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Immediate effects of noxious and innocuous thermal stimulation on brain activation in patients with stroke

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Abstract

Case-control studies have shown that noxious thermal stimulation (TS) can improve arm function in patients with stroke. However, the neural mechanisms underlying this improvement are largely unknown. We explored functional neural activation due to noxious and innocuous TS intervention applied to the paretic arm of patients with stroke. Sixteen participants with unilateral cortical infarctions were allocated to one of two groups: noxious TS (8 patients; temperature combination: hot pain 46°C to 47°C, cold pain 7°C–8°C) or innocuous TS (n = 8; temperature combination: hot 40°C–41°C, cold 20°C–21°C). All subjects underwent fMRI scanning before and after 30 min TS intervention and performed a finger tapping task with the affected hand. Immediate brain activation effects were assessed according to thermal type (noxious vs. innocuous TS) and time (pre-TS vs post-TS). Regions activated by noxious TS relative to innocuous TS ($P < .05$, adjusted for multiple comparisons) were related to motor performance and sensory function in the bilateral primary somatosensory cortices, anterior cingulate cortex, insula, thalamus, hippocampus and unilateral primary motor cortex, secondary somatosensory cortex at the contralateral side of lesion, and unilateral supplementary motor area at the ipsilateral side of lesion. Greater activation responses were observed in the side contralateral to the lesion, suggesting a significant intervention effect. Our preliminary findings suggest that noxious TS may induce neuroplastic changes unconstrained to the local area.

Trial registration: NCT01418404

Abbreviations: ACC = anterior cingulate cortex, AlphaSim = Alpha probability simulation, BI = Barthel index, fMRI = functional magnetic resonance imaging, *in*TS = *innocuous* TS, M1 = primary motor cortice, MAS = modified Ashworth scale, MNI = Montreal Neurological Institute, *n*TS = *noxious* TS, S1 = primary somatosensory cortex, S2 = secondary somatosensory cortex, SMA = supplementary motor area, TS = thermal stimulation, UE-Br = upper extremity Brunnstrom recovery stage.

Keywords: brain activity, functional magnetic resonance imaging, rehabilitation, stimulation, stroke

1. Introduction

Thermal stimulation (TS) is a simple, practical, and convenient approach used in rehabilitation clinics.[1–4] Because TS has been shown to induce cortical activation in healthy individuals and patients with stroke, it is now being utilized in stroke rehabilitation to facilitate the functional recovery of affected extremities.[5,6] Two randomized controlled clinical trials assessed using traditional rating scales, like the Fugl–Meyer Assessment and the Action Research Arm Test, as measures of the primary outcome have demonstrated that TS can improve arm function following stroke.[1,2] Although these measures assess motor impairment and provide relevant clinical information, they do not consider neuroplastic changes in the brain. To date, the neural mechanisms underlying improvement in motor function following TS in patients with stroke have not been investigated directly and remained largely unknown.

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique that allows functional exploration of the human brain, providing novel insights into the mechanisms of neurorehabilitation.[7] Previous fMRI studies have shown that TS activates the premotor and primary motor cortices (M1) of healthy participants.[8–10]The secondary somatosensory cortex (S2), posterior insular cortex, and premotor area are exclusively activated by noxious hot and cold TS but not innocuous hot and cold TS.[8] The brain regions activated by TS are common to those activated by the perception of pain produced by noxious hot or cold stimulation of the dorsum of the hand accompanying

Editor: Geun Hee Seol.

This study was approved by the ethics committee of the university hospital (KMUHIRB-2011-06-03(II)). All participants gave written informed consent before data collection began.

This study was supported by the grants from the National Health Research Institutes (NHRI-EX103-9907PI), the Ministry of Science and Technology (MOST 108-2314-B-037-078) and Kaohsiung Medical University Research Foundation (KMU-M105006, KMU-M106027 and KMU-M108012) in Taiwan.

The authors declare that there is no conflict of interest.

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How to cite this article: Chen SJ, Hsu MJ, Kuo YT, Lin RT, Lo SK, Lin JH. Immediate effects of noxious and innocuous thermal stimulation on brain activation in patients with stroke. Medicine 2020;99:9(e19386).

Received: 17 July 2019 / Received in final form: 23 January 2020 / Accepted: 27 January 2020

http://dx.doi.org/10.1097/MD.0000000000019386

more defined activation in the posterior region of the anterior cingulate cortex (ACC) and supplementary motor area (SMA),[9,10] both of which are associated with movement.[11] Therefore, noxious TS appears to promote greater motor-induced brain activation in healthy adults than innocuous TS.

These fMRI studies of healthy individuals suggest a possible mechanism for improvement in arm function in patients with stroke following noxious TS. Our team has revealed that TS is able to improve upper and lower extremity movement and function in patients with stroke after two month TS intervention (30 min/day and 3 days/week).[2,3] However, because the responses of brain activation to noxious TS may differ after stroke, research is needed to verify the generalizability of this theory. Hence, we performed a quasi-experimental study on immediate cortical changes due to noxious and innocuous TS intervention in patients with stroke. Functional imaging by fMRI was used to observe neuroplasticity in functional connectivity in the brain activation following TS.

2. Materials and methods

2.1. Participants

Patients with stroke receiving regular rehabilitation therapy were recruited from a medical center at our university hospital. The lesion location and clinical symptoms was confirmed by a clinical physician in the rehabilitation department. The inclusion criteria were:

(1) first ever ischemic stroke confirmed by computed tomography and/or MRI;
(2) unilateral hemiplegia;
(3) stroke onset more than 3 weeks and less than 8 months;
(4) no obvious cognitive deficit;
(5) able to sit on a chair independently for more than 30 minutes;
(6) willing to participate in this study and provide consent; and
(7) right handedness.

Patients who met any of the following criteria were excluded:

(1) skin injuries, burns, or fresh scars at the site of affected upper extremity or contraindications for thermal intervention;
(2) inability to follow commands due to aphasia;
(3) musculoskeletal or neuropathic diseases affecting the upper extremities;
(4) diabetic history or sensory impairment attributable to peripheral vascular disease or neuropathy;
(5) pacemaker or other metallic implants; and
(6) history of brain surgery.

Eligible subjects were randomly assigned to either the noxious TS group (*n*TS) or innocuous TS group (*in*TS) according to their order of entry into the study until an equal sample size per group was achieved. The research protocol was reviewed and approved by the ethics committee of the university hospital (KMUH-980318) and registered at https://clinicaltrials.gov (NCT01418404). All participants provided written informed consent.

2.2. Procedures

Demographic data, including age, gender, time in months after stroke onset, and lesion location, were obtained from the participants' medical records. Motor-related abilities were assessed by a well-trained physical therapist prior to study. The Brunnstrom recovery stage was determined to evaluate the motor control status of the affected upper extremity.[12] The modified Ashworth scale was used to assess the muscle tone of the affected elbow flexor.[13] The Barthel index was used to assess performance in activities of daily living.[14] After assessment, all patients performed a functional motor task during an fMRI scanning session, and thermal intervention with a specific temperature combination was performed between 2 fMRI scanning sessions. Figure 1 outlines the experimental procedure. To avoid any bias caused by low data quality due to patient

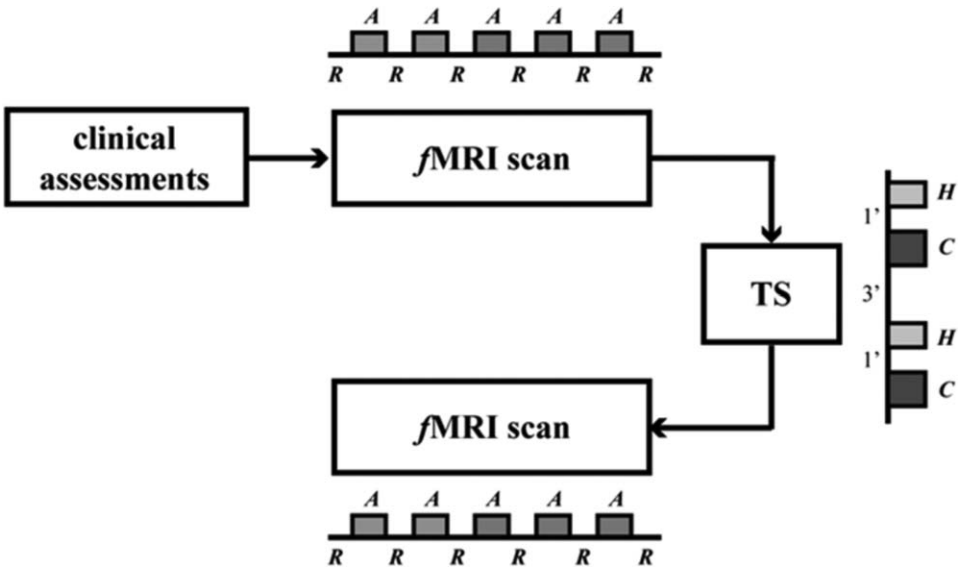

Figure 1. Flowchart of study protocol. This protocol includes four parts: (1) clinical assessment of motor performance and function using UE-Br, MAS, and BI; (2) fMRI scan before TS intervention for the finger tapping task; (3) TS intervention for the thermal application at the given temperature combination; and (4) fMRI scan after TS intervention for the finger tapping task. A, finger tapping; R, rest; H, hot; C, cold. BI = Barthel index, MAS = modified Ashworth scale, UE-Br = upper extremity Brunnstrom recovery stage.

fatigue, the whole experimental session was completed within 1 hour according to the sequence of a 5 minutes fMRI scan, 30 minutes of TS and another 5 minutes fMRI scan.

2.3. Intervention

A custom-made system was used to administer TS at constant temperatures. The closed-loop system consisted of 2 thermal stimulators (heater: FISTEK, Model-B300, Taiwan; cooler: Model-B401) and their respective flexible therapeutic pads ($38 \times 55\,cm^2$, TP22E, Gaymer Corp, USA) through an isolated plastic tube. The heater and cooler produced specific temperatures, designated according to the temperature assignment for each group. For the *n*TS group, the heater and cooler generated a hot pain temperature of 46°C to 47°C and a cold pain temperature of 7°C to 8°C, whereas in the *in*TS group, the temperature was at 40°C to 41°C and 20°C to 21°C, respectively. Details of TS intervention were given in a previous study[15] in which the TS trial procedure was modified, with alternating hot and cold TS. By manipulating the TS temperature contrast, brain activity can be evoked temporally. In the present study, each TS intervention cycle comprised 10 times of heating followed by 10 times of cooling after 1 minute rest through a therapeutic pad wrapped around the participant's affected forearm and hand. To prevent burns or frostbite, the maximum duration of one time was limited to 15 seconds for heating stimulation and 30 seconds for cooling stimulation.[1,2] As Figure 1 shows, one TS trial consisted of two alternating cycles of TS intervention with 3 minutes rest between cycles. One TS trial lasted approximately 30 minutes in total.

2.4. fMRI protocol and functional task

Each subject underwent fMRI scanning before and after TS intervention to assess cortical excitability caused by TS. Anatomical and functional images were acquired using a 3.0 T GE Signa HD scanner (Milwaukee, WI) equipped with a standard head coil. High-resolution ($1\,mm^3$), T_1-weighted, 3D anatomical images (3D-FSPGR sequence, TR = 6.72 ms, TE = 2.82 ms, FA = 12°) of the entire brain were acquired to identify appropriate landmarks and serve as a template upon which the functional images were superimposed. Functional images were collected based on fluctuations in blood oxygen level, termed blood oxygen level dependence, by the T_2-weighted gradient-echo sequence with an echo planar imaging protocol (2000 ms repetition time, 30 ms echo time, 90° flip angle, $22 \times 22\,cm^2$ field of view, 165 volumes, 28 slices per volume, 4 mm thickness per slice).

While lying in the MRI scanner, each subject performed a motor task for 5 minutes, consisting of alternative 30 seconds of finger tapping and 30 seconds of rest. During finger tapping, the thumb tapped each finger in turn at a pace of 1.5 Hz for 30 seconds. During rest, subjects were asked not to tap their fingers for 30 seconds. The whole task included 5 active periods of tapping and 6 control periods of rest. Two sets of fMRI data were acquired for each patient, one before and another after TS intervention. All data was imported into the statistical analysis system following data preprocessing and feature calculation of task-related functional connectivity.

2.5. Data analysis and functional connectivity calculation

Imaging data was preprocessed according to the fMRI data analysis guidelines conducted in the MATLAB (MathWorks) environment. The Data Processing and Analysis of Brain Imaging (DPABI, http://rfmri.org/DPABI) toolkit was used for data preprocessing and subsequent statistical analysis.[16] The general preprocessing included synchronizing the functional response over slices to the middle slice within a volume, correcting motion artifacts over the scanning period to the first volume, normalizing the data onto the spatially standardized Montreal Neurological Institute (MNI) head with an averaged template of 512 images, resampling the spatial resolution in $3 \times 3 \times 3\,mm^3$ voxel size, and spatially smoothing with a Gaussian kernel of 4 mm full-width at half maximum on the normalized data. Next, linear detrending of the time course was performed on the smoothed data to eliminate systematic magnetic field drift. To increase statistical power for group inference of the thermal effect, the images were flipped right-to-left if the lesion was located in the right hemisphere (7 of 16 subjects) before the data were preprocessed. All data passed the quality check for image registration, normalization, head coverage, and head motion, constrained within 2° of rotation and 2 mm translation distance.

Because hemodynamic dispersion between patients with stroke may reduce the reliability of functional assessment, performance in motor tasks was evaluated by a seed-based method based on endogenous connectivity of functional response to motor movement, with the time course of the given seed as the personal pattern of response to motor movement.[17] Later, functional connectivity was determined through correlation calculations (Pearson correlation coefficient method) between the time course of the predefined seed region and the time course of the remaining brain regions.[18] Seed-based functional connectivity features endogenous clustering of tissue characteristics because a functional unit in the brain should have a similar hemodynamic response to specific stimulation. Hence, regions belonging to the same functional unit are strongly correlated with the hemodynamic response of the seed region. A candidate seed at the contralateral primary motor cortex, assumed to be a left motor lesion for right hemiplegia, was predefined to calculate the connectivity of the motor-related network. This seed was located at (−39,−6, 51) on the MNI template, in the mass center of the left primary motor cortex, which is critical to functional recovery after M1 damage.[19] The reference time course associated with motor performance was determined by averaging the time course of a 5 mm radius around the seed.

Activated brain regions were extracted after thresholding the correlation intensity across voxels, which confined the statistical hypothesis ($P < .05$). An extra constraint on cluster size, Alpha probability simulation (AlphaSim), was used to correct wrongly clustered bias within clusters. This correction for activations within a cluster appears to generally multiple comparisons in case of the probability of a random field of noise, such as the activated voxels determined by the statistical threshold under the hypothesis of a distance length of activated voxels within 18 mm (about 4 voxels) with a 5% error tolerance of 1000 Monte Carlo simulation trials.

2.6. Statistical analysis

The Fisher exact test or Chi-square test was used to examine the group difference for nominal data such as items of gender, affected limb side, and infarction area. A Wilcoxon rank-sum test was used for interval data such as age, time since stroke onset, and motor behavior performance. For functional images, a between-group comparison was performed with two-way

analysis of variance to determine whether the immediate effect of TS was induced by two factors of TS-event (data acquired before and after TS, pre-TS and post-TS), TS-type (data acquired with noxious and innocuous TS, *n*TS and *in*TS), and their interaction. Within the statistical model, the levels of TS-event were assumed to have equal variance for the repeated measurements and the levels of TS-type were assumed to have approximately equal variance (after Levene test for homogeneity between groups) for the independent intervention types of temperature combination. The level of statistical significance was set at $P < .05$

3. Results

3.1. Patient characteristics

Of 46 patients admitted to our institution, a total of 16 participated in the study. Of these, 8 (3 males, 51.7 ± 8.7 years; 5 females, 67.8 ± 16.1 years) were assigned to the noxious group (*n*TS group) and 8 (6 males, 64.2 ± 10.2 years; 2 females, 70.0 ± 4.2 years) to the innocuous group (*in*TS group). No adverse events or side effects, such as burns, frostbites, and headaches, were reported during TS intervention or fMRI scanning. Table 1 presents the patients' demographics; most had mild disability with average Barthel index scores (19.3 ± 1.8 for *in*TS and 18.0 ± 2.3 for *n*TS). No significant between-group differences were found on demographic and clinical characteristics.

3.2. Functional response to thermal stimulation

Two-way ANOVA on the TS-event factor (with pre-TS and post-TS 2 levels) and TS-type factor (with *in*TS and *n*TS 2 levels) was performed to assess the immediate effect of thermal stimulation on brain activation. The resultant statistical maps are presented in Figure 2 and represent the affected degree of TS after thresholding of statistical significance ($F_{1,27} > 4.06$, $P < .05$) plus activating cluster size constraints (Monte Carlo simulation, clusters $\geqq$ 15 voxels, $P < .05$) and controlling according to a covariate of time since stroke onset. The main effect of TS-event (Fig. 2A) was observed in activated regions in the left primary somatosensory cortex (S1), left putamen, right angular gyrus, right middle frontal lobe, right secondary somatosensory cortex (S2), right primary motor cortex (M1), and right inferior-middle temporal lobe. The main effect of TS-type (Fig. 2B) was activation in both calcarine sulcus, both inferior-middle frontal lobes, both insula, both M1, both S1, both precunei, both superior-middle temporal lobes, the right middle-inferior occipital lobe, right parahippocampus, right S2, right orbital frontal cortex, right inferior temporal cortex, and left superior frontal lobe. Similar to the main effect of TS-event, not only was the contralateral M1 activated but also the contralateral S1, S2, and insula. Interestingly, greater activations were observed at the contralateral side of the lesioned left M1 more than the TS-event factor. Furthermore, significant interactive activations of TS-event and TS-type were also observed (Fig. 2C), involving regions mainly in the contralateral hemisphere of the lesion side. Bilateral activation was observed in the anterior-middle-posterior cingulate cortex, caudate nucleus, angular gyrus, superior-middle frontal cortex, inferior-middle occipital cortex, S1, precuneus, inferior temporal, and thalamus. Unilateral activation was only observed in the non-lesion right hemisphere, including the orbital frontal cortex, fusiform gyrus, hippocampus, parahippocampus, insula, lingual gyrus, superior occipital cortex, S2, M1, putamen, and superior-middle temporal cortex.

The scatterplots of 2 groups (*in*TS and *n*TS) as a function of signal changes of pre-TS and post-TS were plotted upon the aforementioned regions in Figure 3. As Figure 3A–C shows, a differentiable distribution of activated regions was presented between *in*TS and *n*TS groups. The dynamic range with greater eigenvalue (long axis in an elliptical shape) in the *n*TS group compared to the *in*TS group implied that the noxious TS might create greater functional provocation of cortical activation. These variant distributions were demonstrated later with a projected distribution of signal changes (Figure 3D–F), wherein the presented distribution was modified in the form of a normalized distribution according to the mean and standard deviation of samples. Moreover, with this information, the between-group comparisons for each examined effect were demonstrated as shown in Table 2 with univariate ANOVA followed by a Levene homogeneity test and controlled by a covariate with the baseline response at the pre-intervention state. In the three effects, the homogeneity between groups ranged from $P = .03$ to .17, indicating that the variation between two groups was not sufficient to proceed to model testing. The whole model tested for three effects showed a significant difference according to TS_type ($P < .01$) and interactive effect ($P < .01$), whereas differences for TS_event were not statistically significant ($P = .39$).

Table 1

Demographic and clinical characteristics of enrolled patients (*n* = 16).

	*in*TS (n = 8)	*n*TS (n = 8)	*P value*
Age	65.9 ± 9.4	58.8 ± 19.1	.52(W)
Gender (male/female)	6/2	3/5	.32(F)
Duration of onset (month)	4.5 ± 3.0	2.8 ± 2.1	.59(W)
Affected limb side (left/right)	5/3	4/4	1.00(F)
Infarction area Cortical/ subcortical/ brain stem	1/5/2	3/4/1	.48(χ^2)
UE-Br, distal part	5.7 ± 0.5	5.6 ± 0.5	.60(W)
MAS	0.3 ± 0.5	0.4 ± 0.5	.60(W)
BI	19.3 ± 1.8	18.0 ± 2.3	.27(W)

χ^2 = Chi-square test, F = Fisher exact test, W = Wilcoxon rank-sum test.
BI = Barthel index, *in*TS = Innocuous thermal intervention group, MAS = modified Ashworth scale, *n*TS = Noxious thermal intervention group, UE-Br = upper extremity Brunnstrom recovery stage.

4. Discussion

To the best of our knowledge, this is the first study to provide insights into the understanding of the immediate effects of TS on neuroplasticity in patients with stroke. We demonstrated that 30 minutes of noxious TS intervention to the paretic hand immediately enhanced corticomotor excitability, consistent with previous studies on healthy participants.[9,10] Noxious TS intervention promoted broader brain activation relative to innocuous TS, and also caused greater signal change accompanying the manipulation of motor tasks. Simultaneous activation of many brain areas may have helped trigger sensorimotor interactions, promoting the desired rewiring of brain function[8,20] and facilitating the functional recovery.[1,2]

Many regions were activated and presented varying significance in 3 effects of thermal-associated factors, involving ipsilateral non-lesion or bilateral mid-cerebellar activations through nociceptive processing in pain perception. First, the effect of TS_type factor indicated that greater temperature contrast in TS intervention mainly induced ipsilateral activations of the affected hand in the inferior-middle frontal cortex,

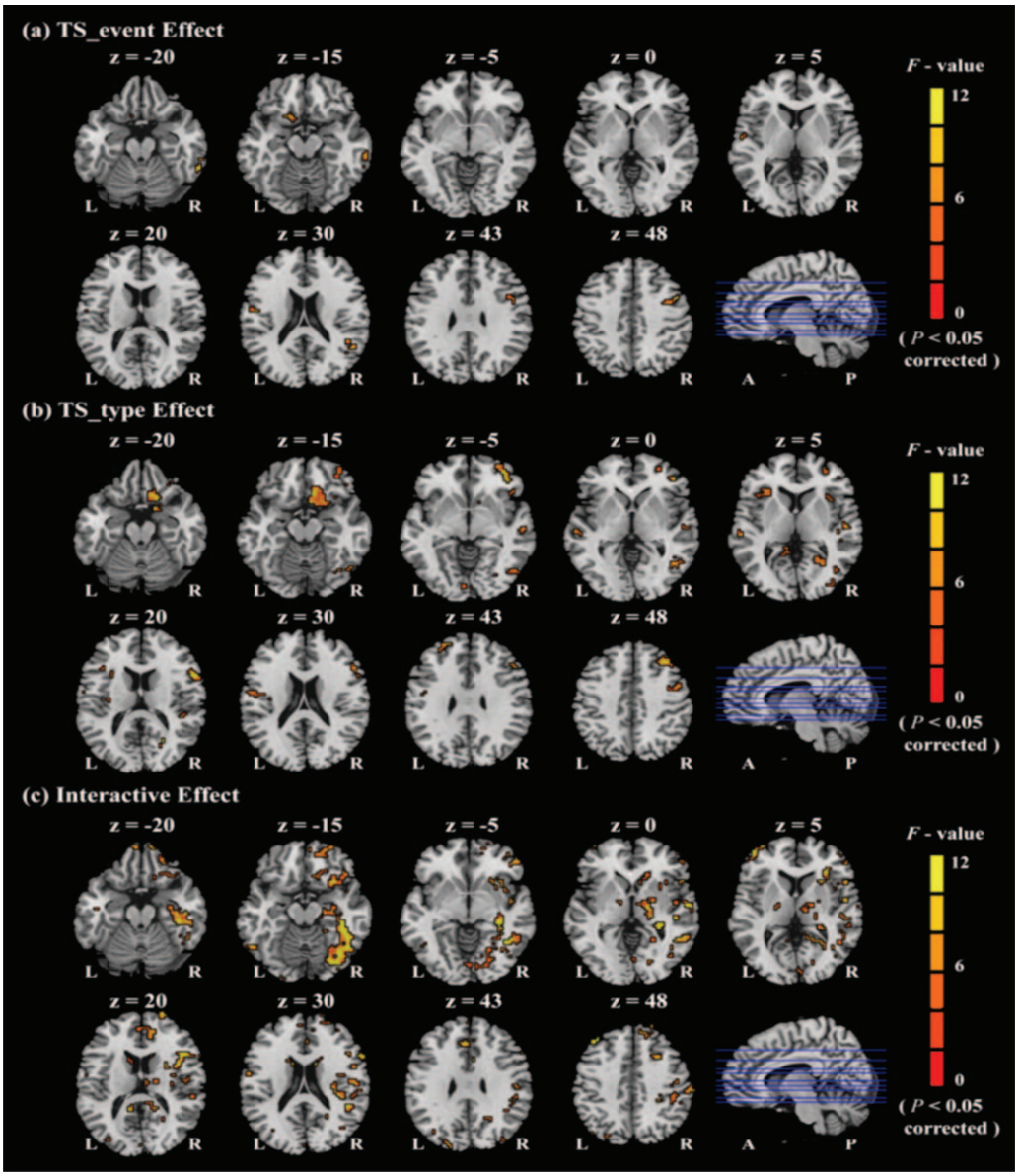

Figure 2. Activation map after two-way ANOVA. Variance analysis consisted of two factors (TS_event and TS_type) and a controlled covariate (time since stroke onset). (A) The main effect of TS_event was determined by contrasting pre- and post-TS between the 2 TS groups. (B) The main effect of TS_type was tested by contrasting *n*TS and *in*TS over two sessions. (C) The interaction effect of TS_event and TS_type was examined to determine whether TS interventions were effective due to the thermal combination. Clusters were selected according to a *P* value = .05 and the extra constraint of cluster size ($P < .05$). *in*TS = innocuous TS, *n*TS = noxious TS.

superior-middle temporal cortex, insula, M1 and S1, which direct two functional pathways. One, the emotional and/or sensory integration circuit, is distributed along with the ventral side of brain, and the other, the arousal and/or motor planning circuit, is directed to dorsal side of brain. This phenomenon is in accordance with the outcomes of previous studies[8,21,22] and supports the idea that thermal effects can promote brain excitability; whereas the innocuous TS brings out nonsignificant cortical excitability. Second, similar activation distribution was found in the effect of TS_event factor but less activation was distributed in the ipsilateral hemisphere of the paretic hand, compared to the situation in the effect of the TS_type. From the distribution comparison of motivated activation, the cortical excitability would be evoked bilaterally by TS and noxious TS is much better to promote the excitability on the ipsilateral hemisphere of the paretic hand. This alteration reflected its immediate influence on thermal neuronal response through TS application and temperature manipulation. Third, the examination of the interactive effect facilitated to confirm the crossover influence by two factors. The influenced cortical regions were prominently observed in both aforementioned directions and also the arousal-associated system, including bilateral ACCs and thalami. Notably, all of these regions are integrated into the pain sensation circuit of the medial-lateral-thalamus pathway,[22] involving in the nociceptive circuits of pain-related perception. Fourth, a consistent activation at the contralateral M1 of lesioned hemisphere was observed across the three significant effects. This contralateral promotion of cortical function has not been defined

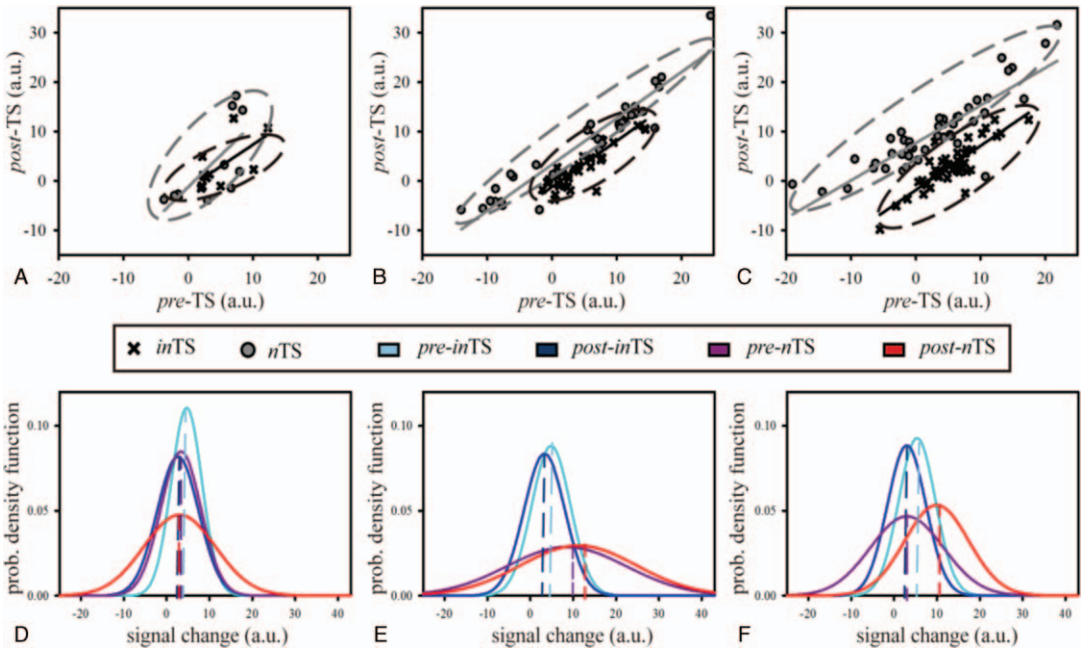

Figure 3. Scatterplot and histogram over the three effects of two-way ANOVA. (A)–(C) Scatterplots of post-TS vs pre-TS as the function of signal change compared to the basement for the main effect of TS_event, main effect of TS_type, and their interactive effect. ×, *in*TS; ○, *n*TS. (D)–(F) Histograms of 2 temperature combinations of TS for the 3 effects. The dashed line shows the location measure. *in*TS = innocuous TS, *n*TS = noxious TS.

in healthy subjects[8–10] but has been observed in the present study, which might explain neuronal plasticity to the contralateral side of lesion for patients with stroke.[7,23,24] The extent evidence provided as the distribution of signal changes across all activated regions also showed differentiation between the two TS temperature combinations.

After the calculation of eigenvalue and the statistical examination of signal changes, we found that noxious TS possessed greater range in functional alteration (with longer axis of regional distribution) and greater functional promotion (with higher mean value of distribution) than the innocuous TS condition. This influence caused by TS was also supported by the behavior observation of motor performance in previous study.[2,3]

TS drove functional response via the thermal-pain sensation pathway in the lateral and medial pain system.[22] It has been previously reported that noxious TS promotes excitability mainly in motor-related areas, such as M1, S1, and SMA, via the medial-thalamus pathway,[8,21] while innocuous TS motivates a strong thermal sensory response in the thalamus, insula, and S2 via the lateral-thalamus pathway.[8] Moreover, with consideration of noxious and innocuous thermal together, activations in the middle-inferior frontal cortex, ACC, and midbrain are driven.[25] Although the underlying of brain response to thermal manipulation is not clear, we have observed these thermal-associated responses through manipulation of hot and cold temperature combination. This phenomenon implies that noxious TS stimulated activity in both pain system pathways in patients with stroke to rewire motor function.[26,27] Interestingly, attention-related activation of the ACC and caudate were evoked by alternative TS between hot and cold pain temperature such as noxious TS design in this study. On the other hand, the activated responses occurred in multiple areas in the contralateral hemisphere of lesion, potentially pointing to functional compensation from the impairment of lesion hemisphere. Our result provided a possible approach to understand brain responsive underlying of TS for patients with stroke' neurorehabilitation. Future research should approach to quantify the influence of TS on the functional plasticity by manipulating a varying applied duration and the thermal intensity.

The thermal-induced brain activation is possibly achieved through a lasted stimulation in the somatosensory pathway in our

Table 2

Between-group comparisons for thermal-associated effects with ANOVA univariate analysis.

	*in*TS		*n*TS			
	Pre	Post	Pre	Post	Levene*	Statistics†
TS_event	4.68 ± 3.60	2.63 ± 4.87	3.34 ± 4.70	3.04 ± 8.38	0.17	.39
TS_type	4.85 ± 4.52	3.31 ± 4.77	8.47 ± 13.92	11.24 ± 13.53	0.03	< .01
Interactive	5.56 ± 4.23	3.10 ± 4.40	3.18 ± 8.33	10.22 ± 7.29	0.05	< .01

The cells in each condition were presented with the (mean ± standard deviation) value of group performance.

* homeogenesis test with Levene test.

† univariate analysis controlled by the *pre*-TS data with ANOVA.

*in*TS = Innocuous thermal intervention group, *n*TS = Noxious thermal intervention group.

assumption. Somatosensory stimulation such as electrical stimulation of the nerve afferents of the hand is known to elicit an increase in the corticomotor excitability of the body part representations that control the stimulated body part, resulting in reorganization of the motor and somatosensory cortices.[28,29] Previous studies have indicated that somatosensory stimulation leads to specific task-related increases in fMRI response in cortical areas such as the M1, S1, and S2 that outlast the stimulation period.[11,28,30] It was inferred that S1 receives direct input from the stimulated hand and has direct anatomic projections to the M1, premotor area, and S2.[28,30] These projections modulate neuronal activity in the M1 and associated areas, providing a likely anatomic substrate for the effects described in animal studies.[31,32] Thermal-induced brain activation has observed in the contralateral and ipsilateral activity of lesion and shares similarities to mechanisms implicated as relevant for reorganizational processes for functional recovery after stroke.[33] The effect of noxious TS on M1 increased the excitability of the motor cortical representations that may control muscle movement of the stimulated body part, possibly through modulation of GABAergic neurotransmission and long-term potentiation-like processes.[34,35] A study revealed that heat sensitivity in somatosensory neurons was triggered by permutation of the TRPM2 ion channel,[36] which may explain why thermal response is directly linked to motor action. Although we had presented the brain activation caused by thermal stimulation, a further causal relationship between influenced regions is necessary to validate the role of regions in the pain perception. Taken together, our findings help elucidate that the underlying mechanisms associated with improvement in arm function by noxious TS in patients with stroke might be rewired through the neuronal compensation by the non-lesion side.

This study is subject to 3 main limitations. First, we only considered the immediate effects of TS on brain activation in patients with stroke. However, whether the functional reorganization caused by TS is specific to patients with stroke or is a general phenomenon in elderly individuals requires further research. Second, sample selection was limited to patients with ischemic stroke hospitalized at a medical center; therefore, the results may not be generalizable to a broader stroke population or to all thermal-based interventions. Third, the aftereffects of TS require further study to quantify the influence of neuroplasticity.

5. Conclusions

Our preliminary results indicated that 30 minutes of noxious TS intervention not only promoted immediate brain activation in the lesioned hemisphere but also induced functional compensation to the contralateral hemisphere of the lesion and evoked extra activities in the arousal system. These findings suggest that thermal intervention combined with high temperature contrast of hot and cold thermal such as noxious TS situation in our work may induce neuroplastic changes that would facilitate the neurorehabilitation of patients with stroke.

Acknowledgments

The authors thank the Statistical Analysis Laboratory, Department of Medical Imaging, Kaohsiung Medical University Hospital, and Kaohsiung Medical University for their help.

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