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Study on the Role of Acupuncture in the Repair of Neural Circuits

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ABSTRACT

Ever-increasing numbers of researchers have targeted brain plasticity through the modulation of neural networks using diverse stimuli and interventions applied to the human body. Studies on resting-state functional connectivity and brain networks are in agreement with those using graph theoretical analyses in various natural, social, and cultural studies. However, such hodological studies have rarely been carried out to study acupuncture, which is one of the most important alternative medicines. We hypothesize that a graph theoretical approach will have theoretical implications allowing the interpretation of the very mechanisms by which acupuncture may promote brain plasticity. The network analysis is wellsuited to exploring how several brain regions come into play by this treatment, beyond differentiating only the centers that are selectively involved in therapeutic effects. Although the therapeutic value and neural effects of acupuncture are still under investigation, our study may shed light on the neural underpinnings of the effects of acupuncture on the act of swallowing.

KEYWORDS

Functional connectivity; Graph theory; Swallowing; Acupuncture.

1. Introduction

Ever-increasing numbers of researchers have targeted brain plasticity through the modulation of neural networks using diverse stimuli and interventions applied to the human body. Studies on resting-state functional connectivity and brain networks are in agreement with those using graph theoretical analyses in various natural, social, and cultural studies. However, such hodological studies have rarely been carried out to study acupuncture, which is one of the most important alternative medicines1-4). Admittedly, many studies have explored the cerebral regions preferentially involved in the responses to acupuncture stimulation. Specifically, functional magnetic resonance imaging (fMRI) techniques have been used to study the analgesic effects of acupuncture. These studies have been used to determine brain areas selectively engaged in the processing of somatic signals from acupoints. This underlying mechanism is particularly highlighted for the characteristic feeling called “De Qi”, which propagates along ascending pathways and reaches brain areas involved in pain responses 5-7). However, prior studies in this field have not fully attempted to mathematically overlay the transformation of a graph representing resting-state functional connectivity onto those of neural circuits associated with the effects of acupuncture.

We hypothesize that a graph theoretical approach will have theoretical implications allowing the interpretation of the very mechanisms by which acupuncture may promote brain plasticity. The network analysis is wellsuited to exploring how several brain regions come into play by this treatment, beyond differentiating only the centers that are selectively involved in therapeutic effects.

In fact, a previous case report indicates that acupuncture may be effective for the treatment of poststroke swallowing disorder in patients without brainstem lesions 8-10). According to this report, applying needles to four acupoints (KI3: Taxi, ST36: Zusanli, bilateral) on the legs may significantly shorten the latency time of the swallowing reflex. Furthermore, an interesting recent study found that ST36 stimulation leads to stronger network integration 11). Based on these valuable findings, we replicated an acupuncture experiment described previously 8) in healthy subjects, who underwent restingstate fMRI prior to and after needle manipulation. We were thus able to evaluate longitudinal differences in functional connectivity. To the best of our knowledge, network theory analysis of resting-state fMRI has yet to be used to search for therapeutic effects of acupuncture for the treatment of control failures such as dysphagia.

2. Methods

2.1 Participants

Twelve healthy subjects participated in this study (8 men and 4 women ranging in age from 22 to 45 years), which was carried out at the Tokyo Institute of Technology in Japan. Ethical approval was obtained from the Human Investigation Committee of this university. Taking into consideration the psychological strain that may result from acupuncture and the neuroimaging manipulations, the participants in our experiment were limited to candidates who had experienced acupuncture therapy. One male subject was removed from the analysis due to structural anomalies.

2.2 Procedure

No stimulus was presented in the scanner during the fMRI except for a fixation mark on the screen, which helped the participants rest without performing eye movements. Task-free resting-state fMRI sessions were split into two 6-minute-long runs. These runs were set up consecutively, although there were short breaks between runs.

After the first session, each subject exited the magnet room to undergo acupuncture treatment while seated in the room adjacent to the scan equipment. This move was due to security considerations discussed in the Human Investigation Committee and a posture optimization requiring participants to bend their knees at a 90-degree angle in a sitting position. This posture was not tense and was thus the most comfortable for the subjects. It was the most appropriate posture for placing needles into the four acupuncture points on the legs (bilateral KI3 and ST36). Disposable needles (40 mm, No16, stainless steel; Seirin, Japan) were inserted straight to a depth of 1 to 2 cm and retained in place for 10 minutes.

After pulling out the acupuncture needles and confirming that the participant did not feel vertigo, pain, or fatigue, we reintroduced him/her into the magnet room to obtain new resting-state fMRI data under the same conditions as those used for the previous scan before the acupuncture treatment.

2.3 Image Acquisition

Functional MRI was performed using a 3.0-T General Electric Signa scanner at Tokyo Institute of Technology, Japan. Functional scanning was performed using an echo planar imaging sequence with a repetition time of 2,000 ms, an echo time of 30 ms, a 192mm field of view, a 64 x 64 acquisition matrix, a voxel size of 3 mm x 3 mm x 3 mm, and a flip angle of 90 degrees.

2.4 Data processing

The initial data processing was performed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology; London, UK). Functional connectivity analyses were carried out using the CONN-fMRI functional connectivity toolbox v16b12). Seed-to-voxel and region of interest (ROI)-toROI functional connectivity maps were created for each participant. First-level connectivity analyses were carried out to collect the graph theoretical coefficients from the resting state networks of an individual subject separately before and after the acupuncture manipulation. We used the brain atlas of the CONN, which was named "brain.nii". The graph coefficients presented below were all computed using the module implemented in this toolbox.

3. Results

None of the subjects complained of pain throughout the experiment. However, a heavy and listless feeling of intrusion was reported by all subjects. This intrusion sensation might be considered "De Qi". We extracted significant brain regions relevant to the temporal difference in association strength or graph theoretical coefficient values using paired t tests applied to the subjectwise sessions prior to and after the acupuncture manipulation. However, in the control analysis, we removed regions that may also be considered significant within the scope of continuous runs, i.e., the split halves of each session, from the list. These regions included 1) anterior division of left inferior temporal gyrus (ITG), 2) anterior division of left temporal fusiform cortex (TFusC), 3) left temporal occipital fusiform cortex, and 4) right cerebellum crus 2. These regions were excluded from the main analyses, since they were thought to be affected by physical or physiological fluctuations.

The most intriguing effect of the manipulation was a network structure modification recorded in several areas as value changes in the graph theoretical coefficients ($p < 0.05$ FDR). According to the network theory secondlevel analyses, 17 regions displayed at least one significant change in either betweenness centrality, local efficiency, clustering coefficient, cost, degree, average path length, or global efficiency(*. The most striking finding was that 6 regions showed significant changes in the positive direction for clustering coefficient or local efficiency, even though the changes in degree were at the chance level. These regions were the pars opercularis of the left inferior frontal gyrus (IFG oper l), right precentral gyrus (PreCG r), left accumbens (Accumbens l), left cerebellum crus 1 (Cereb1 l), right cerebellum 9 (Cereb9 r), and vermis 6 (Ver6).

Focusing on a local graph in the vicinity of these nodes, we detected a significant decrease in connectivity between accumbens and the left insular cortex ($t(10) = -4.43$, $p = 0.0257$, FDR). Bidirectional modulation was observed for edges with one endpoint listed here according to the network coefficient. This finding is consistent with previous connectivity studies on acupuncture stimuli at ST367). For instance, the direction was negative for the link between the posterior division of left temporal fusiform cortex and the right intracalcarine cortex ($t(10) = -4.68$, $p = 0.0009$, uncorrected.)

Conversely, connectivity was enhanced between cerebellar and non-cerebellar regions. For instance, three subareas of the vermis were characterized by network coefficient changes, as follows: between vermis 9 and postcentral gyrus (PostCG) right ($t(10) = 3.86$, $p = 0.0032$, uncorrected), between vermis 8 and the inferior division of the left lateral occipital cortex (t (10) = 3.89, p = 0.003, uncorrected), and between vermis 7 and the posterior division of the right parahippocampal gyrus (t (10) = 4.24, p = 0.0017, uncorrected.)

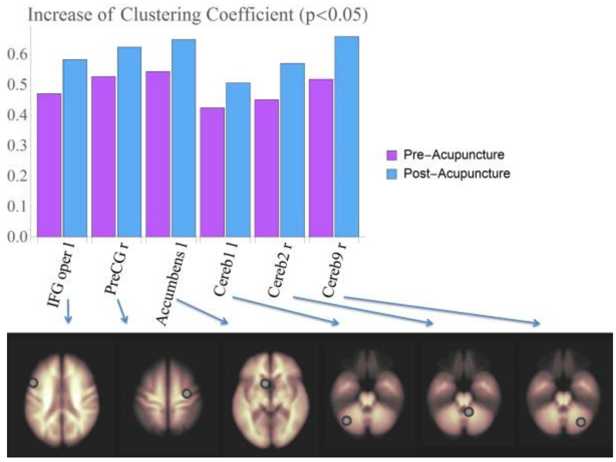

Figure 1. Areas (nodes) with significant changes (all increases) in the clustering coefficient

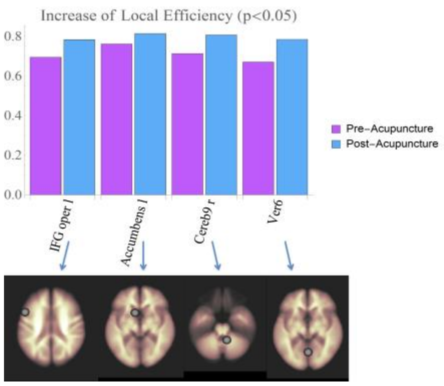

Figure 2. Areas (nodes) with significant changes (all increases) in the local efficiency

4. Discussion

The experimental setting of this study involves the difficult problem of baseline control for acupuncture experiments13-16). These issues were inevitable here due to several factors. Experience with acupuncture therapy was required in order to produce a homogeneously treated cohort of subjects. However, sham needles were visually recognizable outside the scanner and easily noticed due to their visibility in the sitting position, and, above all, prior knowledge of the experimenter regarding acupuncture. It was thus difficult to deceive experienced subjects by applying a needle only to the surface of the skin.

To overcome this constraint, we resorted to an alternative within-subject control paradigm to remove or change factors that might have originated from physical or physiological fluctuations. We used two consecutive 6-minute-long runs within each resting-state session (12 minutes total) prior to or after the acupuncture treatment. We split the sessions to eliminate brain regions that had at least one network coefficient that was different based on paired t tests between continuous runs.

Given the limitations regarding the controls, we are not yet in a position to make a conclusive statement regarding the effects of acupuncture on resting-state functional connectivity. Nevertheless, we can safely state that our data may lead to insight regarding the neural correlates of acupuncture at leg acupoints, as our findings exactly replicate those of a previous study on needle therapy for dysphagia8), and we measured corresponding changes in functional connectivity in the brain. The key finding here is that modulations in local structure rather than those in edge association strength might have a pivotal role in the neural plasticity following acupuncture. Almost all of the nodes displaying significant changes in graph theoretical coefficients represented brain areas considered to be selectively associated with acupuncture, pain, or somatosensory processing, and expressly, swallowing17-20). These regions are the insula, operculum, PreCG, PostCG, and accumbens. Our observations suggest that brain regions subject to graph structure changes are frequently identified in patients with supranuclear disorders.

Prior studies on acupuncture and brain imaging have shown that stimulation at ST36 with "De Qi" evokes neural activation in the insula, accumbens, vermis 6-8, cerebellum 2, and cerebellum 921). KI3 stimulation led to reinforcement of connections in the superior temporal gyrus and the PostCG, as indicated by Granger causality analysis22). Moreover, some regions pertaining to pain and somatosensory processing were found to be significant in our graph theoretical analysis. These regions were the insula, pars opercularis of the left IFG, PostCG, and accumbens. Under the same conditions, the insula, pars opercularis of the left IFG, PostCG, and PreCG have been shown to be crucial for the control of normal swallowing.

The above 17 regions, which were characterized by at least one significant change in graph coefficients, might be prominently involved in the paradigmatic system linking acupuncture and swallowing via pain and somatosensory processing. Among these regions, IFG oper l, Accumbens l, and Cereb9 r displayed significant changes in both clustering coefficient and local efficiency transition, although they did not have significant changes in vertex degree. Quite interestingly, the remaining 11 nodes, which persisted unaltered for both of the two network coefficients, had significant changes in degree, with the exception of the PostCG right.

This intriguing mutually exclusive relationship convincingly highlights the idea that acupuncture may lead to rewiring of areas pertaining to both acupuncture and swallowing, as indicated by resting-state connectivity changes. In other words, the acupuncture stimulation at ST36 and KI3 reinforces the neural response responsible for modulation in the direction of information integration, or what one calls the "smallworld" network structure of brain areas relevant to deglutition. The reason for this reinforcement in areas responsible for swallowing and its relevancy to the previously reported improvements in swallowing8) are yet to be determined. It is well acknowledged that the neural response to acupuncture is generated via signals transmitted through the pain conduction path and spread broadly in the brain. Likewise, in our experiment, a vague sensation may have ascended through the nerve system via the primordial receptor, and led to the induction of neural plasticity in regions subserving swallowing. We may assume that improvements in swallowing function (shortening of latency time) seen following acupuncture therapy8) might involve the network modulation observed in regions closely related to pain in addition to swallowing.

The nucleus accumbens, whose clustering coefficient and local efficiency were significantly increased as a part of a dopaminergic neural circuit, is presumably associated with swallowing, although it is distinct from the neural pathway involving substance P receptors 23,24). Our results highlight the presence of higher nervous control, which may involve cortical processes beyond reflexes. This is supported by the binding features of the operculum, insula, and motor cortex, which are recognized as loci for voluntary executive control. Brain areas with prominent connectivity changes were the same as those known to be involved in the physiological underpinning of swallowing disorder (concomitant with cerebrovascular accidents, known as opercular syndrome). It is also worth noting here that the cerebellum, which comprises some of the crucial nodes in our network analysis, plays a pivotal role in cocooperativity adjustment for swallowing via a close neuronal connection with the IFG. The acupuncture stimulus may thus give rise to a moderate network commutation in this path, as it affects the very structures of cortical and cortico-subcortical subgraphs in the resting-state connectivity of the brain.

5. Conclusions

In this study, we used resting-state functional connectivity MRI to analyse brain responses induced by acupuncture at KI3 and ST36. Differences in graph theoretical coefficients before and after the intervention were assessed to uncover effects on neural correlates that remained unchanged after unthreading the needle. Our findings were consistent with previous studies, although the most interesting finding was that the brain regions that displayed conspicuous rewiring in functional connectivity were well compatible with those recognized as responsible for swallowing. In the medical context encompassing acupuncture and dysphagia, the results of our study support the argument originally put forth by the previous report8) of successful treatment of dysphagia by stimuli at these acupuncture points.

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