy system used in the present study. Step 1：Patients will undergo multi-sensory training under a visual feedback device, including (A) Tactile training for patients with different materials, textures, objects; (B) Proprioceptive control of hand gestures; (C) 2-point discrimination with tools. Step 2：All sensory stimuli will be visually blocked and visually exposed in all patients. Step 3：The multi-sensory feedback therapy combined with task-oriented training will increase motivation for sensorimotor tasks.

Task-oriented training (TOT)

There has been sufficient evidence that occupational therapy can restore upper limb motor function well [39]. However, Few evidence that task-oriented training (TOT) is closely related to sensory function in the upper extremities. The training consisting of 60-min task-oriented training without any focus on multi-

sensory re-learning. The training principle and items will be similar to those applied for the MSFT group [40]. The session content of functional task practice will be individualized to patients' interests、social roles、life roles、and lever of sensorimotor function. The tasks will be designed for the patients by the therapists.

All task-oriented training will be functional with exercises of (1) the active movement of the upper limbs, such as reaching for some objects forward or upward, opening or closing doors and drawers, transporting items to/ from various shelf heights, etc、(2) fine motor training and bimanual tasks、such as manipulation of coins, doing buttons, pulling up a zipper, sewing, and tying shoe laces; (3) strength training for the upper limbs with a Theraband, etc; (4) hand-eye coordination and cognitive training, such as pouring water for a drink, brushing, dealing, flipping, playing board games, etc; (5) the richness of daily activities,such as shopping in the supermarket, cleaning rooms, doing housework, etc. The therapists will also encourage participants to use their affected UL at home, and give
suggestion and countermeasure as much as possible in daily activities.

The conventional group

Participants in the control group will receive hand therapy in accordance with usual care, which will be delivered by the therapists. The conventional group will comprise dosage-equivalent interventions of occupation therapy and physiotherapy, with 60 minutes of intervention focused on the forearms, wrists and hands. The therapists will pay close attention to the participants' functional limitations and aims, after assessing sensorimotor function, they will give specific advice and exercises items. The therapists typically provide the conventional therapeutic exercises for 4 weeks, and 3 times assessment at baseline, one month and two months. The exercise items and training principle will be similar to those applied for the MSFT and TOT groups. For basic hand therapy and usual care, the content and frequency of occupation therapy and physiotherapy to improve upper limbs function is variable. The design of training program in the control group will be drawn up according to the different conditions of the patients' upper limbs. Conventional rehabilitation will be captured on recording sheets that will be completed by occupational therapists and physiotherapists who will record the frequency, content and duration of conventional treatment, including the times of repetitions in all intervention sheets developed by Donaldson et al. [41].

Outcome measures

Baseline assessments will be conducted before treatment starts (<24 h). The assessments will be performed at 4 weeks after the final study intervention (within 24 h), and follow-up assessments at two months after randomization. Outcome measures will be carried out by two independent assessors who are not involved in the administration of study interventions, blinded to the group assignments, and

trained in the assessment procedures in hospital. All of the following outcome measures will be undertaken at all three time points: the sensory threshold of Semmes Weinstein monofilaments examination (SWME), two-point discrimination (2PD) test, Action Research Arm Test (ARAT), Nine-Hole Peg Test (NHPT), Wolf Motor Function Test (WMFT), Box and Blocks Test (BBT), Modified Barthel Index (MBI), Instrumental activities of daily living (IADL) and Generalized Anxiety Disorder 7-Item Scale (GAD-7).

Functional sensory assessments should be the primary outcome measures, which will determine whether this trial is a feasibility study. Two outcome measures of sensory function in upper limbs will be assessed to determine which will be most matched for the recruited sample size and the level of functioning of participants: the SWME [42] and the 2PD test.

In contrast to other handheld test equipment in a variety of clinics, the SWME provides higher reliability and validity to measure diminished cutaneous sensation, which is considered as a repeatable instrument stimulus with a small standard deviation [43,44]. As a feasible and optimum choice for clinical use, the SWME is a well-established test for improved sensitivity of quantitative sensory testing, and widely applied in the assessment of neuropathy in the hospitals[45,46]. The SWME has been used in previous studies to determine sensory dysfunction at least 6 months post stroke [47].The SWME is composed of a hierarchical set of twenty monofilaments (Touch Test Sensory Evaluators, Stoetling Co., Wood Dale, IL, USA) [48].The range of monofilaments can distinguish significant sensory thresholds, including normal sensation, diminished tactile sensation, decreased protective sensation, and loss of protective sensation [49]. The assessors will start each test with a stiffness of filament with the participants' eyes closed. The force of filaments will be carried out to stimulate the surface of the skin vertically until the instrument just begins to bend for approximately one second. The assessors will depend upon the data result to determine whether the patients could detect the threshold and stimulus of the arms and hands, then choose which one will be applied (filaments of lesser or greater stiffness). Ultimately, the threshold will be record, it is regarded as the range for skin sensitivity in the upper limbs.

Two-point discrimination (2PD) test is also the primary outcome measurement. 2PD test is chosen because it is related to the severity of upper extremity hemiplegia, and 2PD test is the best predictors to restore functional sensorimotor capacity which is a primary goal of many occupational therapy and/or physiotherapy interventions post-stroke [50]. The 2PD test is widely applied in clinical practice to measure the central somatosensory function and tactile acuity. The assessors conduct 3 repeatable evaluations of discrimination sensation in fingers among the patients to ensure repeatability and reliability [51]. Moreover, previous studies in chronic stroke patients that involved sensory impairment have most often used 2PD test -related primary outcome measure [52,53]. Many study results have been shown 2PD test to be a simple, valid, and quick diagnostic instrument in Central nervous lacerations and an accurate monitor and prognosticator during sensory rehabilitation following nerve repair [54].

There will be seven secondary outcome measures.

(1) The Action Research Arm Test (ARAT). The sensory function of the upper limb is closely related to the motor capacity. The ARAT reflects arm motor function on a broad range of upper extremity activities [55],

which consists of 19 items, including reaching and grasping different shape and size objects, lifting them onto a shelf, and a section for rating gross upper extremity motor skills. The ARAT is a reliable and valid measurement with higher values indicating better performance [56] for patients at least 6 months post-stroke.

(2) The Wolf Motor Function Test (WMFT). The WMFT is a time-based assessment with high construct validity and interrater reliability to measure upper limbs functional performance [57]. The WMFT quantifies arm motor function through providing insight into timed single or multiple joint-specific, and total limb functional tasks for chronic stroke population. The first six tasks of the WMFT involve timed joint-segment movements, and tasks seven to fifteen are composed of timed integrative functional movements. It can generate data that reflects obvious links between planning intervention and arm functional restitution [58]. The tasks are carried out in order of progress from proximal to distal joint involvement and complexity.

(3) The Nine-Hole Peg Test (NHPT). There are composed of nine pegs (0.64 cm wide, 3.2 cm long), and the board (10.16 cm x 10.16 cm) with nine holes spaced 2.54 cm apart [59]. The participants pick up the pegs to place them into the holes, then remove them from the holes with either left or right hand as fast as possible. The evaluator will record time to complete the assessment [60]. If the participants cann't place nine pegs into the holes within one minute, they will be asked not to continue the test [61]. The NHPT reflects upper limb motion speed and movement function, and dexterity disability is best assessed using the Nine-Hole Peg Test [62].

(4) The Box and Blocks Test (BBT). The box separated by a partition consists of 150 blocks (2.54 cm x 2.54 cm x 2.54 cm) placed in the same one side [63]. The participants sit down in front of the wooden box that bisects the midline of his/her body [64]. The assessors instruct patients to put one block at a time as fast as possible, and transfer it to the other side. Scores of dexterity tests are recorded as the number of blocks within one minute for each hand [65].

(5) The Modified Barthel Index (MBI). Independence in activities of daily living is a general outcome measure used in rehabilitation of people after stroke in community and home. It reflects the impact of difficulty in self-care of patients. Sensory disorders of the upper limbs often lead to a decline of social participation and daily activities [66]. The MBI is usually used in physical medicine and rehabilitation [67], which is high validity and reliability [68].

(6) The Instrumental activities of daily living (IADL). The IADL reflects competence and subjective well-being after stroke [69]. As the secondary outcome measurement, IADL is also applied to explore the relationship with sensory deficits. Patients with sensory disorders have less interaction with the environment of leisure activities. The capacity related to IADL that may need more interaction with the environment, appears to be a prerequisite for functional recovery and independent living [70]. In stroke rehabilitation, leisure activities should be considered in evaluating function and effective interventions [71].

(7) The Generalized Anxiety Disorder 7-Item Scale (GAD-7). Anxiety disorders and anxiety symptoms occur frequently after chronic stroke. Generalized anxiety disorder (GAD) is one of the most common mental disorders. However, there is uncertainty regarding the relationship between the sensory loss and negative psychological consequences [72,73].The GAD-7 is a valid efficient and valid scale for assessing for GAD and the severity. It has good reliability, criterion, construct, factorial, and procedural validity [74,75].

Adverse events

In the trial, research group will identify the methods used to measure adverse events and errors. We will focus on the incidence and preventability of adverse events. Errors and adverse events (diseases or symptoms occurring in the experiment) will be evaluated and recorded at per session of treatment. The major adverse events and errors include allergic reactions, falls, abnormal gastrointestinal reactions, dizziness, and other serious medical conditions. There is a low risk of adverse events in the trial based on previous studies of sensory rehabilitation [76]. The research group will assess the severity and relevance of the adverse events. Patients are discouraged to participate in the research trial if their adverse events are serious, and the patient is unanimously deemed unfit to continue by the research group.

Quality control and Data monitoring

The ethics committee of Shanghai Jing An District Central Hospital will act as the data monitoring committee (DMC) during the study. This committee will identify the problems, control the bias, give advice on the modification or termination, and finally make the decision to terminate the trial. The committee is independent from the sponsor and has no competing interests. In order to guarantee the quality of the research, the research will be carried out in three hospitals, then the collected data will be recorded and submitted on time. The researchers will receive professional training to ensure the quality of this study. The therapists have educational background in the World Confederation for Physical Therapy (WCPT) or the World Federation of Occupational Therapists (WFOT). To ensure the uniform implementation of the trial in the three hospitals, we will conduct two intensive trainings for the assessors and rehabilitative therapists before the trial starts. A qualified clinical trial specialist will be invited to monitor the randomized controlled trial.

Statistical analysis

For the clinical data, all calculations will be performed using SPSS 22.0 statistics software (IBM Corporation, Armonk, NY, USA). Data will be analyzed on Intention to treat (ITT) and per-protocol. Data will be held independently on a database at the Chinese Clinical Trials Unit. Before the data analysis

process, the statisticians will be given the statistical scheme that includes processing methods and required data by research group. Statistical analysis will be completed by statisticians who are blinded to each randomisation allocation.

Both between and within groups, the numerical variables include the clinical data collected from the SWME, 2PD test, ARAT, NHPT, WMFT, BBT, MBI, IADL, GAD-7. As there are 3 groups (the MSFT group, the TOT group, the conventional group) with 2 main time points (before and after intervention), the repeated measures analysis of variance (ANOVA) will be used to analyze the experimental data. As appropriate, statistical methods to assess differences between groups and within groups will be also Student's t test (normally distributed data) or Mann-Whitney test (non-normally distributed data) for continuous variables, and Fishers exact or Chi-squared test for categorical variables. All data are presented as the mean ± standard deviation (SD). A p-value<0.05 will indicate statistical significance, the two-sided test is applied. The statisticians will list the adverse events and use a Fisher's exact test or chi-squared for the safety analysis.

Clinical trial registration

Ethics approval was granted by the Shanghai Jing An District Central Hospital Institutional Review Board on 30 October (2019-34). The trial is registered with Chinese Clinical Trials Registry (registration number: ChiCTR1900027914, registered on 4 December 2019). This research program was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [77]. We plan to submit the results to a peer-reviewed journal and present them at conferences, rehabilitation forums and to the general public.

Discussion

Multi-sensory feedback training via the afferent pathways is necessary to generate suitable motor commands which reach the upper extremity muscles via the efferent pathways. The possibility to regain motor function after stroke depends on the intactness of sensorimotor pathways [78]. In the rehabilitation of chronic stroke patients, clinicians and therapists generally pay attention to movement disorders, such as restriction of joint motion and spasm of upper limbs. While sensory and perceptive phenomena are always neglected, although production and perception of grip force are just as important [79]. In addition, stroke survivors with somatosensory loss have difficulty in activities of daily living(ADL) with coordination disorder: dressing, personal hygiene, and eating skills [80]. Light touch disorders often result in impaired hand flexibility and mobility [81]. Patients usually can't manipulate an object for the loss of sensibility to deep pressure, reduced protective sensibility of the hand, and with insufficient sensibility remaining to prevent injury [82]. Increased hand flexibility and mobility is due to finger tactile and proprioception feedback during the stable grasping control [83]. Selective proprioceptive loss from the upper limb is shown to be significantly related to motor recovery, as well as handicap situations during daily activities [84].Negative psychology is also associated with reduced activity participation [85]. The

patients might feel tired, anxious, and lose self-confidence. Given that a majority of patients have sensory impairments that give rise to mental health issues, it is valuable to facilitate population's access to sensory intervention such as touch, vision and audiological rehabilitation [86].

High intensity and large doses of task-related training (TOT) with many repetitions have been identified as key factors for hand motor recovery after chronic stroke [87]. However, TOT is often limited to hand movement therapy. There is little objective data between TOT and sensory function in chronic stroke. There are also little studies in the published literature that adequately describe the multi-sensory feedback therapy (MSFT) combined with TOT on the hemiparetic upper limb. Multi-sensory feedback therapy based on TOT has the potential to increase intensity of sensomotor training, the range of possible functional tasks and it may also boost the motivation of patients by adding a playful element to therapy.

The multi-sensory feedback therapy study is an innovative randomised controlled trial investigating the effect of multisensory therapy on motor ability, ability to perform daily hand activities, social participation, and psychological status. What makes the multisensory therapy study different from previous studies is that the participants will receive visual and auditory feedback therapy for upper limb, in addition to tactile learning, proprioception joint stability exercise and two-point discrimination training. And invariable environment, limited social participation and restricted level of activity will lead to a state of sensory impairment and anxiety [88]. In this trial, multi-sensory feedback therapy will be combined with task-specific training in chronic stroke, which may also contribute to patients' enthusiasm for rehabilitation and improvement of anxiety and and depression after stroke.

This is part of a larger study to investigate the relationships between sensory function and other functions after stroke. In the future, the results of this study will provide the effectiveness of the trial on the recovery of mental and physical functions after stroke. The results can reveal information on how to design a fully powered trial.

Trial Status

The trial is currently in the participant recruitment stage. The recruitment of participants began on 1 November 2019. So far, 31 participants have been recruited and have completed the intervention. The trial is expected to continue until 1 November 2021.

Abbreviations

SWME: Semmes Weinstein monofilaments examination; 2PD: Two-point discrimination; ARAT: Action Research Arm Test; NHPT: Nine-Hole Peg Test; WMFT: Wolf Motor Function Test; BBT: Box and Blocks Test; MBI: Modified Barthel Index; IADL: Instrumental activities of daily living; GAD-7: Generalized Anxiety Disorder 7-Item Scale; ANOVA: Analysis of variance; TOT: Task-oriented training; MSFT: Multi-sensory feedback therapy; RCT: Randomized controlled trial; SD: Standard deviation.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Jiali Lin drafted the manuscript. All authors participated in developing the design of the study, contributed to and critically appraised the manuscript. All authors have read and acknawledged the final manuscript.

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Ethics approval

This study was approved by the Jing An District Central Hospital Institutional Review Board on 30 October 2019 (Lun 2019-34) in Shanghai, China.

Author details

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Figures

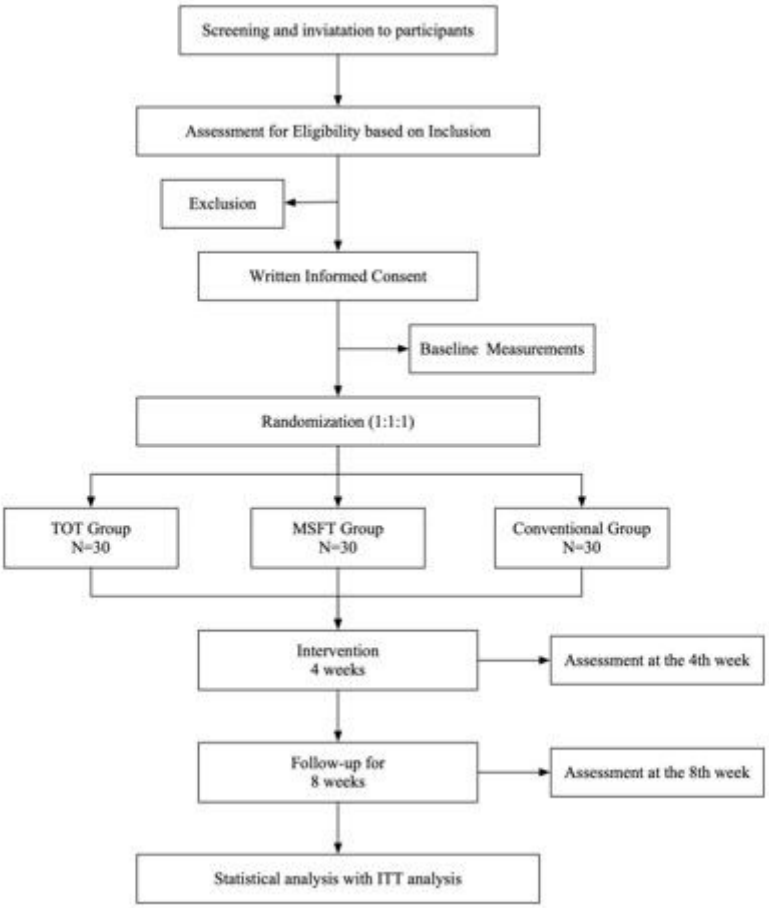

Figure 1

Flow chart of the study design

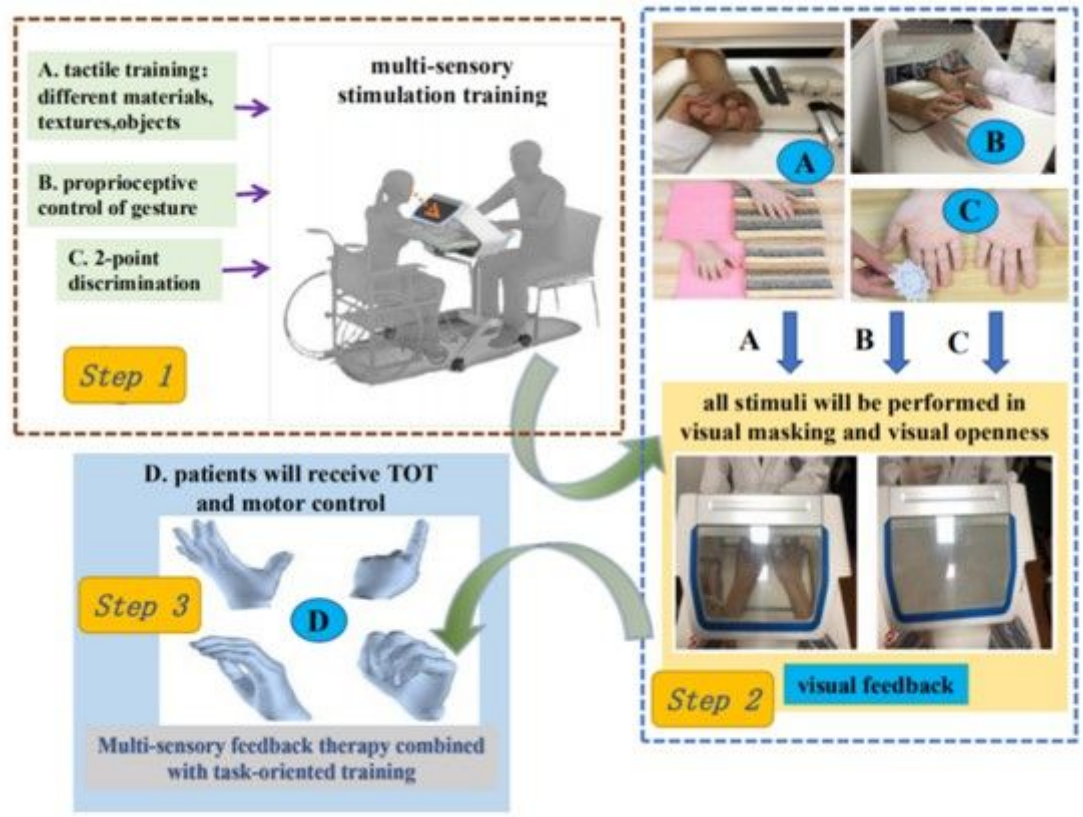

Figure 2

The multi-sensory feedback therapy system used in the present study. Step 1：Patients will undergo multi-sensory training under a visual feedback device, including (A) Tactile training for patients with different materials, textures, objects; (B) Proprioceptive control of hand gestures; (C) 2-point discrimination with tools. Step 2：All sensory stimuli will be visually blocked and visually exposed in all patients. Step 3：The multi-sensory feedback therapy combined with task-oriented training will increase motivation for sensorimotor tasks.