Study Protocol and Statistical Analysis Plan

Title: The efficacy of Cognitive training in patients with VAsCular Cognitive Impairment, No dEmentia (the Cog-VACCINE study): study protocol for a randomized controlled trial

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Study Protocol

Objective: Vascular cognitive impairment, no dementia (VCIND), which is also termed mild vascular cognitive disorder, refers to cognitive deficits associated with underlying vascular causes that fall short of a diagnosis of dementia. Although early intervention of VCIND holds the potential to delay or even reverse cognitive impairment, no treatment is available to prevent further decline in patients with VCIND. To date, no cognitive intervention study on VCIND has been published. Whether and how cognitive training improves cognitive function in patients with VCIND remains largely unknown. This trial is the first study to test the efficacy of cognitive training on VCIND using a double-blinded, randomized controlled trial design. To evaluate the efficacy of cognitive training, both traditional outcomes, such as neuropsychological assessment, and neuroplasticity outcomes, such as brain microstructure index, will be used.

Design: This study will be implemented as a three-center double blinded randomized trial. The study was registered under clinicaltrials.gov (NCT02640716). This study will be reported in accordance with both the CONSORT statement and the CONSORT statement for non-pharmacological interventions. The primary objective is to assess whether cognitive training in patients with subcortical VCIND improves their cognitive abilities. The second objective is to evaluate the effect of cognitive training on neural plasticity. Finally, possible genetic and plasma biomarkers related to the effect of the training will be examined.

Methods

Participants

Sixty patients with subcortical VCIND will be recruited on fulfillment of the inclusion criteria. The patients will be randomly allocated into the experimental group or the control group. Patients will be recruited in neurology clinics at Beijing Friendship Hospital, Xuan Wu Hospital, and the geriatric clinic at Fu Xing Hospital, Capital Medical University.

Inclusion criteria

1) Literate Han Chinese, aged 50 years or older, with a consistent caregiver who accompanies the subject at least 4 days per week. Patient or informant report of cognitive impairment involving memory or other cognitive domains lasting for at least 3 months

2) Neither normal nor demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, with a Clinical Dementia Rating ≥ 0.5 on at least one domain and a global score ≤ 0.5; a Mini-Mental State Examination score ≥ 20 (primary school), or ≥ 24 (junior school or above).

3) Normal or slightly impaired activities of daily living as defined by a total score of ≤ 1.5 on the three functional Clinical Dementia Rating domains (home and hobbies, community affairs, and personal care).

MRI entry criteria:

1) At least three supratentorial subcortical small infarcts (3–20 mm in diameter), with or without white matter lesions of any degree; or moderate to severe white matter lesions (score ≥2 according to the Fazekas rating scale) with or without small infarcts
2) Absence of cortical and watershed infarcts, hemorrhages, hydrocephalus, and white matter lesions with specific causes (e.g., multiple sclerosis)
3) No hippocampal or entorhinal cortex atrophy (score 0 according to the medial temporal lobe atrophy scale of Scheltens).

Exclusion criteria

1) Severe aphasia, physical disabilities, or any other factor that might preclude completion of neuropsychological testing
2) Clinically significant gastrointestinal, renal, hepatic, respiratory, infectious, endocrine, or cardiovascular system disease; cancer; alcoholism; drug addiction
3) Disorders other than subcortical VCIND that might affect cognition; a Hamilton Depression Scale score >17 or schizophrenia; new strokes within 3 months before baseline; inherited or inflammatory small vessel disease
4) Use of medications that may affect cognitive functioning, including tranquilizers, anti-anxiolytics, hypnotics, nootropics, and cholinomimetic agents; and inability to undergo brain MRI

Randomization

Participants will be randomly allocated to either the intervention group or the control group in a ratio of 1:1. After participants have given their informed consent, randomization will be performed by an independent statistician who is blinded to the patient interventions using simple randomization of random number table method in SAS software (SAS Institute, Inc., Cary, NC, USA). Afterwards, the sealed randomization codes and intervention number are sent out to each center. Blinding will be broken only if a participant needs emergency treatment. Once the blinding is broken, the participant will be managed as off-trial.

Blinding

Patients, caregivers, radiologists, statisticians, and neuropsychologists who measure the outcomes will be blinded to the randomization status. Blinding will also be maintained for data management, outcome assessment, and data analysis.

Intervention

Previous studies showed that training approaches with multi-domain, personalized, and adaptive training features are more effective. Therefore, cognitive training will be a computerized multi-domain adaptive training program in this trial. Training paradigms that were successfully used in previous studies will be adopted, including processing speed, attention, long-term memory, working memory, flexibility, calculation, and problem solving. Specific training paradigms include a time perception task, visual search task, rapid serial presentation task, delayed match to sample task, paired-

associate recall task, attention span task, digit span task, go–no go task, Stroop task, task switching, and n-back working memory task. To enable adaptive training, each task was designed with several difficulty levels. Based on previous tests with a large size sample, the tasks will be further grouped in each domain with varied task difficulty. At the beginning, assignment tasks from these domains will be similar across participants. On each training day, five tasks (2 min per task, each three times, in total 30 min per day) will be assigned.

Within each task, high accuracy (>80 %) is required to upgrade. To manipulate the adaptive change, the number of types of stimuli, the presentation probability of each type of stimuli, and the size and duration of a stimulus were systematically set. To keep a systematical setting, only one parameter will be changed, while the other parameters will be kept as constant in one level upgraded. Once the task performance is higher than 80 % of the norm performance of a normal aging population, the task will be replaced by a harder task from the same domain. The training is thus also adaptive at participant level, with a similar setup but personalized progress across participants.

For the control group, processing speed and attention tasks are included, with five tasks and 30 min training in each day. Importantly, a fixed, primary difficulty level for all participants in the control group is set. The training will be completed at home and supervised by an independent neurologist over the internet (www.66nao.com).

MRI data

MRI data collection

The MRI data were acquired on a 3·0T Siemens scanner. High-resolution T1-weighted images covering the whole brain were taken using a sagittal 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence: repetition time (TR) = 1690 ms, echo time (TE) = 2·56 ms, slice thickness = 1 mm, flip angle = 12◦, field of view (FOV) = 256 × 256 mm2. Rest-fMRI scan was acquired using multiband echo-planar imaging (EPI) sequence: TR = 2000 ms, TE =30 ms, 35 slices, voxel-size = 3·5 × 3·5 × 3·5 mm3, flip angle = 83◦, FOV = 224 × 224 mm2. DTI images were acquired by using a diffusion-weighted double spin-echo EPI sequence: TR = 8000 ms, TE = 96 ms, 64 diffusion weighted directions with a b value of 1000 s/mm2 and 11 images with a b value of 0 s/mm2, flip angle = 90◦, FOV = 224 × 224 mm2, in-plane resolution = 1·75 × 1·75 mm2 voxels, 54 contiguous two-mm thick axial slices.

Primary outcome measures

The primary outcome measures are global cognitive function measured by the Montreal Cognitive Assessment (MoCA) and executive function measured by the Trail Making Test B-A (TMT B-A).

Secondary outcome measures

The secondary outcome measure is neuroplasticity changes, as measured by MRI. Specifically, the brain functional response, including regional activation magnitude and functional connectivity across regions will be assessed. For fMRI, both before and after the trial, a resting state scan, a scan with a cognitive control task, and a scan with an

episodic memory task will be included. The brain response change during the tasks and functional connectivity across regions in the task and the resting state sessions will be examined between groups. The structural change, including gray matter volume, measured by voxel-based morphometrics, and white matter microstructure, measured by diffusion tensor imaging, will be assessed.

Statistical Analyses

In preliminary tests, the observed mean difference in change from baseline in the MoCA, Digit Span, WHO-UCLA Auditory Verbal Learning Test (WHO-UCLA AVLT), and Boston Naming Test (BNT) scores between training and control groups were 1·62, 14·92, 3·35, and 7·59, respectively, and the standard deviations were1·93, 18·41, 4·05, and 9·06, respectively. According to these data, sample sizes of 44, 48, 46, and 46, respectively, were needed to obtain a statistical power of 80% with a significance level of 5%. We used the largest sample size of 48, and the inclusion number has been set to 60 patients, allowing for a maximum dropout rate of 20%. In this study, a statistically significant difference (2-tailed $p<0·05$) on any of the two primary outcomes at the end of the intervention would be considered preliminary evidence of efficacy.

Performance changes in the assessment scores related to global cognitive function (MoCA) and executive function (TMT B-A) are the primary outcome measures of interest. An independent sample t test will be used separately for the assessment criterion and the rating scales of function, to ensure that baseline levels are comparable between the training and control groups. A paired-samples t test will be conducted to compare the changes in scores in the trained tasks to investigate the training efficacy. The performance change of the trained tasks will be further correlated with the neuropsychological change. To test whether the training will improve neuropsychological performance in the control group, correlation analysis will be conducted between the performance of trained tasks and the neuropsychological change. To determine the training transfer effect, a series of 2 × 2 ANOVAs will be conducted with group and time points as the two factors. For all analyses, significance levels will be set to 0.05, and effect sizes refer to partial η-square values. Statistical analysis will be conducted using SPSS20.0 software. Imaging data will be analyzed using FSL to detect any changes in brain function and structure due to cognitive training.