PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The efficacy and neural mechanism of acupuncture treatment in older adults with Subjective Cognitive Decline: study protocol for a randomized controlled clinical trial
AUTHORS	Yan, Chao-qun; Zhou, Ping; Wang, Xu; Tu, Jian Feng; Hu, Shang-Qing; Huo, Jian-Wei; Wang, Zhong-Yan; Shi, Guangxia; Zhang, Ya-Nan; Li, Jun-Qiu; Wang, Jun; Liu, Cun-Zhi

VERSION 1 – REVIEW

REVIEWER	Bryce P Mulligan The Ottawa Hospital (Canada)
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	Overall/major comments _____ This is a very timely and exciting project. Kudos to the authors for seeking effective treatments for SCD. I encourage the authors to revise this manuscript according to the suggestions of the reviewers and persevere with the publication of this study protocol (not to mention the ensuing study)! I cannot comment on the acupuncture/electro-acupuncture methodology. I have 2 major concerns (1 methodical, 1 stylisitic) outlined here, and several minor comments (below). 1) My major methodoligical concern is with respect to how you intend to screen participants in to your study. You note that participants must have "Self-reported persistent memory decline compared with a previous normal status within the last 5 years, which was confirmed by caregivers." How do you intend to decide if a particular individual is experiencing "persistent memory decline"? Will it be a yes/no question? What is the question? Will you use multiple questions? The precise questions used to ascertain who meets this inclusion criterion are important as variability in classification has caused much confusion and delayed progress in the field. 2) My major stylistic concern pertains to the frequent grammatical errors and their impact on the clarity and readability of the manuscript. The level of English is generally adequate, however there are some sentences throughout the manuscript that are either ambiguous or include grammatical errors that can be distracting or wose.

	That is, there are some instances where the diction and/or grammar results in terms or concepts being mis-construed or mis-represented. It is not clear whether this is due to mis-communication or mis-understanding of the concepts and terminology. For example, on page 4 line 42, the authors state that "subjective cognitive decline (SCD) usually occurs in healthy older adults..." Depending on how the sentence is read, it could imply that SCD is the usual outcome of healthy aging (it is not). On the other hand, it is not clear what is meant by "healthy older adults". Usually in this context, "healthy" denotes someone who has no identified diagnosis of dementia or milld cognitive impairment (MCI); in fact, individuals with SCD differ from "healthy" older adults only in terms of their perception of significant decline. There are additional similar examples below. The entire manuscript thus requires a careful proof-reading by someone fluent in written English before it will be suitable for publication. Specific/minor comments _____ p.3 line 9: the use of the phrase "in perception" is ambuguous in this context and does not convey that the "subjective" in SCD refers to a within-person decline in cognition that is perceived by a person or their friend or family member. p.3 line 15: Why does SCD "provide an opportunity for dementia prevention"? p.4 line 7: "Alterations" is probably intended, rather than "alternations" p.7. line 36: what are the "treatments that would affect cognitive function" listed in your exclusion criteria? p.9 line 18-20: will the medications or participants be "discontinued"? p.10 line 55: I disagree with your characterization of the neuropsychological test battery as "comprehensive" (i.e. "a comprehensive neuropsychological test battery that includes 6 tests"). It would be more accurate to describe the battery as "multi-domain" rather than "comprehensive" (both here and throughout the manuscript). p.11 line 3-14: please cite sources for the normative datasets you will use to compute your z-scores as well as the cutoff scores you will employ to determine "Normal age- and education-adjusted performance" (i.e. one of your main inclusion criteria). p.11 line 41: Why does "This practice task guarantees that the patients understand the rule of the memory task in the scanner"? Do you have a way to determine when participants have practiced enough? p.14 line 24: It would be appropriate to provide a one-line rationale for your use of a per protocol analysis. Will you also do an intent-to-treat analysis to ensure that your results are not biased by dropout rates? (i.e. it is well known that certain people, including

	those who experience no treatment effects, are more likely to drop out). p.14 line 54: it seems you are recommending both a t-test "if it agreed with the normal distribution" or Wilcoxon's test "for normal distribution data". I do not understand the difference.

REVIEWER	Shifen Xu Shanghai Municipal Hosptial of Traditonal Chinese Medicine, Shanghai University of Traditional Chinese Medicine
REVIEW RETURNED	20-May-2019

GENERAL COMMENTS	Strength of this study : 1. This manuscript designed a study of acupuncture for the treatment of SCD, the design has certain novelty. First, they assessed patients with SCD on multiple levels. Second, functional brain alterations also be used as an outcome measures, it can be used as a tool to understand the mechanism of the acupuncture's effects. 2. The design of this study is rigorous. The control group set up reasonably, and the participants, evaluators, and statisticians all blind of the group situation. 3. The channels for recruiting patients are comprehensive and practical. 4. The content of Safety and Monitoring are detailed and operational. 5. The evaluators of this study have received training. The authors use Epidate software to entry data, and double recording can minimize the data entry errors. However, several issues need to be addressed before it can be published. 1. Please mark the specific depth of different acupuncture points. 2. Maybe for patients taking drugs (such as anticholinergic drugs and traditional Chinese medicines) that improve cognitive function should be included into exclusion criteria. 3. Why not add dialectical acupoints in the study to reflect the characteristics of Chinese medicine. 4. The treatment period of intervention is 24 sessions for 12 weeks, how the authors arrange the 24 sessions, twice a week or other? This should be described clearly. 5. Please ensure the implementation of the scales for so many scales used. 6. What is the specific time of MRI measurement? Is it measured immediately after the end of treatment or it can be measured within a certain period of time after the end of treatment? 7. Why there is no standards for drop out? 8. What kind of random system is it? Can it guarantee the implementations of allocation concealment? Maybe should specify it.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Q 1 My major methodoligical concern is with respect to how you intend to screen participants in to your study. You note that participants must have "Self-reported persistent memory

decline compared with a previous normal status within the last 5 years, which was confirmed by caregivers."

How do you intend to decide if a particular individual is experiencing "persistent memory decline"? Will it be a yes/no question? What is the question? Will you use multiple questions? The precise questions used to ascertain who meets this inclusion criterion are important as variability in classification has caused much confusion and delayed progress in the field.

Response: We thank the reviewer for the insightful comments. Definitions of subjective cognitive decline (SCD) complaints and memory decline complaints have not been unified across different countries, and evaluation methods for SCD complaints and memory decline complaints vary in many studies [1]. In our study, the patients who answer “yes” to the question “Do you have problem in memory?” in the initial screening by phone or face-to-face interviews, were selected to nest step. Besides, we used the Subjective Cognitive Decline questionnaire 9 (SCD-Q9) for SCD screening. The SCD-Q9 includes 9 reliable items was identified by adopting the item response theory and the computerizing adaptive test model for SCD screening [2]. Hao et al. in XuanWu Hospital of Capital Medical University had translated SCD-Q9 to Chinese and revised it (Table 1) [3]. The reliability and validity of this revised version were measured as well. The Cronbach’s alpha of reliability was 0.847 and the coefficient of validity was 0.871, which showed that the translated version of SCD-Q9 used in this study is reliable. They also found that the score of the SCD-Q9 gradually increased as the disease progressed (normal control−→SCD−→ mild cognitive impairment−→ Alzheimer’s disease) in China. There was a negative correlation between scores of SCD-Q9 and the Auditory Verbal Learning Test-Long Delay Free Recall. According to Gifford’s work, The 9-item total score had a median of 3.0 for normal control and median of 5.0 for mild cognitive impairment [2]. Therefore, the patients with the score of SCD-Q9 more than 5.0 will pass the screening.

Items			
Do you think you have problems with your memory?			Yes No
Do you have difficulty remembering a conversation from a few days ago?			Yes No
Do you have complaints about your memory in the last 2 years?			Yes No
How often is the following a problem for you: Personal dates (e.g., birthdays)	Always	Sometimes	Never
How often is the following a problem for you: Phone numbers you use frequently	Always	Sometimes	Never
On a whole, do you think that you have problems remembering things that you want to do or say?			Yes No

How often is the following a problem for you: Going to the store and forgetting what you wanted to buy?	Always	Sometimes	Never
Do you think that your memory is worse than 5 years ago?	Yes	No	
Do you feel you are forgetting where things were placed?	Yes	No	

Table 1 The items of Subjective Cognitive Decline questionnaire 9.

References:

1. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. Eur Psychiatry 2008;23(5):321-30
2. Gifford KA, Liu D, Romano R, 3rd, et al. Development of a subjective cognitive decline questionnaire using item response theory: a pilot study. Alzheimers Dement (Amst) 2015;1(4):429-39.
3. 3. Hao L, Wang X, Zhang L, et al. Prevalence, Risk Factors, and Complaints Screening Tool Exploration of Subjective Cognitive Decline in a Large Cohort of the Chinese Population. J Alzheimers Dis 2017;60(2):371-88.

Q 2 My major stylistic concern pertains to the frequent grammatical errors and their impact on the clarity and readability of the manuscript. The level of English is generally adequate, however there are some sentences throughout the manuscript that are either ambiguous or include grammatical errors that can be distracting or wose.

That is, there are some instances where the diction and/or grammar results in terms or concepts being mis-construed or mis-represented. It is not clear whether this is due to mis-communication or mis-understanding of the concepts and terminology. For example, on page 4 line 42, the authors state that "subjective cognitive decline (SCD) usually occurs in healthy older adults..." Depending on how the sentence is read, it could imply that SCD is the usual outcome of healthy aging (it is not). On the other hand, it is not clear what is meant by "healthy older adults". Usually in this context, "healthy" denotes someone who has no identified diagnosis of dementia or milld cognitive impairment (MCI); in fact, individuals with SCD differ from "healthy" older adults only in terms of their perception of significant decline.

Response: We are sorry for that we did not describe clearly in the manuscript. We have examined the grammatical errors carefully. The language in the manuscript has been improved by a professional native English editor.

For the sentence “subjective cognitive decline (SCD) usually occurs in healthy older adults...”, we are sorry for the confusion. We have delete the word “healthy”.

Specific/minor comments

Q2-1 p.3 line 9: the use of the phrase "in perception" is ambuguous in this context and does not convey that the "subjective" in SCD refers to a within-person decline in cognition that is perceived by a person or their friend or family member.

Response: We are very grateful for your constructive suggestion. As mentioned by the reviewer, the word “perception” is ambuguous in this context. We have amend this sentence, as shown below. Subjective cognitive decline (SCD) refers to individuals’ perceived decline in memory and/or other cognitive abilities relative to their previous level of performance, while objective neuropsychological deficits are not observed.

Q2-2 p.3 line 15: Why does SCD "provide an opportunity for dementia prevention"?

Response: Three stages in disease progression are commonly recognized by The United States National Institute on Aging-Alzheimer’s Association group: the preclinical stage without symptoms (cognitively normal), mild cognitive impairment, and the final stage of Alzheimer’s disease, which are stratified into mild, moderate, and severe phases [1-4]. SCD is associated with preclinical AD, and the evidences demonstrated SCD occurs at the preclinical stage of AD and may serve as a symptomatic indicator of preclinical AD. Some longitudinal data demonstrated that SCD is a risk factor for future cognitive decline as well as for MCI and AD dementia [5-9].

Drug development for AD has been proven to be very difficulty [10]. Most drugs entering the AD drug-development pipeline have failed. Many explanations have been proposed for the failures of trials of disease-modifying drugs for Alzheimer’s disease. Starting the test of therapies too late in disease development is one of the reasons [11]. WHO and the G8 Dementia Summit (2013) emphasized prevention as a key element to counteract the dementia epidemic [12-13]. For individuals with SCD, prevention-intervention could slow the rate of incipient decline to prolong and preserve cognitive and functional abilities. At this very early stage of decline, it is presumed that individuals have sufficiently intact cognitive function that can be harnessed toward either compensation or restitution of function. The individuals with SCD within the context of mood/anxiety, personality, and health concerns, intervention could improve psychological functioning and overall quality of life [14].

It should not be ignored that the intervention for SCD is important to prevent dementia. But, in this manuscript, the sentence “It provides an opportunity for dementia prevention” is not described clearly. We have amend this sentence, as shown below.

In abstract section: SCD may represent a preclinical phase of Alzheimer’s disease. At this very early stage of decline, intervention could slow the rate of incipient decline to prolong and preserve cognitive and functional abilities.

In introduction section: The long “preclinical” phase of AD provides an opportunity for individuals to participate in treatment trials to delay or prevent cognitive decline.

References:

1. Jack CR, Jr., Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for

Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7(3):257-62.

2. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7(3):270-9.
3. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7(3):280-92.
4. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7(3):263-9.
5. Glodzik-Sobanska L, Reisberg B, De Santi S, et al. Subjective memory complaints: presence, severity and future outcome in normal older subjects. Dement Geriatr Cogn Disord 2007;24(3):177-84.
6. Dufouil C, Fuhrer R, Alperovitch A. Subjective cognitive complaints and cognitive decline: consequence or predictor? The epidemiology of vascular aging study. J Am Geriatr Soc 2005;53(4):616-21.
7. van Oijen M, de Jong FJ, Hofman A, et al. Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2007;3(2):92-7.
8. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry 2010;67(4):414-22.
9. Reisberg B, Shulman MB, Torossian C, et al. Outcome over seven years of healthy adults with and without subjective cognitive impairment. Alzheimer's & dementia : the journal of the Alzheimer's Association 2010;6(1):11-24
10. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014;6(4):37.
11. Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades? Alzheimer's & dementia : the journal of the Alzheimer's Association 2016;12(1):60-4.
12. WHO. Dementia: a public health priority. Geneva: World Health Organization—Alzheimer's Disease International, 2012. http:// www. who.int/ mental_health/ publications/ dementia _ report _ 2012 /en/(accessed Sept 29, 2014).
13. G8 dementia summit declaration. https://www.gov.uk/government/publications/g8-dementia-summit-agreements (accessedApril 28, 2014).

14. Rabin LA, Smart CM, Amariglio RE. Subjective Cognitive Decline in Preclinical Alzheimer's Disease. Annu Rev Clin Psychol 2017;13:369-96.

Q2-3 p.4 line 7: "Alterations" is probably intended, rather than "alternations"

Response: We are sorry to make this confusion. The word has been amended, as shown below.

Compared with the neuropsychological tests alone as efficacy evaluations, the combination with in-vivo measures of brain alterations in this study will be more sensitive in detecting acupuncture efficacy.

Q2-4 p.7. line 36: what are the "treatments that would affect cognitive function" listed in your exclusion criteria?

Response: We are sorry that we did not describe the exclusion criteria clearly in the manuscript. We have listed the treatments in exclusion criteria, as shown below.

Treatments which would affect cognitive function (e.g., treatment for an acute psychiatric episode, therapy with memantine, rivastigmine and donepezil, traditional Chinese medicines which improve cognitive function such as Bushen capsule).

Q2-5 p.9 line 18-20: will the medications or participants be "discontinued"?

Response: As we know, the medications may affect cognitive function, including tranquilizers, antianxiolytics, hypnotics, nootropics, and cholinomimetic agents. We will tell the patients not to take the medications until end of the intervention. If the patient still want to take, his study will be discontinued. Because we can't distinguish the improvement of cognitive function from drug therapeutic or acupuncture. According to the Review 2 suggestion, we have add this in the standards for drop out, as shown below.

During the trial period, patients with SCD who meet the following criteria will be excluded from the study:

- taking medication or receiving additional treatment that is expected to affect the cognitive function (e.g., tranquilizers, antianxiolytics, hypnotics, nootropics, and cholinomimetic agents);
- withdrawal of consent for study participation because the patients does not wish to continue;
- missing more than 5 of 24 acupuncture treatment sessions;
- occurrence of a serious adverse event that the doctors consider should termination;
- critical protocol violation such as violation of eligibility criteria.

Q2-6 p.10 line 55: I disagree with your characterization of the neuropsychological test battery as "comprehensive" (i.e. "a comprehensive neuropsychological test battery that includes 6 tests"). It would be more accurate to describe the battery as "multi-domain" rather than "comprehensive" (both here and throughout the manuscript).

Response: We are very grateful for your constructive suggestion. The word of “multi-domain” is better than “comprehensive” to describe the neuropsychological test batteryaccurately. We have revised this in the manuscript.

Q2-7 p.11 line 3-14: please cite sources for the normative datasets you will use to compute your z-scores as well as the cutoff scores you will employ to determine "Normal age- and education-adjusted performance" (i.e. one of your main inclusion criteria).

Response: We are sorry to make this confusion. The sources that we will use to compute z-scores have been cited in the corresponding part. (Reference: 32. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA internal medicine 2013;173(9):797-804.) But we can’t list the cutoff scores of normal age- and education-adjusted performance on neuropsychological test without authorization. Because, we acquired the cutoff scores from the department of neurology, Xuanwu Hospital, Capital Medical University. The cutoff scores is their unpublished data. We are sorry for not providing the cutoff scores in this manuscript.

Q2-8 p.11 line 41: Why does "This practice task guarantees that the patients understand the rule of the memory task in the scanner"? Do you have a way to determine when participants have practiced enough?

Response: We are sorry that we did not describe this clearly in the manuscript. Usually, participants had brief practice about the tasks before scanning in task-evoked functional magnetic resonance imaging study [1-2]. We wrote a practice version of memory task paradigm in Matlab softwore. The practice version of memory task paradigm is a mini-version of memory task paradigm that the patients will finish in the scanner, which is a mock test with less spending time. Before the patients enter to the scanning room, a researcher will instruct the patients to response by pressing one button in computer. A blocked periodic design incorporated alternating 1-back, and 2-back tasks will be used. Each back have three stimuli, and there is six stimuli in the practice version of memory task paradigm. If the patient got five right response, we consider the patients understand the rule of the memory task. In order to better readability, we have amended this part, as shown below.

The patients will be trained before entering the fMRI scanner. They will complete a practice version of the memory task paradigm in computer. This practice mock test will show the correct number, and they need to perform the tasks over an accuracy criterion of 80% to ensure that the patients understand how to complete the memory task in the scanner.

References:

1. Gordon BA, Zacks JM, Blazey T, et al. Task-evoked fMRI changes in attention networks are associated with preclinical Alzheimer's disease biomarkers. Neurobiol Aging 2015;36(5):1771-9。

2. Chen CJ, Chen CC, Wu D, et al. Effects of the apolipoprotein E epsilon4 allele on functional MRI during n-back working memory tasks in healthy middle-aged adults. AJNR Am J Neuroradiol 2013;34(6):1197-20.

Q2-9 p.14 line 24: It would be appropriate to provide a one-line rationale for your use of a per protocol analysis. Will you also do an intent-to-treat analysis to ensure that your results are not biased by dropout rates? (i.e. it is well known that certain people, including those who experience no treatment effects, are more likely to drop out).

Response: Thanks very much for the reviewer's valuable opinion. A per protocol analysis is not rationale. As the reviewer mentioned, the intent-to-treat analysis can maintains prognostic balance generated from the original random treatment allocation. It provides an unbiased estimate of treatment effect, and minimizes type I error due to cautious approach. In this study, intent-to-treat analysis and per protocol analysis will be used. We have amended this part, as shown below.

In this study, intent-to-treat analysis and per protocol analysis will be used. In this study, the intent-to-treat population consisted of all randomized patients who received at least one dose of treatment and had a complete baseline assessment.

Reference:

1. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res 2011;2(3):109-12.

Q2-10 p.14 line 54: it seems you are recommending both a t-test "if it agreed with the normal distribution" or Wilcoxon's test "for normal distribution data". I do not understand the difference.

Response: We are sorry that we did not describe this clearly. We have amend this sentence, as shown below.

For the other outcomes, if it agreed with normal distribution, an independent T-test will used. Otherwise, for abnormal distribution, the data will analyzed with Wilcoxon's test.

Response to Reviewer 2

Q 1 Please mark the specific depth of different acupuncture points.

Response: We are very grateful for the reviewer's constructive suggestion. We have add the depth of different acupuncture points in the section of methods (Table 2), as shown below.

Table 2. Location of Acupoints Used in the Acupuncture Group

Acupoints	Location	Depth
Baihui (DU20)	5 cun directly above the midpoint of the posterior hairline, or at the midpoint of the line connecting the apexes of the two auricles.	0.2 cun
Shengting (DU24)	1.0 cun directly above the midpoint of posterior hairline.	0.2 cun
Fengfu (DU16)	On the back of neck, 1 cun directly above the midpoint of the posterior hairline, directly below the external occipital protuberance.	0.5~0.1 cun

Fengchi(GB20)	On the nape, below the occiput, at the level of Fengfu, in the depression between the upper portion of sternocleidomastoideus and trapezius muscle.	0.5~0.8 cun
Danzhong (RN17)	On the anterior median line of the chest, at the level of the fourth intercostal space, at the midpoint between the two nipples.	0.5 cun
Zhongwan (RN12)	On the the anterior median line of the upper abdomen, 4 cun above the umbilicus.	1~1.5 cun
Qihai (RN6)	On the anterior median line of the lower abdomen, 1.5 cun below the umbilicus.	1~1.5 cun
Neiguan (PC6)	On the palmar aspect of forearm, 2.0 cun above the transverse crease of the wrist, between the tendons of palmaris longus and flexor carpi radialis muscle.	0.5~0.1 cun
Tongli (HT5),	On the radial aspect of the tendon of the ulnar flexor muscle of the wrist, and 1 cun above the carpal crease.	0.3~0.5 cun
Xuehai (SP10)	When the knee is flexed, on the medial aspect of the thigh, the point is 2 cun above the mediosuperior border of the patella, on the bulgs of the medial portion of muscle quadriceps femoris.	0.8~1 cun
Zusanli (ST36)	3 cun directly below Dubi* and one finger-breadth lateral to the anterior border of the tibia.	0.8~1 cun
Zhaohai (KI6)	On the depression below the tip of the medial malleolus.	0.5~0.8 cun
Xinshu (BL15)	1.5 cun from the lower border of the spinous process of the fifth thoracic vertebra.	0.3~0.5 cun
Yixi (BL45)	3 cun from the lower border of the spinous process of the sixth thoracic vertebra.	0.5~0.8 cun

Dubi* location = When the knee is flexed, the point is at the knee, below the patella, in the depression from the patella ligament.

Q 2 Maybe for patients taking drugs (such as anticholinergic drugs and traditional Chinese medicines) that improve cognitive function should be included into exclusion criteria.

Response: We are very grateful for the reviewer's constructive suggestion. We have listed the drugs in the section of exclusion criteria, as shown below.

Treatments which would affect cognitive function (e.g., treatment for an acute psychiatric episode, therapy with memantine, rivastigmine and donepezil, traditional Chinese medicines which improve cognitive function such as Bushen capsule).

Q 3 Why not add dialectical acupoints in the study to reflect the characteristics of Chinese medicine.

Response: Thanks very much for the reviewer's valuable opinion. There are two reasons that we did not add dialectical acupoints in the study. First, in a randomized, open-label, multicenter randomised controlled clinical trial performed previously, we found that compared with citicoline, acupuncture has comparable and even superior efficacy with improved cognitive and daily living performance for vascular cognitive impairment no dementia [1]. Hence, we used the same acupoints in this study for a better clinical effect. Second, the main purpose of this study is to explore the neural mechanism of acupuncture treatment in older adults with SCD. Acupuncture on different acupoints can contribute to different brain responses [2]. A group of fixed acupoints may reduce the difference of brain responses to acupuncture in patients.

References:

1. Yang JW, Shi GX, Zhang S, et al. Effectiveness of acupuncture for vascular cognitive impairment no dementia: a randomized controlled trial. Clin Rehabil 2019;33(4):642-52.
2. He T, Zhu W, Du SQ, et al. Neural mechanisms of acupuncture as revealed by fMRI studies. Auton Neurosci 2015;190:1-9.

Q 4 The treatment period of intervention is 24 sessions for 12 weeks, how the authors arrange the 24 sessions, twice a week or other? This should be described clearly.

Response: We are very grateful for the reviewer's constructive suggestion. We have amend this in the section of methods, as shown below.

Patients will receive 24 acupuncture treatment sessions over 12 weeks (twice a week).

Q 5 Please ensure the implementation of the scales for so many scales used.

Response: Thanks very much for the reviewer's insightful comments. Cognition is the mental action or process of acquiring knowledge and understanding through thought, experience, and senses, which encompasses processes such as memory, association, concept formation, pattern recognition, language, attention, perception, action, problem solving and mental imagery [1-2]. The multi-domain neuropsychological test battery could objectively reflect the cognitive function. Many studies had used the neuropsychological test battery to assess the cognitive function [3-6]. In line with those studies, we used multi-domain neuropsychological test battery as the outcome of interest to detect the acupuncture effect. We have implemented a pilot study, and the patients can certainly completed the scales [7].

References:

1. Sensation & Perception, 5th ed. 1999, Coren, Ward & Enns, p. 9.
2. Cognitive Psychology, 5th ed. 1999, Best, John B., pp. 15–17.
3. Thow ME, Summers MJ, Saunders NL, et al. Further education improves cognitive reserve and triggers improvement in selective cognitive functions in older adults: The Tasmanian Healthy Brain Project. Alzheimers Dement (Amst) 2018;10:22-30 ..
4. Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. Lancet Neurol 2017;16(12):965-75.
5. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA internal medicine 2013;173(9):797-804.
6. Engvig A, Fjell AM, Westlye LT, et al. Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment. J Alzheimers Dis 2014;41(3):779-91.
7. Zhou P, Yan CQ, Hu SQ .et al. Effect of acupuncture on cognitive function of individuals with subjective cognitive decline. Chin J Mult Organ Dis Elderly,2019,18(03):169-173.

Q 6 What is the specific time of MRI measurement? Is it measured immediately after the end of treatment or it can be measured within a certain period of time after the end of treatment?

Response: We are sorry that we did not describe this clearly. We have amend this sentence, as shown below.

Before the acupuncture treatment, patients will completed the fMRI scan within 3 days. They will also have the follow up fMRI scan within 3 days after the completion of their intervention.

Q 7 Why there is no standards for drop out?

Response: Thanks very much for the reviewer's insightful comments. We have add the standards for drop out in the section of Methods, as shown below.

During the trial period, patients with SCD who meet the following criteria will be excluded from the study:

- taking medication or receiving additional treatment that is expected to affect the cognitive function;
- withdrawal of consent for study participation because the patients does not wish to continue;
- missing more than 5 of 24 acupuncture treatment sessions;
- occurrence of a serious adverse event that the doctors consider should termination;
- critical protocol violation such as violation of eligibility criteria.

Q 8 What kind of random system is it? Can it guarantee the implementations of allocation concealment? Maybe should specify it.

Response: We are sorry that we did not describe this clearly. We have amend this in the section of Methods, as shown below.

Eligible patients will randomly assigned into either the acupuncture or sham acupuncture group after signed written informed consent forms via a randomization digital table with a 1:1 ratio. Blocked randomization with a block size of 6 will employed to ensure balance within the two groups. The randomization sequence will be generated by a third-party professional statistician using computer-generated the randomization digital table using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The randomization list will stored by a noninvolved investigator and out of reach and sight of the involved investigators. The allocation schedule using a telephone randomization procedure. The randomization list was restricted to this research coordinator and was concealed from other study personnel. The patients, outcome assessors, and statisticians will blinded to treatment allocation. Patients are told that they will receive one of two effective interventions randomized after enrolment. During the acupuncture treatment, the adhesive pads are pasted on the acupoints or sham acupoints after skin disinfection. The true or sham needles with a blunt tip will place in the adhesive pads. Patients in different groups will be separated into cubicles to refrain from communication.

VERSION 2 – REVIEW

REVIEWER	Bryce P Mulligan The Ottawa Hospital Canada
REVIEW RETURNED	26-Jul-2019

GENERAL COMMENTS	I appreciate the reviewer's thorough response to my queries. The one outstanding issue is pertaining to their method for screening participants into their study. While they give appropriate details and rationale in their response, the detail has not been added to the methods section of the paper as far as I can see. Namely, the methods should include the exact screening question as well as a description of the standardized questionnaire-based inclusion criteria. To be perfectly clear, the manuscript must include the following information (copied form the author's reviewer response letter): "In our study, the patients who answer “yes” to the question “Do you have problem in memory?” in the initial screening by phone or face-to-face interviews, were selected to nest step.... the patients with the score of SCD-Q9 more than 5.0 will pass the screening." My apologies if I have missed your addition of this information elsewhere. Aside from this one concern, I think this paper would make an excellent addition to the literature. All my best to the authors in seeing this study through to its conclusion!

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1

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My apologies if I have missed your addition of this information elsewhere.

Aside from this one concern, I think this paper would make an excellent addition to the literature. All my best to the authors in seeing this study through to its conclusion!

Response: We thank the reviewer’s insightful comments. We have added the screening step in the section of Method part, as shown below:

In this study, the patients who answer “yes” to the question “Do you have problem in memory?” in the initial screening by phone or face-to-face interviews, will be selected to the next step. Besides, the Subjective Cognitive Decline questionnaire 9 (SCD-Q9) are further used for SCD screening. Only the patients with the SCD-Q9 score more than 5.0 will pass the screening.