

# Study Protocol

## **The Effect of Venlafaxine on Language Function in Patients with Subcortical Aphasia: A fMRI Study**

**Identifiers: NCT03588572**

**Unique Protocol ID: LY-81471172**

**A randomized, single blind, controlled, longitudinal study of the effects of Venlafaxine Hydrochloride Capsules on the language function of the aphasia patients after subcortical cerebral infarction with a functional magnetic resonance imaging.**

**August 2018**

# Study Protocol

## 1. Research object and Study design

### 1.1 Research object

The cases will recruit from patients with acute ischemic stroke in Department of Cerebrovascular, the Guangzhou General Hospital of Guangzhou Military Command from August 2018 to June 2019. The diagnose of ischemic stroke is base on the diagnostic criteria of the International Association of Neurological Diseases and Stroke Association in 1982. The classification criteria for subcortical ischemic stroke are based on the current international TOAST etiological classification method.

#### 1.1.1 Inclusion criteria

- (1) The first stroke of the left single subcortical areas, within 72 hours.
- (2) Primary school or higher level, aged between 18-75, native language Chinese.
- (3) According to the commonly used eye chart examination, the corrected visual acuity is more than 1.0.
- (4) According to the Edinburgh Handedness Questionnaire (EHQ), participants are identified as right-handed.
- (5) The language function is normal before the stroke onset. After the onset, the language function was mildly to moderately impaired with Western Aphasia Battery (WAB), which Aphasia Quotient (AQ) between in 60 to 88.
- (6) The patient cooperate with the examination, they or their guardian sign the informed consent.

#### 1.1.2 Exclusion criteria

- (1) History of organic diseases of nervous system and history of TBI(Traumatic brain injuries)
- (2) History of epilepsy and psychosis.
- (3) History of material abuse.
- (4) Decompensation of important organic function.
- (5) Hamilton Depression Scale(HAMD )>8 points.
- (6) Hamilton Anxiety Scale(HAMA )>7 points.

- (7) The Mini-Mental State Examination (MMSE) score <20 points.
- (8) Dysphagia (difficult to take capsules).
- (9) A history of allergens in component of venlafaxine capsule.
- (10) Pregnant women and breast-feeding women.
- (11) Any contraindication of MRI.

## 1.2 Study design

It is a randomized, controlled, single-blind, longitudinal trial which has approved by the ethics committee of Guangzhou General Hospital of Guangzhou Military Command. All patients and their guardian will sign an informed consent. The patients will divide into the venlafaxine group and the control group according to the principle of randomization (random number table). The patients in the venlafaxine group begin to take a venlafaxine hydrochloride capsule (EFFEXOR XR: each containing venlafaxine 75mg, qd) after enrollment, until 4 weeks after randomization, and the control group do not. Assessments of language functional behavior and examines of functional magnetic resonance imaging (fMRI) should be performed on the first days (Visit1, V1), 28±3 days (Visit2, V2) and 90±3 days (Visit3, V3) after randomization. Language functional behavioral assessments include the Chinese version of Western Aphasia Battery (WAB), spontaneous language frequency test (SLFT) and picture naming test (PNT). Examine of fMRI include task-state fMRI, resting-state fMRI, and DTI (Diffusion Tensor Imaging). All patients will receive language rehabilitation training (twice a week, one hour each) which are conducted by a professional rehabilitation physiotherapist from the V1 to the V3. The blood pressure and heart rate of each patient will be monitored and recorded on each visit. Two routine blood tests are performed at V0 and V3, including the blood routine and the liver and kidney function. The technical roadmap is shown in Figure 1.

The sample size is estimated by the professional software nQuery Advisor 7.0. According to the previous literature on the efficacy of venlafaxine, the main evaluation index of the effect of the experimental group and the control group are 7.5±3.8 and 4.3±2.6 respectively. The standard deviation are 3.26, and the statistical meaning level (double tail) is 0.05. The test efficiency are set to 0.83. The balance

design will be used to estimate the sample size. Finally, the sample size of the experimental group and the control group are 16 cases respectively. In addition, considering the 20% missing rate, a total of 45 samples will be included in the study.

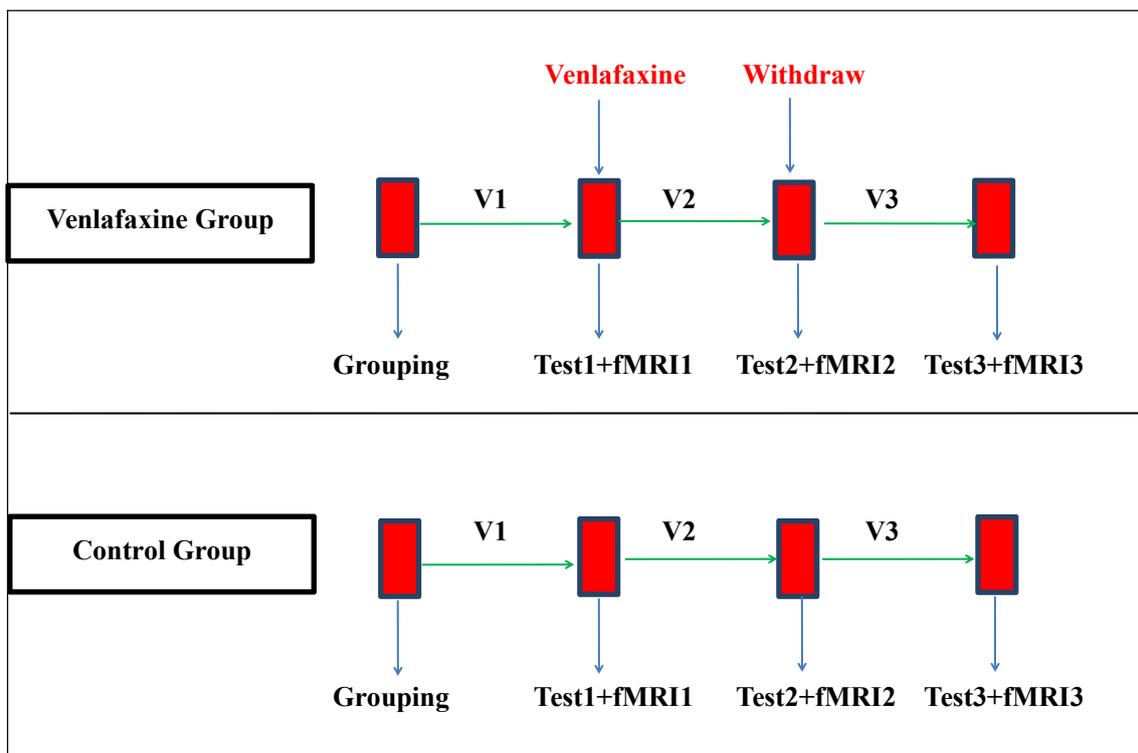


Figure 1 Technical roadmap for research and design

### 1.3 Functional magnetic resonance (fMRI)

#### 1.3.1 Functional magnetic resonance (fMRI) design

Task-state fMRI: an fMRI block design will be adopted, and DMDX software will be used to present each picture in series alternated between baseline (B) and activation (A) [B–A–B–A–B...]. Thirty-six animal pictures and 36 tool pictures from the Snodgrass picture database will be recognized by all subjects. Six blocks of animal naming and six blocks of tool naming will be repeated, and each block continue for 18s with six pictures. The abstract picture of an American skunk which is unrecognized by all the subjects will be selected for baseline of animal naming. A schematic drawn arrow will be chosen for baseline of tool naming. Patients will be required to silently name the object in each picture without moving their lips. To avoid practice effects, the pictures used for fMRI will not appear in the behavioral

evaluation. In the baseline phase, the participants will be asked to identify the orientation of the pictures by silently saying ‘upright’ or ‘inverted’. The subjects will receive task familiarization training prior to the test to ensure that there will be no substantive picture naming but only positional judgment in the baseline task. The design as shown in Figure 2.

Rest-state fMRI: During the rest-state fMRI scan, no task instruction will be given to the patient, and the patient will be completely relaxing, closing his eyes, breathing calmly, keeping his head still, but can not fall asleep, try to avoid any systematic thinking activities, scanning 8min.

DTI: The patient will remain quiet and awake during the DTI data scan.

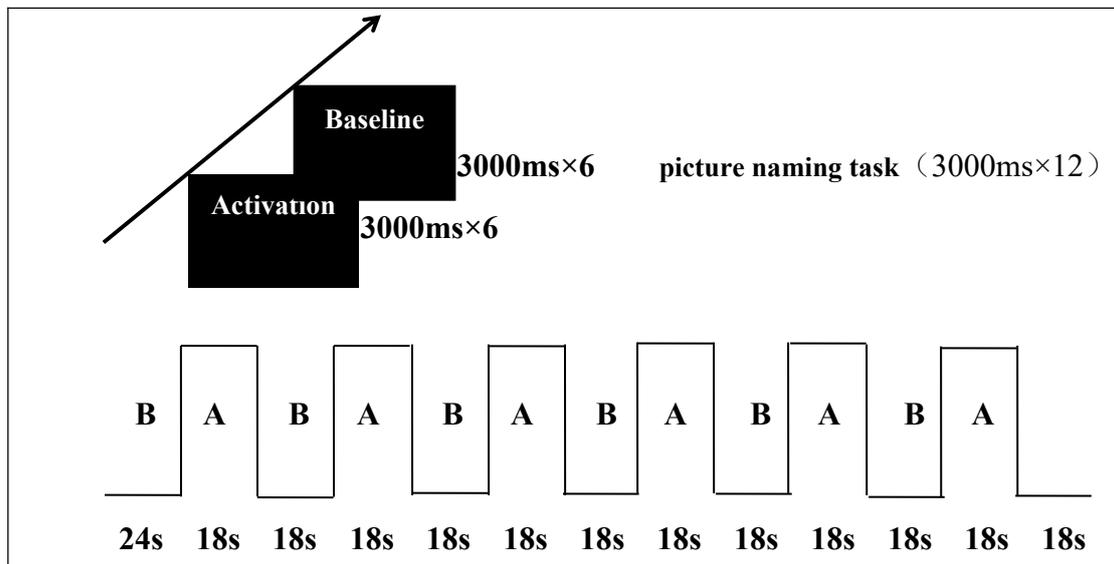


Figure 2 Picture naming task group block design sketch map

### 1.3.2 Functional magnetic resonance data acquisition

The fMRI scan will be performed by using the US GE HDX3.0 Tesla superconducting magnetic resonance imaging system. The scanning sequence and parameters are as follows:

(1) In order to obtain the whole brain anatomical structure image data, a three-dimensional fast spoiler gradient echo (FSPGR BRAVO sequence) is used. The parameters included: time of repetition, 8.86 ms; time of echo, 3.52 ms; field of view, 24x24 cm<sup>2</sup>; in-plane resolution, 256x256; slice thickness, 1mm; interslice gap, 1 mm;

and number of slices, 176.

(2) Echo-Planar Imaging (EPI) is used to acquire task-state fMRI data. The parameters included: time of repetition, 3000ms; time of echo, 40 ms; field of view, 24×24 cm<sup>2</sup>; in-plane resolution, 64×64; slice thickness, 4mm; interslice gap, 1 mm; and number of slices, 34. Scan a sequence of 240s, a total of 12 min.

(3) Echo-Planar Imaging (EPI) is used to acquire rest-state fMRI data. The parameters included: time of repetition, 3000ms; time of echo, 40 ms; field of view, 24×24 cm<sup>2</sup>; in-plane resolution, 64×64; slice thickness, 4mm; interslice gap, 1 mm; and number of slices, 34. A total of 8 min.

(4) Echo-Planar Imaging (EPI) is used to acquire DTI data. The parameters included: time of repetition, 8500ms; time of echo, 93 ms; field of view, 24×24 cm<sup>2</sup>; in-plane resolution, 128×128; slice thickness, 3mm; interslice gap, 0 mm; b-value=1000mm<sup>2</sup>/s.

#### 1.4 Outcome Measures

##### 1.4.1 Primary Outcome Measure:

(1) A change of outcome measure: the Chinese version of Western Aphasia Battery (WAB)

The main outcome measure for this scale is Aphasia Quotient (AQ) which mainly tests the ability of spontaneous speech, oral comprehension, repetition, and naming, and reflects the severity of aphasia, and can be used as a reliable indicator to evaluate the improvement and deterioration of aphasia. Score fluctuation is 0-100 points, the normal value is 98.4-100 points, AQ < 93.8 can be judged as language dysfunction.

Time Frame: This is an outcome measure to assess the improvement of language function from onset to 3 months after treatment. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days (V3) after randomization.

##### 1.4.2 Secondary Outcome Measure:

(1) A change of outcome measure: Spontaneous Language Frequency Test (SLFT)

This test mainly assesses spontaneous speech fluency of participants. It requires participants name as many food names as possible within one minute, and each correct one to give one point. The higher the score, the better the language function.

Time Frame: This is an outcome measure to assess the improvement of language function from onset to 3 months after treatment. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days(V3) after randomization.

(2) A change of outcome measure: Picture Naming Test(PNT)

This test mainly assesses the ability of picture name of participants. we used a program for displaying named pictures on a computer screen (60 photos in total, of which 20 were Chinese celebrity faces). Each image was displayed in 3 seconds, and 1 point was correctly named for an image. The faces of celebrities were selected from the picture database of Chinese celebrities in the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. Score fluctuation is 0-60 points, the higher the score, the better the ability of picture name.

Time Frame: This is an outcome measure to assess the improvement of language function from onset to 3 months after treatment. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days(V3) after randomization.

(3)Follow-up measurement: Hamilton Depression Rating Scale (HAMD)

The Hamilton Depression Rating Scale (HAMD) has proven useful for many years as a way of determining a patient's level of depression before, during, and after treatment. It generally takes 15-20 minutes to complete the interview and score the results. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine items are scored from 0-2. HAMD Scoring Instructions:0-7=Normal, 8-13 = Mild Depression, 14-18 = Moderate Depression, 19-22 = Severe Depression, ≥ 23 = Very Severe Depression(i.e., the higher the score, the greater the likelihood of depression).

Time Frame: We must determine that the participant is not in depression at each follow-up. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days (V3) after randomization.

(4) Follow-up measurement: Hamilton Anxiety Rating Scale (HAMA)

The Hamilton Anxiety Rating Scale (HAMA) is a widely used and well-validated tool for measuring the severity of a patient's anxiety. The HAMA is composed of 14 items and takes 15-20 minutes to complete the interview and score the results. Each item is scored on a 5-point scale, ranging from 0=not present to 4=severe. HAMA Scoring Instructions: 0-8=Normal, 8-13= Possible Anxiety, 14-17 = Mild Anxiety, 18-24 = Moderate Anxiety, 25-30 = Severe Anxiety(i.e., the higher the score, the greater the likelihood of anxiety).

Time Frame: We must determine that the participant is not in anxiety at each follow-up. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days (V3) after randomization.

(5) Follow-up measurement: Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. Administration of the test takes between 5 and 10 minutes. The MMSE test includes simple questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetic such as the serial sevens, language use and comprehension, and basic motor skills. Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment. The raw score may also need to be corrected for educational attainment and age.

Time Frame: We must determine that the participant is not in moderate or more cognitive impairment at each follow up. Thus, participants will undergo this assessment on the first days (V1), 28±3 days (V2), and 90±3 days (V3) after randomization.

(6) Other observational outcome

Edinburgh hand check (EHQ) : It is used to assess the habitual hand of patient.

National Institute of Health stroke scale(NIHSS ): It is used to assess neurological deficits in patients with aphasia

Water swallow test(WST) : It is used to assess the swallowing function of patients with aphasia.