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Capturing Amplitude Changes of Low-Frequency Fluctuations in Functional Magnetic Resonance Imaging Signal: A Pilot Acupuncture Study on *NeiGuan* (PC6)

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Abstract

Objectives: This study aims to examine amplitude changes of low-frequency oscillations (fALFF) in the blood-oxygen level-dependent (BOLD) signal associated with acupuncture on *NeiGuan* (PC6).
Experimental design: Ten (10) healthy adults participated in a functional magnetic resonance imaging (i.e., nuclear medicine; fMRI) study. During the brain-imaging procedure, the participants were instructed to lie quietly; they did not perform any cognitive task.
Main outcome measures: Three (3) fMRI scans were conducted for each participant: a first resting-state scan (R1), a stimulating-acupoint scan (AP), and a second resting-state scan (R2) after AP. Individual fALFF maps were calculated for each scan.
Results: During R1, consistent with previous studies, the default network regions showed significantly detectable fALFF amplitudes. Acupuncture on PC6 increased fALFF amplitudes within the anterior cingulate cortex (ACC), occipital fusiform gyrus, posterior cingulate cortex, and precuneus (PCC/PCU). In contrast, during R2, fALFF within PCC is still significantly higher than R1 while ACC and cerebellum showed decreased fALFF.
Conclusions: These findings imply that stimulating PC6 can change the amplitude of the intrinsic cortical activity of the brain. In particular, a continuous and temporally consistent effect of acupuncture within PCC not the common brain circuit of pain including ACC and cerebellum was observed. Considering the cognitive functions and deficits of the relevant areas in mild cognitive impairment and Alzheimer disease, acupuncture on PC6 could potentially affect both psychiatric and neurological disorders. Thus, stimulating PC6 may be a candidate method for improving cognitive impairment.

Introduction

Compared to PET and SPECT, functional magnetic resonance imaging (fMRI) is more commonly used to investigate the centrum mechanism for meridian and acupoint due to its inherent advantages, notably safety, economy, and high spatial-temporal resolution. Recently, researchers found that some brain regions are activated when an acupoint is stimulated.[1–4] Task-based fMRI is typically used to study acupuncture, but the complexity of various cognitive tasks used during fMRI research complicates the results. For example, clinical populations often have difficulties performing tasks, preventing researchers from capturing the necessary signals (e.g., Alzheimer disease,[5] attention deficit/hyperactivity disorder,[6] and schizophrenia[7]). In contrast, resting-state fMRI (R-fMRI), by definition, avoids the use of complex cognitive tasks,[8–10] and thus may be better suited for studying acupuncture.

NeiGuan (i.e., PC6, 2 cm above the transverse crease of the wrist, between the tendons of *m. palmaris longus* and *m. flexor*

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radialis) is one acupoint belonging to the *Xin-Bao* meridian, which is thought to be related to mind–mental disorders and heart diseases in Traditional Chinese Medicine (TCM).[11] Evidence for this association comes from task-based fMRI studies demonstrating that various brain regions associated with high-order cognitive function were significantly correlated with each other after stimulating PC6.[12,13] However, despite increasing R-fMRI studies on other acupoints,[14–20] PC6 has rarely been investigated with R-fMRI, except for one notable example (Dhond et al.[21]). Yet this study did not examine regional changes in intrinsic activity within brain regions, but rather the relationship between brain regions.[21]

In the current study, a recently developed amplitude measure of regional brain activity, known as the fractional amplitude of low-frequency fluctuations (fALFF),[22,23] was employed to investigate the effects of acupuncture on PC6 on spontaneous fluctuations in the resting-state blood-oxygen level-dependent (BOLD) fMRI signal. Amplitude measures, such as fALFF, have proven to be a reliable means[24] of assessing local brain activity, and have also been used to investigate various clinical disorders.[22,25–28] Of particular importance, fALFF was validated recently with a very large sample (>1000 participants).[10] On the basis of previous R-fMRI acupuncture studies, it is expected that acupuncture on PC6 will change the fALFF of intrinsic cortical brain activity.

Materials and Methods

Subjects

Ten (10) healthy adults (5 males, age: 21.30 ± 1.06, height: 163.30 ± 4.69 cm, weight: 57.06 ± 5.42 kg) participated in this study, which was approved by the local ethics committee in the Department of Acupuncture, No. 3 Affiliated Hospital, Henan University of Traditional Chinese Medicine. All participants were right-handed and never had acupuncture during the 3 months prior to scanning. Individual acupuncture response indices were collected for each subject. Heart rate, respiration, and blood oxygen saturation were recorded by an electrocardiogram monitor connected to the subjects while stimulating uniformly on the PC6. Meanwhile, the visual analogue scale was adopted to record subjects' pain response. The above physiologic data were not used in the current preliminary study but are intended for use in future studies. All subjects had no history of psychiatric or neurological disease and gave written informed consent.

Experimental design

A Philips Achieva 1.5-T scanner was used to collect imaging data. A vitamin E soft gelatin capsule was pasted on the left *apex satyri* for each participant before scanning to ensure accurate left-brain detection in the data. During scanning, participants were instructed to lie quietly and look at the "+" fixed on the screen above their head without performing any cognitive task. For each participant, a high-resolution anatomical image was collected using a T1 Fast Field Echo series (field of view [FOV] = 230, matrix = 256 × 256, slices = 160, thickness = 0.8 mm, repetition time/echo time [TR/TE] = 25/4.6 ms, total scanning time: 6 minutes 56 seconds]. T2-TSE series was used to collect a low-resolution anatomical image [FOV = 230 mm, matrix = 256 × 256, slices = 32, thickness = 4 mm, TR/TE = 3317/100 ms, total scanning time: 3 minutes 12 seconds]. Three (3) continuous-state fMRI datasets were collected based upon an echoplanar imaging-BOLD series (FOV = 230 mm, matrix = 64 × 64, slices = 32, thickness = 4 mm, TR/TE = 3000/50 ms, total scanning time: 6 minutes 6 seconds).

The first fMRI is a resting-state scan (R1) completed in the absence of acupuncture stimulation. Following that scan, a professional acupuncturist (i.e., Y-LZ) located PC6 and inserted a silver needle to a 1.5-cm subcutaneous depth. The acupuncturist manipulated the needle while communicating with the participant in order to determine his/her sense. Once the participants had an obvious *de qi* sense (i.e., the participant could feel the sensation of aching, numbness, heaviness, or distension around the acupoint, while the acupuncturist simultaneously felt heaviness and tension beneath the needle), the acupuncturist further manipulated needle with a twirling-rotating motion (i.e., one of basic acupuncture manipulations: After the needle is inserted to the desired depth, the needle is twirled and rotated backward and forward with the thumb, index and middle fingers of right hand) 30 times in 1 minute. The angle of this manipulation was ± 180°. The manipulation continued for 2 minutes 30 seconds. After the manipulation, the second continuous-state scan with the acupuncture (AP) was started and the total scanning time was 6 minutes 6 seconds. Finally, the third 6-minute 6-second resting-state (R2) scan was performed following the completion of the acupuncture. The T1 and T2 scans (total about 10 minutes) were carried out between AP and R2 to ensure that the sensory effects of the acupuncture stimulation disappear.

Statistical analysis

The data preprocessing and analyses were carried out in a LINUX system. The processing included (1) converting data into NIFTI format by using MRI Convert 2.0 software (http://lcni.uoregon.edu/~jolinda/MRIConvert); (2) calculating individual fALFF maps in the public BASH scripts released with the 1000 Functional Connectomes Project (http:// fcon_1000.projects.nitrc.org); (3) transforming the individual fALFF maps to MNI152 standard brain space; (4) evaluating statistical tests by using AFNI Software (http://afni.nimb.nib.gov/afni). To demonstrate the general amplitude effect of the R-fMRI signal, R1, AP, and R2 ALFF maps were entered into one-sample *t*-tests across all participants separately. Clusters with more than 15 voxels and $t > 2.262$ (i.e., corresponding to an uncorrected $p < 0.05$) were selected as regions showing significantly detectable amplitudes. To find the effect of AP, two paired *t*-tests were carried out between R1 and AP as well as R1 and R2 fALFF maps. Clusters with more than 15 voxels and $t > 2.262$ were treated as significantly detectable regions.

Results

Active regions with high amplitudes in the resting-state brain during R1, AP, and R2

Consistent with previous studies,[22–24] the following brain regions demonstrated high ALFF: bilateral superior frontal gyrus, bilateral medial frontal gyrus, bilateral lingual gyrus, bilateral cerebral tonsil, right precuneus, left posterior cingulate cortex, right superior marginal gyrus, right fusiform gyrus, right anterior cingulate cortex, and left declive (see Table 1 and Fig. 1A for details).

The one-sample *t*-tests on all individual fALFF maps during the acupuncture on PC6 revealed active brain regions showing significantly detectable fALFF amplitudes while participants were stimulated with acupuncture treatment. Specifically, the high amplitudes appeared in bilateral precuneus, left cingulate gyrus, left middle frontal gyrus, left cerebellar tonsil, right inferior parietal lobule, and left posterior cingulate cortex (see Table 1 and Fig. 1B for details). During R2, right precuneus, right supramarginal gyrus, right parahippocampal gyrus, left middle cingulate cortex, and cerebellum exhibited higher fALFF (see Table 1 and Fig. 1C for details).

Active regions showing altered amplitudes between R1 and AP

The two-sample paired *t*-tests indicated brain regions with differences in fALFF between the first resting-state scan (R1) and the stimulating acupoint scan (AP). The increased fALFF appeared in left cingulate gyrus, right precuneus, right occipital fusiform gyrus, and left posterior cingulate cortex as well as decreased fALFF in right superior frontal gyrus, left middle frontal gyrus, left cerebellar tonsil, and left superior medial gyrus (see Table 2 and Fig. 2A for details).

Table 1. Regions with High Fractional Amplitude of Low-Frequency Fluctuations in Human Brain Under Different Conditions

Location	*Peak coordinates (MNI space)* X	Y	Z	*Cluster size (no. of voxels)*
R1 condition				
Right precuneus	2	−62	52	2153
Right middle frontal gyrus	24	26	52	907
Right lingual gyrus	28	−68	−14	563
Left cerebellar tonsil	−6	−64	−38	404
Right medial frontal gyrus	4	52	46	305
Right superior frontal gyrus	2	64	16	276
Left declive	−34	−80	−28	198
Right superior frontal gyrus	6	66	−6	176
Left middle frontal gyrus	−32	2	58	158
Right supramarginal gyrus	54	−56	18	128
Right cerebellar tonsil	44	−60	−42	107
Right fusiform gyrus	44	−52	−20	99
Right anterior cingulate	2	40	30	96
Left medial frontal gyrus	−24	10	56	62
Left cingulate gyrus	−10	−2	44	37
Left superior frontal gyrus	0	38	58	26
Left lingual gyrus	−20	−82	−22	17
AP condition				
Left cingulate gyrus	−10	−14	48	1174
Left cerebellar tonsil	−8	−62	−38	123
Right inferior parietal lobule	52	−50	18	98
Right precuneus	4	−56	44	93
Left middle frontal gyrus	−28	−6	48	76
Left posterior cingulate	−2	−48	26	46
Right precuneus	14	−46	50	20
R2 condition				
Left middle cingulate cortex	−14	−18	54	926
Left cerebellar tonsil	0	−62	−38	179
Right precuneus	8	−54	34	126
Right supramarginal gyrus	52	−52	16	113
Right inferior semilunar lobule	14	−66	−48	18
Left cerebellar tonsil	−16	−52	−40	18
Right parahippocampal gyrus	42	−48	−16	15

Active regions showing altered amplitudes between R1 and R2

The two-sample paired *t*-tests between R1 and R2 revealed brain regions with differences in fALFF. Right declive, right precuneus, right postcentral gyrus, and left posterior cingulate gyrus exhibited increased fALFF. In contrast, left superior/medial/middle frontal gyrus and left cingulate gyrus showed deceased fALFF (see Table 2 and Fig. 2B for details).

Discussion

Raichle and colleagues first observed that the human brain has a so-called default mode network (DMN).[29–31] The DMN primarily includes the posterior cingulate gyrus, precuneus, and medial prefrontal cortex.[32] Ongoing large-amplitude, low-frequency (0.01–0.1 Hz) spontaneous fluctuations[22,24] in these DMN areas are actively correlated with each other during the resting state.[33,34] Activity in this network has also been studied with regard to various mental disorders.[35–38] While there are several studies reporting changes of interregional functional connectivity introduced by acupuncture,[14–20] no study explores acupuncture-induced changes in regional activity of low-frequency fluctuations. In this study, using fALFF, the centrum effect on PC6 was demonstrated by comparing fALFF between the resting-state brain and brain when it is being stimulated with acupuncture. Increasing evidence is mounting for neural activity as the primary contributor to the low-frequency fluctuations.[39] First, the dominant low-frequency fluctuations in gray matter compared to white matter suggest a possible link to neuronal processes. Second, greater test–retest reliability for fALFF in gray matter provides further support for such a link.[24] The most intriguing findings directly linked low-frequency BOLD fluctuations to those observed in electroencephalograms.[40] Thus, the greater amplitude of such fluctuation that were observed during the acupuncture might reflect the effect of this intervention modulating the regional neuronal activity to a higher-level baseline via brain–body interactions.

Compared to the whole brain baseline, across three states (i.e., R1, AP, and R2) DMN regions exhibiting higher amplitude were posterior cingulate cortex, precuneus, inferior parietal lobule, and cerebellar tonsil. In relation to a previous study on PC6 conducted by Dhond et al.,[21] the amygdala and hippocampus—regions reported in Dhond et al.[21] an ICA-based connectivity study—were not found to be active in the current study. In addition, cerebellar activity was demonstrated in this study, but this did not appear in Dhond et al. [21] Of note, in the study by Dhond et al., a control group of false-stimulus modality was conducted, and data were analyzed using a functional connectivity method. It was possible that the regions active during the AP scan exhibited different properties due to the two different R-fMRI measures or lack of a control design. It is valuable to perform a

FIG. 1. Significantly detectable amplitude of spontaneous low-frequency fluctuations in the resting-state brain during R1, AP, and R2. Group-level T-statistic maps showing significantly detectable amplitude of low-frequency oscillations (i.e., fractional amplitude of low-frequency fluctuations) across the whole brain for three states: **(A)** R1, **(B)** TAP, and **(C)** R2. A one-sample statistical *t*-test was carried out with a random-effects model across 10 participants. A moderate cluster-level multiple comparisons correction was performed ($T > 2.262$; uncorrected $p < 0.05$, number of voxels in a cluster > 15). The number in the left-top corner of each coronal slice is 24-mm spaced and indicates the *y*-coordinate in the MNI standard brain space. L, left hemisphere; R, right hemisphere.

direct comparison of results between different analytic strategies based on a larger sample in future.

The paired *t-test*s between resting-state and acupuncture-stimulated brain amplitudes demonstrated acupuncture stimulation effects. Specifically, enhanced low-frequency amplitudes of brain activity were demonstrated within the left middle/posterior cingulate gyrus, right precuneus, and occipital fusiform gyrus as well as decreased low-frequency amplitudes of R-fMRI signals in right superior frontal gyrus, left middle frontal gyrus, left cerebellar tonsil, and left medial frontal gyrus. Typically, intrinsic activity in the resting-state brain is spontaneous and persistent. This activity can be suppressed within the DMN when the resting-state brain is involved in specific cognitive tasks. In this trial, similarly, some DMN regions (e.g., the medial frontal gyrus) were suppressed. Interestingly, however, regions such as the posterior cingulate cortex and precuneus associated with mind wandering and episodic memory,[41–44] which are closely related to the therapeutic effects of PC6, actually were enhanced by the acupuncture on PC6. This can be further confirmed with the post-stage continuous acupuncture effects revealed by the paired *t*-tests between pre- and post-acupuncture resting-state scans (i.e., R2 versus R1). Such analysis showed the increases in amplitude of intrinsic brain activity consistently appeared in the posterior cingulated cortex (PCC) during a period even without the acupuncture stimulation while other regions involved in pain circuits (e.g., anterior cingulate cortex and cerebellum) disappeared or exhibited inverse patterns. It is thus argued that the PCC may serve as a specific brain location responding to acupuncture on PC6.

PC6 is the collateral point (i.e., the acupoint where the 15 collaterals stem from the 12 meridians) of the pericardium channel of *Hand Jueyin*. The physiologic function and pathological changes of pericardial disease were related to the consciousness and thoughts, which are claimed in TCM theory.[11] In previous task-based studies,[12,13] brain regions most commonly activated by acupuncture on PC6 include the cingulate gyrus, medial temporal lobe, and cerebellum. All brain functions are not independent: That is, brain regions are intermediated and coordinated with one another. Accordingly, a physiologic change within these regions could reflect a functional change in the brain. The cingulate gyrus, superior frontal gyrus, medial frontal gyrus, and cerebellum are mainly involved with various high-order cognitive functions. In the current study, activity in PCC was enhanced according to the amplitude measure by stimulating PC6. This enhancement could strengthen the neuronal activity related to cognition and consequently improve cognitive deficits. Within PCC, the deceases in fALFF have been related

Table 2. Brain Regions Showing Different Fractional Amplitude of Low-Frequency Fluctuations Across Conditions

Location (peak T-statistic)	*Peak coordinates (MNI space)*			*Cluster size (no. of voxels)*
	X	Y	Z	
AP versus R1				
Left cingulate gyrus (+5.6)	−6	−30	40	78
Right precuneus (+3.1)	4	−56	42	48
Right occipital fusiform gyrus (+3.8)	6	−76	42	48
Right superior frontal gyrus (−8.8)	4	16	64	47
Left middle frontal gyrus (−4.9)	−36	8	62	47
Right precuneus (+3.1)	4	−72	56	38
Left posterior cingulate (+5.5)	0	−48	26	36
Left cerebellar tonsil (−3.5)	−8	−68	−40	16
Left superior medial gyrus (−3.5)	0	30	62	16
R2 versus R1				
Right declive (+3.7)	28	−62	−24	70
Left middle frontal gyrus (−3.9)	−34	4	64	64
Left medial frontal gyrus (−5.2)	−2	8	70	56
Left cingulate gyrus (−3.3)	−10	2	46	54
Left medial frontal gyrus (−3.9)	−6	64	22	31
Left superior frontal gyrus (−3.6)	0	18	58	28
Right precuneus (+3.8)	14	−82	52	27
Right postcentral gyrus (+3.1)	8	−52	68	22
Left posterior cingulate (+3.0)	−4	−48	26	18

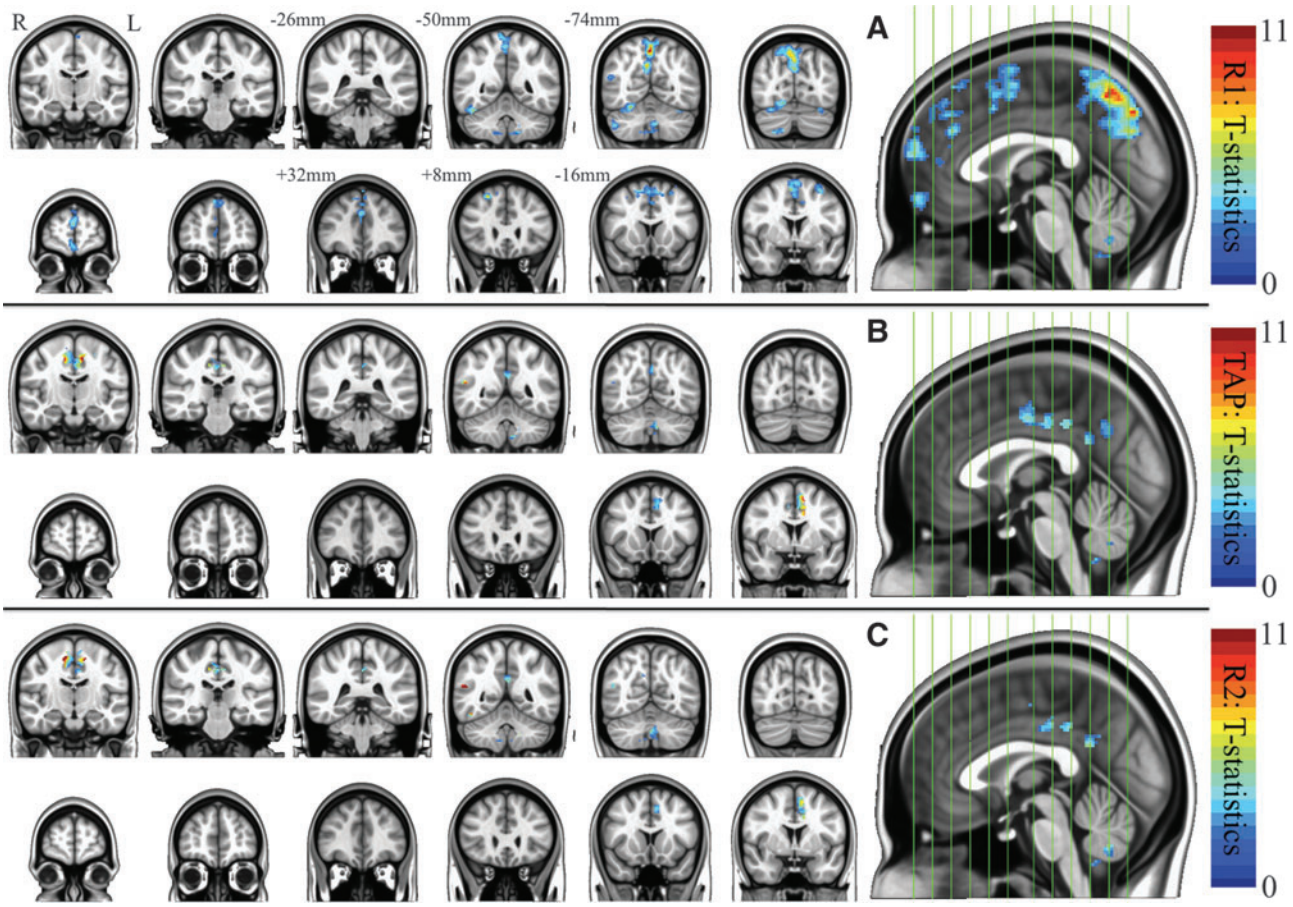

FIG. 1. See previous page.

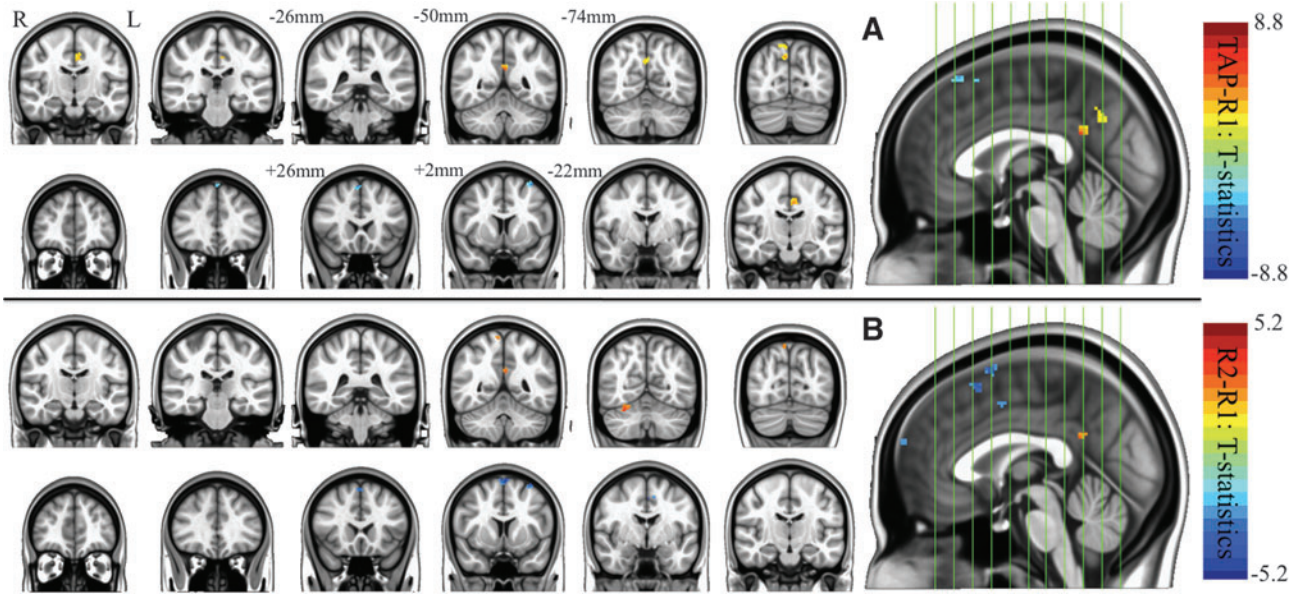

FIG. 2. Significant amplitude changes of amplitude of spontaneous low-frequency fluctuations introduced by acupuncturing PC6 and its post-stage effects. Group-level T-statistic maps show significant differences in amplitude of low-frequency oscillations (i.e., fractional amplitude of low-frequency fluctuations) across the whole brain between resting state and acupuncturing state **(A)** as well as the postacupuncture resting state **(B)**. A paired two-sample statistical *t*-test was carried out with a random-effects model across 10 participants. A moderate cluster-level multiple comparisons correction was performed ($T > 2.262$; uncorrected $p < 0.05$, number of voxels in a cluster > 15). The number in the left lower corner of each coronal slice is 24-mm spaced and indicates the *y*-coordinate in the MNI standard brain space. L, left hemisphere; R, right hemisphere.

to the normal aging process in a very large sample.[10] Weaker fALFF within this region was also observed in amnestic mild cognitive impairment.[45] Previous PET/SPECT studies have also reported PCC-related hypoperfusion and hypometabolism in mild cognitive impairment and Alzheimer disease.[46,47] Moreover, several recent R-fMRI studies have suggested reduced regional activity of PCC in mild cognitive impairment/Alzheimer disease.[5,48,49] Considering the fact that there is increased fALFF of PCC by performing acupuncture on PC6, it is argued that AP-PC6 may potentially serve as an alternative treatment for MCI or AD.

Several limitations should be considered when interpreting the findings observed here. First, as a preliminary study, the sample size is small (10 young participants). This could be the reason that there is no finding in the regions related to regulation of the cardiac rhythm or myocardial ischemia, which are thought to be associated with PC6 acupuncture function in TCM.[11] Second, in considering such a small sample, only a modest threshold was used for correcting for multiple statistical comparisons. Third, it may also benefit the current study to include a control state on the real-needle acupuncture by using sham acupuncture. In the future, these findings need to be further confirmed by increasing sample size, optimizing statistical comparisons, and including a control state for the acupuncture.

Conclusions

In summary, using the amplitude measure of low-frequency fluctuations, the hypothesis of high amplitude of default-mode network activity was verified and acupuncture-induced amplitude changes in these regions was demonstrated. It was proposed that some brain regions including the frontal lobe, cingulate cortex, and cerebellum were activated by the acupuncture on PC6. In particular, gaining enhancement of brain activity within the posterior cingulate cortex may reflect the fact that acupuncture location PC6 has potential treatment effects for Alzheimer disease. Using neuroimaging, the current results provide evidence that TCM theory has a potential neuroscientific basis.

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Disclosure Statement

No competing financial interests exist.

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