Identify potential neuroimaging-based scalp acupuncture and neuromodulation targets for anxiety

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ARTICLE INFO
Received: 25 February, 2021
Revised: 20 May, 2021
Accepted: 25 May, 2021

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KEYWORDS
scalp acupuncture, neuroimaging, meta-analysis, magnetic resonance imaging (MRI), anxiety

ABSTRACT
Anxiety is a common psychiatric symptom with unsatisfactory treatment. Scalp acupuncture is a new type of acupuncture based on the functions of different brain regions. However, recent brain neuroimaging findings have not been well-integrated into scalp acupuncture practice and research since it was developed. In parallel, recently developed brain stimulation methods have also been applied to treat anxiety. In this study, we integrated meta-analysis (using Neurosynth), resting-state functional connectivity, and diffusion tensor imaging (using the amygdala as the region of interest) to identify potential locations of scalp acupuncture/neuromodulation for anxiety. We found that the superior/middle frontal gyrus, middle/superior temporal gyrus, precentral gyrus, supplementary motor area, supramarginal gyrus, angular gyrus, and superior/inferior occipital gyrus are involved in the pathophysiology of anxiety, and, thus, may be used as the target areas of scalp stimulation for alleviating anxiety. Integrating multidisciplinary brain methods to identify key surface cortical areas associated with a certain disorder may shed light on the development of scalp acupuncture/neuromodulation, particularly in the domain of identifying stimulation locations.

1 Introduction
Anxiety may be the most prevalent psychiatric symptom in the general population and has a high level of comorbidity with other psychiatric disorders such as depression, obsessive-compulsive disorder, and post-traumatic stress disorder [1]. However, therapeutic outcomes of pharmacologic treatments for anxiety remain unsatisfactory due to the cognitive side effects, withdrawal effects, and the risk of abuse [2]. Thus, there is an urgent demand for a reliable and cost-effective intervention that can relieve anxiety, especially in the face of the COVID-19 pandemic, which creates an ever-changing and uncertain environment in daily life.

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Scalp acupuncture is a modern type of acupuncture developed on the basis of anatomical and neurophysiological knowledge [3]. By stimulating specific brain cortical areas, scalp acupuncture aims to modulate corresponding functional areas, thereby providing benefit for a wide scope of the diseases. Recently, it has been applied to relieve symptoms of anxiety and has achieved some promising results [4–7].

However, the current scalp acupuncture prescription is mainly based on our understanding of brain function in the 1970s, when scalp acupuncture was first introduced. In recent decades, remarkable progress has been made on the neural circuitry of anxiety through cutting-edge brain imaging techniques [8–10]. Unfortunately, this information has not been incorporated into the scalp acupuncture treatment of anxiety.

In addition to scalp acupuncture, recently developed brain stimulation methods have also been used to treat anxiety. For example, transcranial direct current stimulation (tDCS) applies a low intensity, constant electrical current over the scalp to hyperpolarize (cathodal) or depolarize (anodal) neuronal resting membrane potentials, which has shown promising results in ameliorating the symptom of anxiety [11]. Further, transcranial alternating current stimulation (tACS) can modulate the rhythms of endogenous oscillations by applying weak electric fields through the scalp, which demonstrates potential in alleviating anxiety [12]. Additionally, the repetitive transcranial magnetic stimulation (rTMS) has also been suggested for alleviating anxiety [13] by generating strong and rapidly changing electric currents and a magnetic field that travels to reach the neurons of the cortex.

Scalp acupuncture and neuromodulation methods are within the scope of scalp stimulation techniques, but each technique has its own characteristics. Scalp acupuncture is an invasive method which is associated with needle insertion and stimulation. When electroacupuncture is applied, it is more similar to tACS (although the wave form may differ). Furthermore, both transcranial electrical stimulation (tES) (including tDCS, tACS, et al.) and transcranial magnetic stimulation (TMS) are non-invasive brain stimulation techniques. The tES puts a superficial electrode (made of sponges or conductive rubber) on certain scalp locations and applies direct current (tDCS) or alternative current with different frequencies/patterns (tACS) to change the excitability or oscillations of the brain. TMS requires a complicated device, which sends a short, high-power electrical surge to the coil. This short pulse produces a safe, controlled electrical current that flows into and stimulates the subject’s brain through induction to directly activate/deactivate certain brain regions. Nevertheless, many of the studies using different brain stimulation techniques mainly used the prefrontal cortex as the stimulation target [11, 14]. Identifying brain regions (particularly the surface brain areas) involved in anxiety may expand the selection of potential targets of neuromodulation techniques in the treatment of anxiety.

Thus, the current study aims to develop a neuroimaging-based protocol for treating anxiety using scalp acupuncture as well as neuromodulation methods. We first identified anxiety-associated cortical surface regions by completing a meta-analysis on neuroimaging literature. Because scalp stimulation cannot directly target deep brain areas, and some deep brain structures may play an important role in pathology of anxiety, we also applied additional analyses [resting-state functional connectivity (rsFC) and diffuse tensor imaging (DTI)] to
identify brain surface areas that are functionally and structurally connected with these deep brain structures involved in anxiety pathology using amygdala [15–17] as an example.

2 Methods

In this study, we performed three imaging analyses to identify potential locations for scalp acupuncture and neuromodulation methods: a) meta-analysis (Analysis 1) on neuroimaging studies to identify brain regions associated with anxiety disorders, focusing on the surface regions that can be reached by scalp stimulation techniques; b) resting-state functional connectivity analysis using the amygdala as an example (Analysis 2) to pinpoint surface cortical areas functionally connected to the deep brain structure on a cohort of healthy participants; and c) DTI analysis (Analysis 3) on the same participants as Analysis 2 to locate surface cortical targets that are linked with the amygdala anatomically. Last, we used our findings from the three analyses to develop a scalp stimulation protocol for anxiety disorders.

2.1 Analysis 1: Meta-analysis to locate anxiety-associated surface brain regions

We used Neurosynth [18] (http://neurosynth.org, accessed 9 June 2020) as a metadata resource for neuroimaging publications to extract anxiety-associated brain regions. Neurosynth extracted data from a large body of neuroimaging literature and generated a meta-analysis of qualified studies according to the keywords. The search string “anxiety disorder” generated 95 imaging studies (Supplementary Material S1). Different from classic forward inference and the generated positive-associated results, Neurosynth applied Bayesian reverse inference which included all negative results and provided results with a greater specificity. Anxiety-associated brain areas were identified using a uniformity test map.

To identify brain regions on the surface of the brain that can be reached by scalp acupuncture, similar to our previous studies [19–21], we first generated a brain surface cortical mask using SPM Wake Forest University (WFU) PickAtlas toolbox (http://fmri.wfubmc.edu/software/pickatlas, version 3.0.5); a detailed description of the cortical mask can be found in our published studies [19–21].

Next, we took the overlap of the uniformity test map with the brain surface cortical mask to further refine anxiety-associated regions from the meta-analysis. We then identified the coordinates with peak z-scores within all surface clusters larger than 30 voxels on the uniformity test map using xjView toolbox (http://www.alivelearn.net/xjview). Finally, the locations of the brain regions were visually checked to identify potential accessible surface targets for scalp acupuncture.

2.2 Analysis 2: Resting-state functional connectivity analysis to locate anxiety-associated surface regions

The surface brain regions found in the meta-analysis can be stimulated directly by scalp acupuncture, but the deeper brain areas identified, such as the amygdala, cannot be reached by scalp acupuncture. However, these deep regions may be indirectly reached by stimulating surface regions that are anatomically or functionally connected to the deep brain structure.

Recently, resting-state functional connectivity has been used to optimize the locations of brain stimulation methods for mental disorders and have achieved some encouraging results [19, 20, 22]. Thus, in this study, surface targets that are
functionally connected to deep anxiety-associated brain regions were identified using resting-state functional connectivity analysis (Analysis 2).

2.2.1 Participants and MRI data acquisition

We used magnetic resonance imaging (MRI) data from 24 healthy, right-handed participants, all of which provided written, informed consent before participating in the study. The study was approved by the Partners Institutional Review Board (IRB) of Massachusetts General Hospital. Demographic characteristics of participants and a detailed description of the imaging data collection, preprocessing, and analyses can be found in the Supplementary materials and in our previous study [23].

2.2.2 Seed-based functional connectivity analyses

We used the amygdala (AMY) as the region of interest (ROI) as an example to perform seed-to-voxel functional connectivity analysis (left and right AMY separately). The AMY was selected because it was detected from the meta-analysis (Analysis 1), and more importantly, numerous studies suggest that hyperactivation of the AMY is associated with the modulation of the fear response, playing a key role in the pathophysiology of anxiety disorders [15, 24–26]. We used the WFU PickAtlas toolbox to create the ROIs.

2.3 Analysis 3: DTI analysis to find anxiety-associated surface regions

Next, we found surface cortical targets that are anatomically connected to the key deep brain regions of anxiety using DTI analysis (Analysis 3). The same 24 healthy, right-handed individuals used in Analysis 2 were included in the diffusion MRI (dMRI) data analysis. A detailed description of the dMRI data collection, preprocessing, and tractography can be found in Supplementary Fig. S1.

2.4 Summarizing results from neuroimaging analyses

Surf Ice (https://www.nitrc.org/projects/surface) and a standard head using MRicroGL (http://www.mccauslandcenter.sc.edu/mricrogl) with the international 10-20 electroencephalography (EEG) system in Montreal Neurological Institute (MNI) space were used to map the results from Analysis 1, 2, and 3 onto a standard brain. The MNI coordinates of the 10-20 EEG system were obtained from a previous study [27]. Furthermore, we also used the international standard scalp acupuncture lines and acupoints to facilitate choosing the targets of the new scalp acupuncture protocol.

3 Results

3.1 Potential targets from the meta-analysis

Fourteen surface regions were identified from the uniformity test map of the meta-analysis (Table 1). These surface regions included the left superior frontal gyrus (SFG)/superior medial frontal gyrus (SupMFG), middle temporal gyrus (MTG), and middle occipital gyrus (MOG)/inferior occipital gyrus (IOG); the right dorsolateral prefrontal cortex (dIPFC), supplementary motor area (SMA), superior temporal pole (STP), superior parietal lobule (SPL)/supramarginal gyrus (SMG)/angular gyrus (AG), precentral gyrus (PreCG), and superior occipital gyrus (SOG); as well as the bilateral inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and inferior frontal operculum (IFO) [Figs. 1(A)–(E)]. The 10-20 EEG system coordinates corresponding to the center of these regions were located approximately at F3, F7, T5, P3, and O1 on the left side (F4, F8, T6, P4, and O2.

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on the right side), and Fz on the middle line [Figs. 1(B) & 1(D)]. Detailed whole brain results from the meta-analysis can be found in Supplementary Table S1.

### 3.2 Potential targets from the amygdala resting-state functional connectivity analysis

Similar results were produced from the seed-based resting-state functional connectivity analysis using the right and left AMY as seeds. Specifically, we found that the brain surface regions including the left postcentral gyrus (PoCG), the right MTG, superior temporal gyrus (STG), SMA and MFG, as well as the bilateral temporal pole (TMP), IFG, precuneus (PCu), PreCG and operculum were positively correlated with the left AMY. The left SPL, the right inferior temporal gyrus (ITG), as well as the bilateral orbital middle frontal gyrus (OrbMFG), SFG and AG were negatively correlated with the left AMY [Table 2, Figs. 1(A) & 1(B)]. Similarly,
Fig. 1  Potential targets for scalp stimulation for anxiety, identified from imaging research and literature-documented guidelines. (A) and (B) Surface regions identified from meta-analysis and L. AMY-based rsFC. (C) and (D) Surface regions identified from meta-analysis and R AMY-based rsFC. (E) Surface regions identified from meta-analysis and literature-documented scalp acupuncture guidelines. (F) and (G) Fiber paths from the L and R AMY extending toward other brain regions. Abbreviations: L, left; R, right; AMY, amygdala; rsFC, resting-state functional connectivity; MFG, middle frontal gyrus; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; dlPFC, dorsolateral prefrontal cortex; MedFG, medial frontal gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; TMP, temporal pole; SPL, superior parietal lobule; SMA, supplementary motor area; PCu, precuneus; PreCG, precentral gyrus; PoCG, postcentral gyrus; AG, angular gyrus; MOG, middle occipital gyrus; IOG, inferior occipital gyrus; MB, microsystem and scalp points; MS 1, Erbossu; MS 5, Dingezsibang; MS 10, Niehouxian; MS 12, Zhenshang; MS 13, Zhongxian; MS 17, Naohu; GV 18, Qiaoqiao; GV 20, Baihui; GV 21, Queding; GV 24, Shenting; GB 7, Qiben; GB 8, Shuaigou.

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the left SFG, PCu, the right STG, PreCG, SMA, MFG, IFG, as well as the bilateral TMP and operculum were positively correlated with the right AMY. The left SFG and SMG, the right PCu and PoCG, as well as the bilateral SPL, AG and cuneus were negatively correlated with the right AMY [Table 3, Figs. 1(C) & (D)]. Figs. 1(B) & (D) show the 10-20 EEG system coordinates corresponding to the center of these regions.

3.3 Potential targets from the amygdala DTI analysis
The probabilistic tractography revealed that the fiber paths from the left and right AMY toward the brain surface were located approximately at F7, F8, T3, T4, P3, P4, O1, and O2 in the 10-20 EEG system [Figs. 1(F) & (G)].

3.4 Scalp acupuncture protocol based on neuroimaging analyses
We propose a neuroimaging-based scalp acupuncture protocol for anxiety based on the results from Analyses 1-3. Prescription A includes lines from F3 to F7, P3 to T5, and O1 on the left side (lines from F4 to F8, P4 to T6, and O2 on the right side), as well as the Yintang [Governor Vessel (GV) 29], Sishencong [extra points on the head and neck (EX-HN) 1], and
Table 3  Anxiety associated surface regions identified from R/AMY-based rsFC.

| Brain regions | Cluster size | Peak coordinates x | y | z |
|---------------|-------------|--------------------|---|---|
| R.TMP/STG/preoculum | 11843 | 20.56 | 30 | -4 | -24 |
| L.TMP/preoculum | 7839 | 12.70 | -38 | -8 | -8 |
| L.MedFG/SFG | 1790 | 10.47 | -40 | -12 |
| R.PoCG/SMA | 1061 | 8.80 | 8 | -22 | 48 |
| R.MFG/IFG | 131 | 6.30 | 38 | 14 | 32 |
| L.PoCg | 95 | 5.79 | -14 | -40 | 2 |
| R.PCg/cuneus/SPL | 894 | 9.50 | 4 | -70 | 52 |
| L AG/SPL/SMG | 1480 | 9.39 | -46 | -52 | 46 |
| L.MFG/SFG | 412 | 8.07 | -28 | 12 | 62 |
| L.MFG | 623 | 7.73 | -48 | 18 | 42 |
| R AG/SPL/PoCG | 1127 | 7.51 | 38 | -50 | 50 |
| L.MFG/IFG | 781 | 7.15 | -28 | 52 | -2 |
| R MFG | 145 | 6.05 | 30 | 12 | 56 |
| R MFG | 336 | 5.77 | 46 | 30 | 40 |
| L.cuneus/SOG | 193 | 5.36 | 0 | -86 | 38 |
| R.SFG/MFG | 182 | 4.59 | 28 | 64 | 10 |

Notes: Results are significant at cluster P < 0.05 corrected at whole brain level.

Abbreviations: L, left; R, right; AMY, amygdala; rsFC, resting state functional connectivity; STG, superior temporal gyrus; TMP, temporal pole; IFG, inferior frontal gyrus; MedFG, medial frontal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; PoCG, precentral gyrus; PoCG, postcentral gyrus; SMA, supplementary motor area; SPL, superior parietal lobe; PoG, precuneus; SMG, supramarginal gyrus; AG, angular gyrus; SGC, superior occipital gyrus.

bilateral Shuaigu [Gallbladder meridian (GB) 8].

Prescription B includes lines from C3 to F7, P3 to T3 on the left side (lines from C4 to F8, P4 to T4 on the right side), Pz on the middle line, as well as the Shenting (GV 24), Baihui (GV 20), and bilateral Taiyang (EX-HN 5) [Figs. 2(A) & (B)]. We also suggest an alternate use of the prescriptions to eliminate needling resistance.

4 Discussion

Anxiety is a common psychiatric symptom in the general population. The recent pandemic further enhanced the anxiety level across the world. In this study, we integrated multiple neuroimaging modalities (meta-analysis, resting-state functional connectivity, and DTI) to identify potential locations for scalp stimulation techniques (such as scalp acupuncture and neuromodulation methods) for the treatment of anxiety. We found the SFG/MFG, the dlPFC, the STG/MTG, the PreCG, the SMA, the SMG, the AG, and the SOG/IOG to be the target areas of scalp stimulation techniques for alleviating anxiety. The 10-20 EEG system, the International standard scalp acupuncture system, and acupoints were also used to locate these targets.

4.1 Potential targets for the neuroimaging-based scalp stimulation protocol

In this study, we found potential surface brain targets for scalp stimulation methods in treating anxiety. The results are consistent with the function and physiology of these cortical areas.

We found that the SFG/MFG and dlPFC are notable target regions for relieving anxiety. Accumulating evidence has proven that the neural basis for emotion regulation deficits in anxiety disorders center upon abnormalities within the fronto–limbic (cognitive–emotion) pathway. Thus, the normalization of the fronto–limbic pathway would be helpful in regulating emotion. For instance, previous studies revealed that compared with healthy controls, adults and children with anxiety disorders demonstrated a decreased functional connectivity between the amygdala and SFG, MFG, and dlPFC [15, 28], as well as an increased gray matter volume and a decreased structural connectivity between these regions [8]. Another fMRI study revealed that patients with anxiety showed relatively lower connectivity between the right amygdala and SFG, but after the induction of perseverative cognition, the amygdala-
SFG connectivity significantly increased in anxiety patients yet decreased among healthy subjects [15]. In the aspect of therapeutic application, Dikov and colleagues applied 20 Hz rTMS, a non-invasive brain stimulation technique, on the right dlPFC in patients with generalized anxiety disorder, and found patients’ anxiety symptoms were significantly alleviated after 25 sessions of rTMS treatment [29]. Our results also show that targeting the temporal gyrus holds potential in treating anxiety. A previous MRI study observed that
patients with an anxiety disorder demonstrate a significantly larger volume of white and grey matter in the STG [30]. Zhao and colleagues applied fMRI to investigate the activation and connectivity of the STG in patients with anxiety during different tasks and found that the activity of the STG increased during the silence task, while the functional connectivity decreased between the left and right STG during the threat-related task [31]. In another MRI study, researchers applied voxel-based morphometry (VBM) analysis and a Likert-type scale, used to measure anxiety symptoms, in 177 healthy individuals and found a positive correlation between the rating of anxiety symptoms and the grey matter volume in the prefrontal cortex, MTG, and precuneus [32], consistent with previous findings that these regions are involved in both emotion regulation and altered in patients with anxiety disorders [33, 34].

Furthermore, the PreCG is related to the modulation of anticipatory threat and anxiety symptoms. Moon and colleagues investigated brain activation during an explicit verbal memory task with anxiety-inducing words, comparing the healthy individuals and anxiety patients. They found that anxiety patients had significantly higher activity in the PreCG during the presentation of the anxiety-inducing words, compared to healthy controls [35]. However, discrepancies exist in investigations of the effects of anxiety on the grey matter volume of the PreCG. For instance, Makovac et al. found decreased volume in the bilateral PreCG in patients with an anxiety disorder [36], while Strawn et al. observed an increased volume in the right PreCG [33]. Nevertheless, both studies suggest that the PreCG is involved in pathophysiology of anxiety disorders.

Next, it has been shown that anxiety constrains cognition by biasing attention toward the anticipation of threat, and anxiety may reflect the highest level of normal motivational control of working memory [37, 38]. The SMA plays a key role in cognitive performance, especially in working memory. Recently, Coutinho and colleagues demonstrated that damage of the SMA does not affect cognitive process other than working memory, and thus working memory impairment needs to be recognized as part of SMA syndrome [39]. In conclusion, the SMA should also be considered as a crucial region in the treatment of anxiety.

Moreover, the occipital lobe should not be omitted in the treatment of anxiety. A recent meta-analysis found that patients with anxiety disorders presented increased activation in the IOG [40]. Furthermore, anxiety patients, compared to healthy individuals, showed decreased activity in the SOG during both neutral and anxiety-inducing distractors in the working memory task [41], highlighting the principle role of the occipital lobe in emotional regulation and cognitive function.

Finally, we found that the AG and SMG should be considered in the treatment of anxiety disorders using scalp stimulation. In a recent resting-state fMRI study, Modi and colleagues investigated networks associated with trait anxiety of the healthy subjects (high anxious vs. low anxious) using independent component analysis and found that high anxious subjects demonstrated significantly reduced functional connectivity in the AG and SMG, indicating the perceptual, attentional and working memory deficits associated with trait anxiety [17]. Results from our group and other groups support that the AG and SMG, which are involved in episodic memory, self-referential, as well as emotional and perceptual processing, would be altered in anxiety conditions [42].
4.2 Comparison between the neuroimaging-based scalp acupuncture protocol and existing scalp acupuncture protocols for anxiety

Currently, there is no international guidance for scalp acupuncture therapy. Literature suggests that the middle line of the forehead (Ezhongxian, 1 cun long from Shenting (GV 24) straight downward along the meridian, MS 1), the middle line of the vertex (Dingzhexuan, from Baihui (GV 20) to Qioding (GV 21) along the midline of head, MS 5), the posterior temporal line [Niehouxian, from Shuaigu (GB 8) to Qubin (GB 7), MS 11], and the upper-middle line of the occiput [Zhszhang zhengzhongxian, from Qiangjian (GV 18) to Naohu (GV 17), MS 12] were widely recognized for alleviating anxiety using scalp acupuncture [5, 7].

Our neuroimaging-based protocol and the documented protocols in the literature share similarities as well as differences. Both our neuroimaging-based protocol and other protocols use the SFG/MFG, SMA, STG/MTG, and SOG/IOG as stimulation regions. The neuroimaging-based proposal incorporates several addition areas, including the dlPFC, PreCG, SMG, and AG. We recommend including these additional targets in the current scalp acupuncture procedures, as they demonstrate our updated knowledge on the neural pathways associated with anxiety.

It must be mentioned that this study is based on the theory of scalp acupuncture under the guidance of the International Standardized Scalp Acupuncture theory, which proposes that needles are placed along scalp locations corresponding to specific functional regions in order to modulate the function of these brain regions. Other scalp acupuncture theories are not included in the scope of the current study.

4.3 Current neuromodulation protocols for anxiety and their difference with the neuroimaging-based protocol

The target regions proposed in the neuroimaging-based protocol and the current neuromodulation protocols overlap. A recent study reviewed and summarized the stimulation targets of tDCS in patients with an anxiety disorder, and found that 11 of the included research studies targeted the dlPFC in the treatment of anxiety [43]. In addition, tACS on the dlPFC and the occipital cortex has been shown in several studies to reduce the severity of anxiety symptoms [44, 45]. Further, patients with anxiety disorders showed symptom remission after receiving rTMS on the dlPFC [14].

Most of the studies applying different neuromodulation techniques mainly used the dlPFC as the stimulation target for alleviating anxiety [45]. However, the neuroimaging-based protocol also includes the STG/MTG, the PreCG, the SMA, the SMG, and the AG, which may expand the selection of potential targets of neuromodulation techniques in the treatment of anxiety. As a support for our protocol, Salatino et al. found that low-frequency rTMS applied on the SMA can improve awareness in patients with obsessive-compulsive disorder (one type of anxiety disorder), so the SMA may represent a stimulation target for relieving the symptom of anxiety [46]. Another fMRI study on healthy individuals suggests that anodal tDCS applied over the right AG induced resting-state activity changes in sensory, emotional, and cognitive regions [47], which are key components involved in the neurocircuitry of anxiety disorders [48].

4.4 Limitations

First, this study used “anxiety disorder” as the keyword, so further research on a specific subtype of the anxiety (e.g., generalized anxiety...
disorder, social anxiety disorder, panic disorder, etc.) is needed. Thus, clinicians should choose the targets based on the specific symptoms associated with the patients. In addition, we chose to use healthy subjects to provide a more unbiased evaluation in Analysis 2 and 3, because previous studies showed large variability in the degree to which anxiety altered brain connectivity. Second, although we applied different analyses to identify potential targets for anxiety, further investigation is needed to understand the derivatives of the target regions as well as the functions of different brain regions, in order to precisely customize the scalp acupuncture prescription in clinical practice. Third, we only used the amygdala as the region of interest in the functional connectivity and DTI analyses due to its crucial role in the pathology of anxiety, but other deep brain structures associated with anxiety such as the hippocampus, may also be considered as the region of interest to extend the neuroimaging-based acupuncture protocol using resting state and DTI analysis (the details of hippocampus functional and structural connectivity can be found in one of our previous resting-state studies [23]). Finally, high-quality, controlled trials are needed to validate our neuroimaging-based scalp acupuncture and neuromodulation protocol.

5 Conclusion

In summary, combining meta-analysis and neuroimaging data analysis, we have identified brain regions that can be used as targets for scalp acupuncture and neuromodulation for the treatment of anxiety. The proposal includes the following treatment lines/points: from F3 to F7, from P3 to T5, from C3 to F7, from P3 to T3, and O1 on the left side (from F4 to F8, from P4 to T6, from C4 to F8, from P4 to T4, and O2 on the right side correspondingly), as well as the Pz on the middle line. In addition, we also incorporated the acupuncture points (Baihui (GV 20), Shenting (GV 24), Yintang (GV 29), Shuaigou (GB 8), Sishencong (EX-HN 1), and Taiyang (EX-HN 5)) to facilitate locating these target regions. Our research may pave the way to the development of the targets of scalp acupuncture and neuromodulation techniques for the treatment of anxiety.

Conflict of interests

Jian Kong holds equity in a startup company, MNT, and a patent to develop new peripheral neuromodulation devices. All the other authors declare no conflict of interests.

Financial supports

This work is supported by R01 AT008563, R33 AT009310, R33 AT009341, R34 DA046635 (through the NIH HEAL Initiative), and R01 AG063975 from National Institutes of Health (NIH) granted to Jian Kong. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the NIH HEAL Initiative.

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