

# Clinical effect of unilateral transcranial magnetic resonance-guided focused ultrasound thalamotomy in patients with essential tremor as evaluated by functional near-infrared spectroscopy

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## Research article

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# Abstract

**Background:** Transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) surgery is a noninvasive thermal ablation therapy for neurological conditions such as essential tremor (ET). However, most studies on the therapeutic mechanisms of this technique are limited to the visualization of brain structure and network activities with resting state functional magnetic resonance imaging. We aimed to investigate the effect of tcMRgFUS on the cortical level of the motor network using functional near-infrared spectroscopy (fNIRS).

**Results:** Two sample paired t-tests revealed that only channel 6 (left primary motor and somatosensory cortices), and channel 45 (right dorsolateral prefrontal cortex) were significantly activated in the writing task after MRgFUS treatment compared to the task before MRgFUS treatment (CH6:  $t(6) = 3.42$ ,  $p < 0.05$ , Cohen's  $d = 1.29$ ; CH45:  $t(6) = 2.47$ ,  $p < 0.05$ , Cohen's  $d = 0.93$ ).

**Conclusions:** We identified changes in relevant cortical activity after surgery and found that fNIRS can provide an important supplement to objective assessment of the clinical efficacy of tcMRgFUS.

## Background

Essential tremor (ET), the most common movement disorder[1]. At present, the drugs commonly used for the treatment of ET include primidone, propranolol, and arotinolol. Up to 30% of patients with tremors show poor response to first line drugs and are considered to have medically intractable ET[2], which necessitates surgical treatments such as stereotactic radiofrequency ablation, deep brain stimulation, radiosurgery, and transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) surgery[3]. tcMRgFUS is an emerging non-invasive thalamus ablation technology for the treatment of ET with immediate postoperative clinical effects. tcMRgFUS often chooses the ventral intermediate nucleus (VIM) of the thalamus as a target for the treatment of ET[4]. The VIM nucleus of the thalamus receives the output of the cerebellar dentate nucleus and projects to the motor cortex[5]. Therefore, the thalamic VIM nucleus, as a node involved in the tremor motor network, is expected to have an impact on the cortical level after ablation. The aim of this study was to investigate the effect of ablation of VIM nucleus on the cortical level of the motor network using tcMRgFUS, clinical rating scale for tremor, and functional near-infrared spectroscopy (fNIRS).

## Results

### *CRST score*

Seven patients were evaluated before and 1 and 3 months after tcMRgFUS. The result of scoring was shown as mean  $\pm$  standard deviation. Part A score of CRST (before tcMRgFUS:  $17.1 \pm 3.35$ ; 1 month after tcMRgFUS:  $6.7 \pm 2.7$ ; 3 months after tcMRgFUS:  $6.7 \pm 4.35$ ), Part B score of CRST (before tcMRgFUS:  $25.2 \pm 6.78$ ; 1 month after tcMRgFUS:  $10.9 \pm 8.32$ ; 3 months after tcMRgFUS:  $10.9 \pm 7.32$ ), Part C score of CRST (before tcMRgFUS:  $16 \pm 2.63$ ; 1 month after tcMRgFUS:  $1.2 \pm 1.83$ ; 3 months after tcMRgFUS:

1.2±2.41), and total score of CRST (before tcMRgFUS: 58.3±10.59; 1 month after tcMRgFUS: 18.8±12.14; 3 months after tcMRgFUS: 18.8±13.46). Details are shown in Table 1.

### *Activation Maps*

One sample t-test maps of task-related  $\beta$  values for the three kinds of tasks before and after tcMRgFUS treatment showed that, compared to resting-state condition, cortical activity was significantly increased only in the writing task after tcMRgFUS treatment (**Figure 2**). In particular, the cortical activation map showed statistically significant differences in the right dorsolateral prefrontal cortex (rDLPFC), the left primary motor cortex (LM1), and the left primary somatosensory cortex (LS1) during the right hand writing task after tcMRgFUS treatment compared with baseline (channel CH 6:  $t(6) = 6.58$ ,  $p < 0.01$ , FDR corrected; CH8:  $t(6) = 7.47$ ,  $p < 0.01$ , FDR corrected; CH19:  $t(6) = 6.44$ ,  $p < 0.01$ , FDR corrected; CH28:  $t(6) = 6.30$ ,  $p < 0.01$ , FDR corrected but data were poor quality in Participants 5 and 6; CH29:  $t(6) = 4.87$ ,  $p < 0.05$ , FDR corrected but data were poor quality in Participants 5 and 6; CH45:  $t(6) = 4.81$ ,  $p < 0.05$ , FDR corrected). No channel was found to be dramatically activated in the nose pointing with right hand task before or after tcMRgFUS treatment, or the right hand writing task before tcMRgFUS treatment (all:  $p > 0.05$ , FDR corrected).

### *Comparison of activation*

Two sample paired t-tests revealed that only CH6 (which roughly covered LM1 and LS1), and CH45 (which covered rDLPFC) were significantly activated in the writing task after tcMRgFUS treatment compared to the task before tcMRgFUS treatment (**Figure 3**; CH6:  $t(6) = 3.42$ ,  $p < 0.05$ , Cohen's  $d = 1.29$ ; CH45:  $t(6) = 2.47$ ,  $p < 0.05$ , Cohen's  $d = 0.93$ ).

### *Correlation between brain activity and clinical manifestation*

Spearman's rank correlation coefficient was only calculated for CH6 and CH45 in the writing task since these were the only channels and only task with significant activation. The correlation between  $\Delta\beta$  and  $|\Delta\text{CRST-B}|$  in CH45 was significant (**Figure 4**; CH45:  $\rho_1 = -0.464$ ,  $p > 0.05$ ;  $\rho_3 = -0.955$ ,  $p < 0.001$ ), meaning that decreased activation increase in response to decreased tremor in the writing task. There was no significant correlation between  $\Delta\beta$  and  $|\Delta\text{CRST-B}|$  in CH6.

## **Discussion**

Assessing brain activity during motion tasks can shed light on the pathophysiology of ET[6-8]. However, the limited space and motion amplitude in resting state functional MRI machines (the most common method of investigating tremor) may not suffice to capture the severity of tremor in patients with ET[9], and the tasks used in functional MRI are usually not complicated enough to represent typical daily manual activities[8]. Additionally, functional MRI requires that the patient's head be fixed as much as possible during scanning, which makes MRI examination of ET patients more difficult, and the examination results are less reliable. NIRS, which reflects the neuronal activities in the cerebral cortex

based on neurovascular coupling, has the advantage of being noninvasive, immediate, continuous, portable, and interference-free during measurement as compared with functional MRI[10], which enables analysis of patients' functional recovery during their daily activities. In our study, patients showed tremors during the finger-to-nose task (both hands) and writing task before surgery which almost completely disappeared after tcMRgFUS thalamotomy.

Despite this reduction in tremor after surgery, fNIRS examination of brain activity showed significant cortical activation only in the writing task after tcMRgFUS thalamotomy. This finding was confirmed by the examination of healthy controls. There are several reasons that may explain this result.

Methodologically, our analyses were based on patients in motion state rather than in resting state, during which the postural score effect is less than the motion scoring effect. Additionally, the finger-to-nose task (detecting intention tremor) involves only the elbow joints while the writing task (detecting the patient's daily functioning) involves multiple joints such as shoulders, elbows, wrists, and fingers. Based on the results in this study, fNIRS with a lower spatial resolution but a higher time resolution has unique advantages in detecting the brain activities during performing complex tasks compared with the common MRI-based tremor assessment tasks such as finger tapping, finger bending, and hand grasping[11].

In our study, there was significant activation in LM1, LS1, and rDLPFC (consistent with previous literature) during the postoperative writing task. There is evidence that the DLPFC contributes to the skilled grasping motion of hands, mainly reflected in control and prediction[12, 13]. Moreover, DLPFC activity is associated with parallel behavioral factors such as spatial attention, short-term memory of tactile information, choice of motor responses, and concentrative and automatic monitoring of motor performance. Increased DLPFC activation and enhanced motor control and trajectory prediction may be responsible for the fluent writing in our postoperative patients. Additionally, activation increased as the tremor decreased (as measured by CRST) during writing. Collectively, these results suggest that fNIRS can be combined with the CRST scale to provide objective indices for a postoperative patient's recovery.

However, there were also some significant limitations. First, the sample size was small, and it is necessary to conduct studies with larger sample sizes, especially for prognostic analysis in a clinical setting. Second, it is impossible to use the current fNIRS system to study the activities of subcortical regions (such as the basal ganglia) to detect changes in the fibrotic connectivity and cerebellar activation, or to detect changes in neural activation patterns which are potentially associated with the final improvement in clinical symptoms. Third, the fNIRS system can provide patients with real time visual feedback of cortical activities (the occipital cortex, occipital pole, and lingual gyrus play important roles in visual information processing). However, visual feedback was not monitored in this experiment due to lack of channel coverage.

## Conclusion

The cortical activities in ET patients before and after tcMRgFUS were evaluated using fNIRS, which showed the changes in relevant cortical activities after surgery. fNIRS, which is non-invasive, holds

promise for precise assessment of motor function in patients diagnosed with movement disorders after invasive treatment such as deep brain stimulation, radiosurgery, ultrasound thalamotomy, and stereotactic radiofrequency ablation.

## Methods

### *Participants and study criteria*

7 patients with ET (right hand, 5 males and 2 females), with a mean age of  $63 \pm 4.24$  years underwent successful unilateral tcMRgFUS VIM nucleus thalamotomy. The inclusion criteria were age 22 years or more (male or female); diagnosis of ET by neurologists or neurosurgeons specialized in movement disorders according to relevant diagnostic criteria; history of oral administration of antitremor drugs, medically intractable manifestations such as poor response to medications, and intolerance to medications due to adverse reactions; good communication skills; a postural or intention tremor score for the dominant hand/arm of two or more as assessed by the clinical rating scale for tremor (CRST); functional disorders in daily life due to ET (a score of  $\geq 2$  for any item in Part C of the CRST); capability to receive computed tomography (CT) and magnetic resonance imaging (MRI) examinations and an appropriate skull density ratio; agreement on enrollment by two study staff after assessment.

The exclusion criteria were as follows: severe functional disorders in the heart, liver, kidney, or blood coagulation; alcohol or drug abuse; active infection or compromised immunity; history of intracranial hemorrhage, cerebrovascular disease, brain tumor, epilepsy, or other brain diseases; other neurodegenerative diseases; intolerance to holding the supine position for a long time; obvious cognitive impairments; mental illnesses or history of mental illnesses; pregnancy or lactation; previous deep brain stimulation or stereotactic ablation; injection of kreotoxin in the arm, neck, or face within five months before baseline; an overall skull density ratio of 0.3 ( $\pm 0.05$ ) or less (calculated by cranial CT); other incompatible conditions contraindications for CT or MRI examinations. Both fNIRS and CRST scores were determined after pharmacokinetic depletion of oral drugs *in vivo*.

The study was approved by the Ethics Committee of the Chinese Peoples Liberation Army General Hospital (Ethics Committee Approval No.: 2018 LUNSHEN No. 021, 2018 LUNSHEN No. 021-1), and written informed consent was obtained from all participants.

### *Clinical assessment*

The CRST was used to assess tremor symptoms before and after treatment. The CRST is divided into three parts: Part A to assess resting state, postural, and intention tremors; Part B related to the functional assessment during writing and pouring liquids; and Part C to assess life and social activity dysfunction. The scale is designed with a total score of 160; the higher the score, the more severe the tremor. The scoring was performed by two experienced neurologists.

### *Functional imaging experiment*

The patients underwent fNIRS during a finger-to-nose task (both hands, two separate tasks) and dominant hand (right) writing task 24 h before treatment and 1 month after treatment. The patients were prompted to switch from resting state to performing the task. A 3-min break was allowed between resting and task performing states. Participants were informed of the motion tasks they had to complete before each experiment.

### *fNIRS data acquisition*

A 52-channel continuous wave fNIRS system (ETG-4100 Optical Topography System; Hitachi Medical Co., Japan) with a sampling rate of 10 Hz was used to collect the optical absorption of near infrared light at two wavelengths (695 nm and 830 nm) from seven patients. We aimed to primarily measure cortical activation in the dorsolateral prefrontal cortex, primary motor area, primary somatosensory area, and premotor and supplementary area. The setup of the optode probe is shown in **Figure 1**.

### *Statistical analysis of fNIRS signal*

We used NIRS-SPM version 4.1[14] to calculate the activation maps of oxyhemoglobin (OxyHb) which has been reported to be the most sensitive indicator of regional cerebral blood flow[15] and to have a robust correlation with the BOLD signal[16, 17]. Individual analysis of fNIRS data started with the modified Beer – Lambert law in order to transfer optical density variation to the changes in concentration of OxyHb[18]. Spatial registration of channel locations was conducted based on the real coordinates of references (i.e., nasion, the pre auricular points anterior to the left and right ears, inion, Cz), optodes, and channels obtained from the 3D digitizer. After data preparation, a high-pass filter method (wavelet minimum description length detrending algorithm) was employed for the tasks of pointing to the nose with the right hand and writing to eliminate the existing global drifts of optical signal measurements due to respiration, vasomotion, blood pressure variation, movements during the experiments, instrumental instability, or other experimental errors[19]. Then, a low-pass filter (hemodynamic response function) was used in order to smooth the data to attenuate high frequency components. Next, a general linear model were used to compute parameter estimates, that is, task-related  $\beta$ -values as the model's weights:

$$Y = \beta X + \epsilon$$

Y represents a  $N \times M$  matrix of the measured fNIRS data after preprocessing (N means the number of time points; while M means the number of channels); X represents a  $N \times W$  design matrix composed by W-regressors;  $\beta$  represents a  $W \times M$  regression coefficients matrix indicating the contribution of each regressor to Y;  $\epsilon$  represents a  $N \times M$  error matrix that was not able to explain by the model.

For the fNIRS group analysis, a one sample t-test was applied on the task-related  $\beta$  value for each channel across all the ET patients so as to calculate the activation difference between each task and the corresponding resting state condition. To avoid false positives because of multichannel comparison, p values were corrected by false discovery rate (p-value corrected by false discovery rate [FDR] < 0.05).

Next, t-test maps of the activation increase which were smoothed using the spline method were generated using the plotTopoMap tool (<http://www.alivelearn.net/wp-content/uploads/2011/04/plottopomap.m>).

We visualized all the t-test results using the nirs2img function in the xjview toolbox to convert the t-test values of each channel to its corresponding Montreal Neurological Institute coordinates on an image file (<http://www.alivelearn.net/xjview8/>). Then, we applied the BrainNet Viewer toolbox (<http://www.nitrc.org/projects/bnv/>) [20] to project the channel position with its t-test value to the cortical surface using that image file. Finally, for those channels with a significant activation increase after one-sample t-test, we used two sample paired t-tests to compare task-related  $\beta$  values after tcMRgFUS with the task-related  $\beta$  values before tcMRgFUS.

### *Correlation analysis between brain activity and clinical manifestations*

In order to examine the relationship between brain activity and clinical manifestations, for those channels with significant activation increase, Spearman's rank correlation coefficient ( $\rho$ ) was calculated between the task related  $\beta$  value after tcMRgFUS treatment minus the task related  $\beta$  value before tcMRgFUS treatment ( $\Delta\beta$ ) and the score change between CRST testing before and after tcMRgFUS treatment ( $|\Delta\text{CRST-B}|$ ). CRST testing after treatment was measured twice: one month after tcMRgFUS treatment, and again three months after tcMRgFUS treatment.

## **Abbreviations**

CRST - clinical rating scale for tremor

CT - computed tomography

ET - essential tremor

FDR - false discovery rate

fNIRS - functional near-infrared spectroscopy

LM1- left primary motor cortex

LS1 - primary somatosensory cortex

MRgFUS - transcranial magnetic resonance-guided focused ultrasound

MRI - magnetic resonance imaging

OxyHb - oxyhemoglobin

rDLPFC - right dorsolateral prefrontal cortex

VIM - ventral intermediate nucleus

$|\Delta\text{CRST-B}|$  - score change between CRST testing before and after MRgFUS treatment

$\Delta\beta$  - the task related  $\beta$  value after MRgFUS treatment minus the task related  $\beta$  value before MRgFUS treatment

## Declarations

### Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Chinese Peoples Liberation Army General Hospital , and written informed consent was obtained from all participants.

### Consent for publication

Consent granted.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests

### Funding

None.

### Authors' contributions

XG.Y., R.Z. and LS.P.conceived and designed experiments. R.Z.and DS.K. performed the experiments. DS.K.and TY.Z.analyzed the data.DS.K.and TY.Z.wrote the paper.

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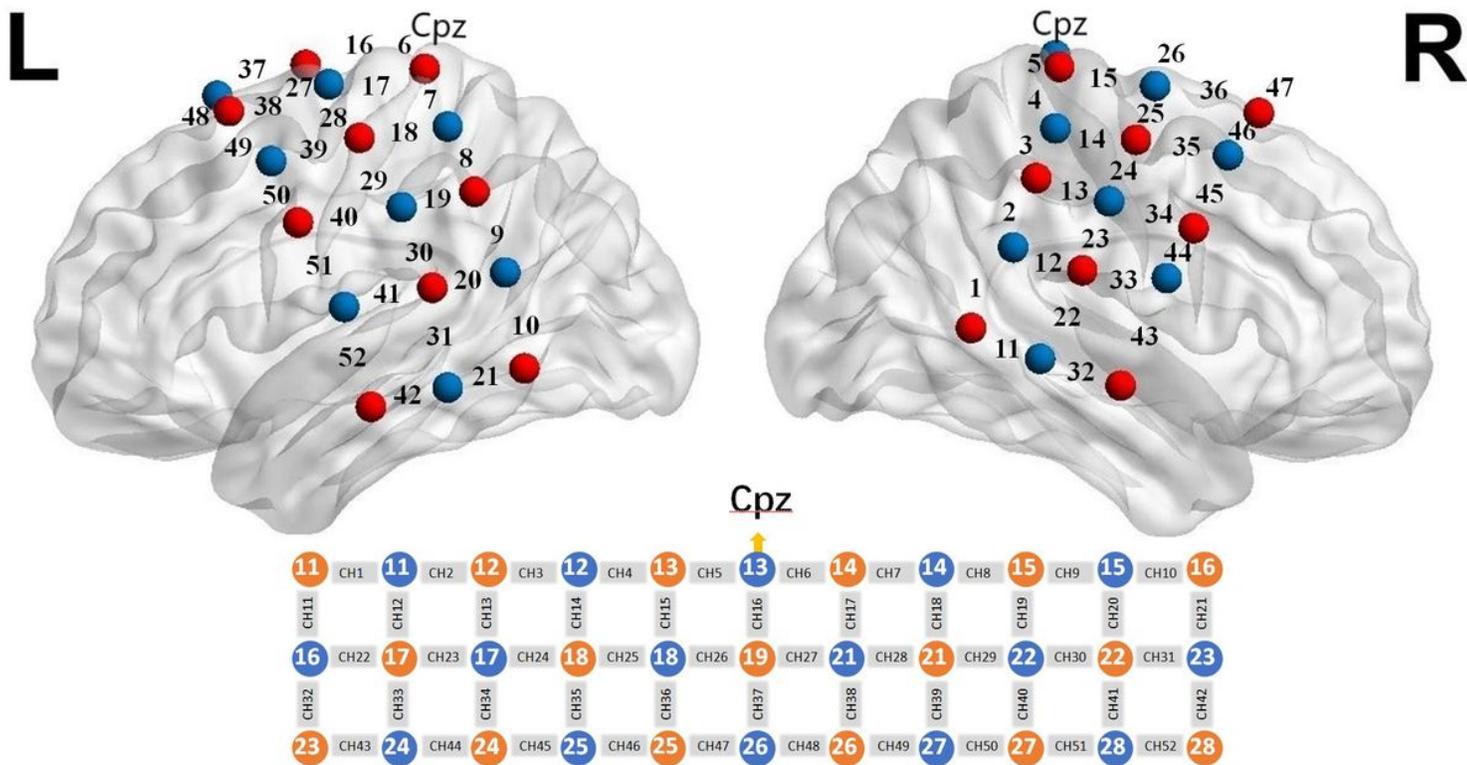
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## Table

**Table 1.** Demographic data & CRST of enrolled patients

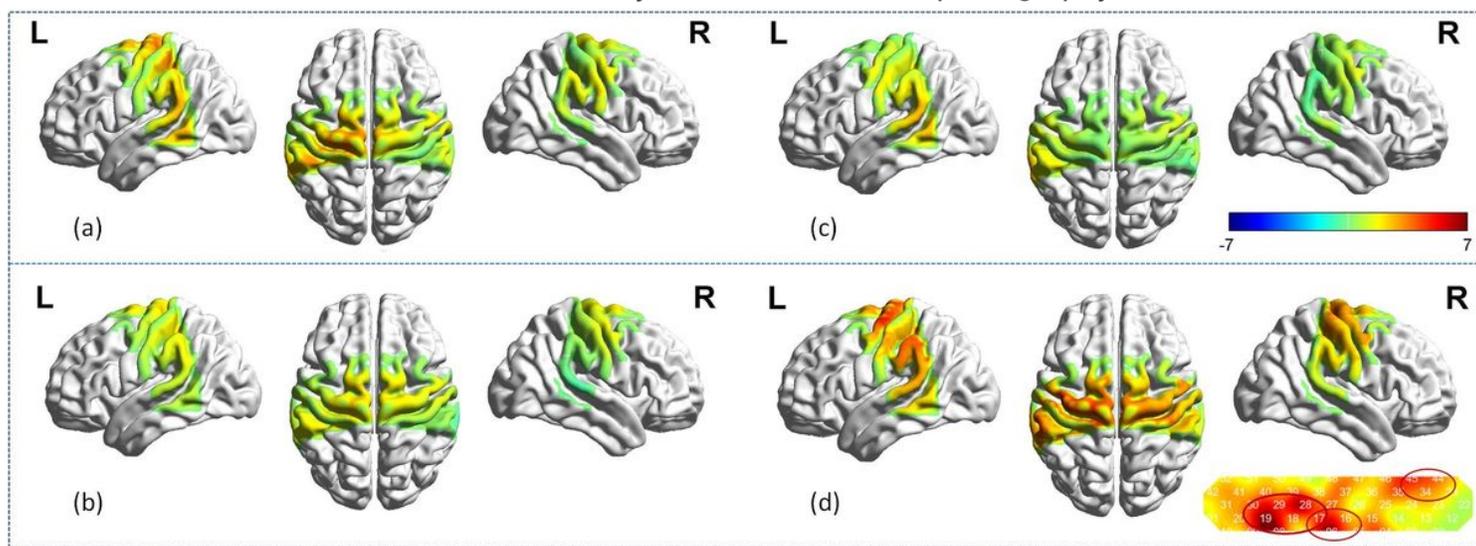
number	Age (yrs),sex	BASELINE				1M				3M			
		A	B	C	TOTAL	A	B	C	TOTAL	A	B	C	TOTAL
1	58,M	11	21	18	50	4	3	0	7	1	2	2	5
2	60,F	18	26	12	56	3	5	1	9	1	9	0	10
3	59,M	17	28	18	63	9	11	1	21	9	15	2	26
4	64,M	16	20	16	52	6	7	0	13	5	8	1	14
5	62,M	19	27	20	66	8	7	0	15	10	16	1	27
6	70,M	18	36	18	72	9	26	5	40	10	25	7	42
7	68,F	11	15	15	41	3	1	0	4	1	6	0	7

## Figures



**Figure 1**

Optode probe setup. A single 3 × 11 optode probe set with 17 emitters (red dots) and 16 detector probes (blue dots) positioned in an alternating array was attached to each participant's head. The interoptode distance was 3 cm so that neural activities approximately 1.5–2.5 cm beneath the scalp were measured. To ensure consistency of optode placement across ET patients, Cpz was located at midpoint of the lowest row of the fiber holder, and the rows of the fiber holder were perpendicular to the nasion–inion line in accordance with the international 10–20 system for electroencephalography.



**Figure 2**

fNIRS activation maps. One sample t-test maps of task related  $\beta$  values for the three kinds of tasks before and after tcMRgFUS treatment, respectively. (a) One sample t-test maps during the nose pointing with right hand task before tcMRgFUS treatment compared to baseline. (b) One sample t-test maps during the right hand writing task before tcMRgFUS treatment compared to baseline. (c) One sample t-test maps during the nose pointing with right hand task after tcMRgFUS treatment compared to baseline. (d) One sample t-test maps during the right hand writing task after tcMRgFUS treatment compared to baseline. The red ellipses circle the serial number of the significant channel in the t-map.

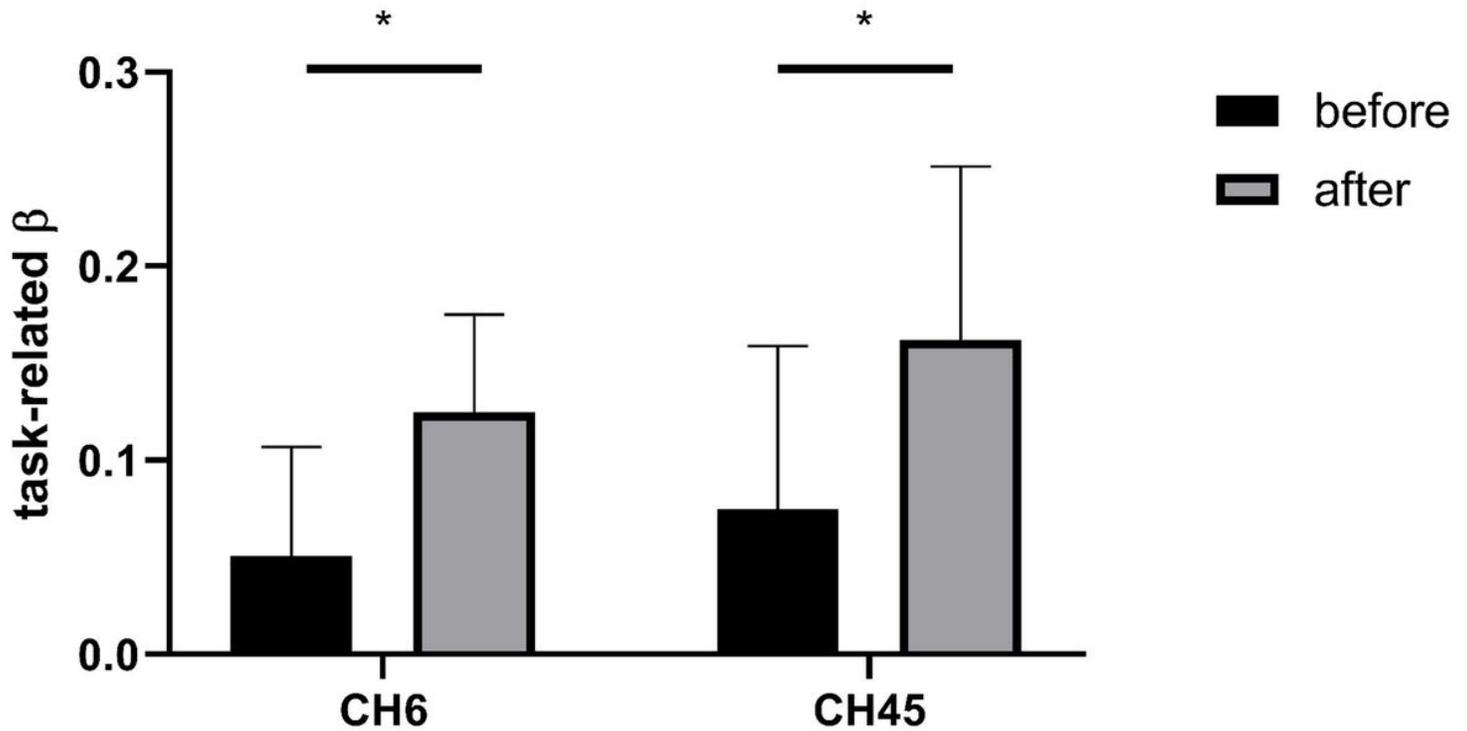


Figure 3

Cortical activation during the writing task before and after tcMRgFUS treatment. Two sample paired t-test of task-related  $\beta$  values showed that only CH6 and CH45 had significantly greater cortical activation in the writing task after tcMRgFUS treatment compared to the task before tcMRgFUS treatment. Error bars indicate standard errors.\* $p < 0.05$ .

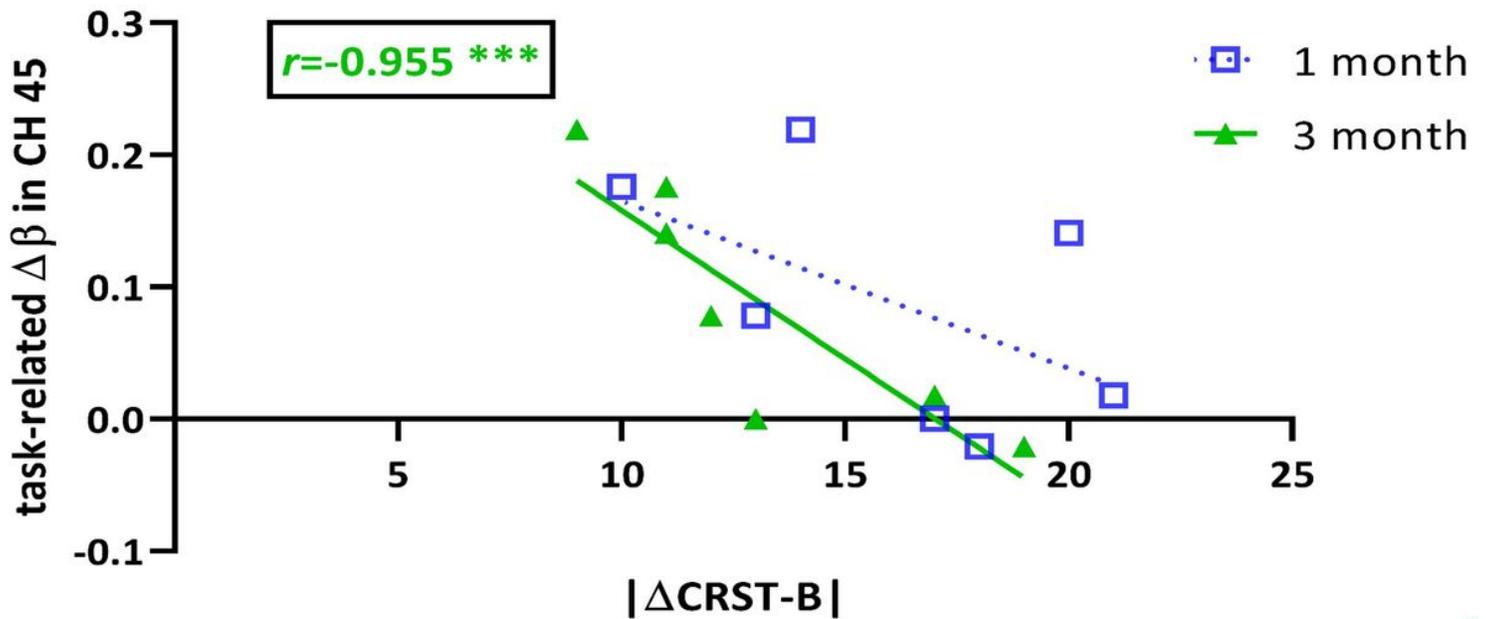


Figure 4

Spearman's rank correlation coefficient between clinical behavior and fNIRS activation. The correlation between  $\Delta\beta$  (the task related  $\beta$  values after tcMRgFUS treatment minus the task related  $\beta$  values in the task before tcMRgFUS treatment) in CH45 in the writing task and  $|\Delta\text{CRST-B}|$  (the score change between the CRST testing before and after tcMRgFUS treatment). The solid line indicates a significant linear relationship, while the dotted line indicates a non-significant relationship. Blue squares represent CRST testing measured one month after tcMRgFUS treatment. Green triangles represent CRST testing measured three months after tcMRgFUS treatment. \*\*\* $p < 0.001$ .