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● *Original Contribution*

NEUROPHYSIOLOGIC CORRELATES OF SONICATION TREATMENT IN PATIENTS WITH ESSENTIAL TREMOR

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Abstract—Transcranial magnetic resonance imaging-guided high-intensity focused ultrasound (MRgHIFU) is gaining attention as a potent substitute for surgical intervention in the treatment of neurologic disorders. To discern the neurophysiologic correlates of its therapeutic effects, we applied MRgHIFU to an intractable neurologic disorder, essential tremor, while measuring magnetoencephalogram mu rhythms from the motor cortex. Focused ultrasound sonication destroyed tissues by focusing a high-energy beam on the ventralis intermedius nucleus of the thalamus. The post-treatment effectiveness was also evaluated using the clinical rating scale for tremors. Thalamic MRgHIFU had substantial therapeutic effects on patients, based on MRgHIFU-mediated improvements in movement control and significant changes in brain mu rhythms. Ultrasonic thalamotomy may reduce hyper-excitable activity in the motor cortex, resulting in normalized behavioral activity after sonication treatment. Thus, non-invasive and spatially accurate MRgHIFU technology can serve as a potent therapeutic tool with broad clinical applications. (E-mail: min_bk@korea.ac.kr)

Key Words: **Mu rhythm, Essential tremor, Magnetoencephalography, Magnetic resonance imaging-guided high-intensity focused ultrasound, Thalamus.**

INTRODUCTION

The use of focused ultrasound in non-invasive tissue ablation has significant potential as a clinical treatment. Since Lynn and Putnam (1944) created cerebral lesions using focused ultrasound in an animal model, the promise of focused ultrasound brain surgery has been of interest for many decades. Initial tests by Lynn and Putnam (1944) revealed that the skull is a major barrier to ultrasound because of its high reflection and attenuation coefficients. Moreover, the variable thickness and heterogeneity of the bone structure led to severe distortion of the ultrasonic beam, thus preventing precise targeting through the skull (Hynynen et al. 2004). Given these obstacles, technological advances in this approach (*e.g.*, phased transducer arrays and computed tomographic correction algorithms) have enabled transcranial sonication through the intact human skull (Aubry et al. 2003; Clement and Hynynen 2002; Clement et al. 2000; Hynynen and Jolesz 1998; Hynynen et al. 2004; Sun and Hynynen 1999). This innovative technique was used to treat malignant glioma (McDannold et al. 2010) and neuropathic pain syndromes (Jeanmonod et al. 2012; Martin et al. 2009). Nevertheless, the use of ultrasonic transcranial brain treatments remains limited by aberrations induced by the skull. Several studies have been developing aberration correction techniques (Hynynen et al. 2006; Marquet et al. 2009, 2013) and dedicated devices (Chauvet et al. 2013; Hynynen et al. 2004, 2006) to achieve effective transcranial sonication.

Furthermore, a magnetic resonance imaging (MRI) technique has enabled precise guidance of transcranial sonication to the treatment location, and real-time monitoring of the sonication intensity is available via thermal imagery (Cline et al. 1993; De Poorter et al. 1995; Ishihara et al. 1995). MRI-guided focused ultrasound (MRgFUS) is considered an important advancement in the non-invasive treatment of neurologic disorders (Tyler et al. 2010). For example, MRgFUS is currently used to thermally ablate malignant brain cells by means of high-intensity focused ultrasound (HIFU) (Dervishi et al. 2013), and transcranial MRI-guided HIFU (MRgHIFU) is used to perform lesion surgery on the central lateral thalamic nuclei in patients with chronic neuropathic pain

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(Martin et al. 2009). To examine the therapeutic administration of MRgHIFU further, this technique was recently applied to an intractable neurologic disorder, essential tremor (ET), which manifests as an involuntary trembling of the body or limbs (Elias et al. 2013; Lipsman et al. 2013). These studies establish the feasibility of transcranial MRgHIFU-mediated thalamotomy for patients with ET and suggest that MRgHIFU might be a tolerable and effective approach for managing the disabling and medication-resistant ET. However, these studies assessed the degree of sonication-mediated improvement using rating scales with discrete and subjective scores (*e.g.*, the Clinical Rating Scale for Tremors [CRST] or Quality of Life in ET questionnaire). If any neurophysiologic correlate can systematically reflect such changes in sonication-mediated improvement, it will be a potent neural index for identifying the therapeutic effects of ultrasound in an objective manner. In the present study, we used magnetoencephalography (MEG) to record the brain activity of patients with ET during a simple movement task before and after MRgHIFU treatment to investigate the neurophysiologic correlates of its therapeutic effect.

In particular, the level of event-related synchronization of brain mu rhythms was considered the neurophysiologic correlate that indicates the degree of movement control (Pfurtscheller 1992; Pfurtscheller and Neuper 1992). The rolandic (central) alpha rhythm, centered around 10 Hz, is called the mu rhythm (Walter 1960). This rhythm is associated principally with functions of the motor cortex, but the contribution of the adjacent somatosensory cortex cannot be ignored (Niedermeyer 1999). Because the patients were required to perform task-oriented movements, the observed mu rhythm was generated predominantly by the motor cortex. Mu rhythm is blocked by movements irrespective of whether they are voluntary, passive or reflexive, and the blocking effect is more pronounced in the central region, contralateral to the movement site (Chatrian 1976; Chatrian et al. 1959). The main features of the rolandic mu rhythm are its event-related changes in synchronization (or desynchronization) (Pfurtscheller 1992; Pfurtscheller et al. 1992). The central mu rhythm is thus a reliable neurophysiologic indicator that reflects the degree of movement controlled at the level of upper motor neurons. Therefore, we investigated any MRgHIFU-mediated changes in event-related mu rhythms of patients with ET to determine the neurophysiologic correlates of the therapeutic effect of MRgHIFU.

METHODS

Participants and procedure

Magnetoencephalography signals were recorded from seven male patients with ET (mean age: 66.6 y) and seven age/sex-matched non-operated healthy volunteers (mean age: 65.6 y), in accordance with the ethics guidelines established by the Institutional Review Board of Yonsei University and the Declaration of Helsinki (World Medical Association, 1964, 2008). Although nine male patients and one female patient with ET were sonication-operated, MRgFUS treatment could be considered complete in only seven of nine male patients with ET (Table 2) (Chang et al. 2014); MEG activity was thus evaluated for these seven patients. Participants provided informed consent before the experiment. All participants had normal or corrected-to-normal vision. The healthy participants were examined by a neurologist to confirm that they were neurologically normal. The patients exhibited bilateral appendicular tremor that was diagnosed as ET by a movement disorder neurologist. They had not undergone any previous neurosurgical procedures, such as stereotactic thalamotomy or deep brain stimulation. All patients with ET met the inclusion criteria listed in Table 1. Exclusion criteria included a diagnosis of a current or past psychiatric illness, current substance abuse, other neurologic disorders that affect brain function (*e.g.*, idiopathic Parkinson's disease), contraindications to MRI and known intolerance or allergies to the MRI contrast agent. The MEG system (SIM-150WH, Korea Research Institute of Standards and Science [KRISS], Daejeon, Korea) has 152 axial first-order double-relaxation oscillation superconducting quantum interference device (DROS) gradiometers on a helmet-shaped surface covering the entire scalp. Patients were instructed to press a button with their right index finger when a letter stimulus was presented. Three hundred trials were employed in the MEG experiment. All responses were performed using only the right hand because the left thalamus was the target for MRgHIFU. The MEG data were epoched from 1600 ms before movement onset to 300 ms after movement onset. Epochs containing ocular or muscular artifacts (maximum amplitude: ± 10 pT) were rejected. Two patients were excluded from further analyses because of poor data quality as a result of high artifact rejection rates ($>30\%$) of the MEG trials caused by patients' prosthetics (see Table 2).

MEG analytic method

The power of oscillatory activity was investigated by convolving the MEG signals with Morlet wavelets (Herrmann et al. 2005). The wavelet transform was conducted for each individual trial, and the absolute values of the resulting transforms were averaged. This measure of signal amplitude in single trials reflects the total activity for a certain frequency range. In contrast, to compute the evoked activity (phase-locked to the stimulus), the wavelet transform was applied to the averaged evoked potential. We confined the mu activity to the frequency

Table 1. Inclusion criteria for patients with essential tremor

1. Aged between 18 and 80 y.
2. Ability and willingness to give consent and attend all study visits.
3. Diagnosis of essential tremor, as confirmed by clinical history and examination by a movement disorder neurologist.
4. Tremor refractory to adequate trials of at least two medications, one of which should be either propranolol or primidone. An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
5. The ventralis intermedius nucleus of the thalamus can be targeted by the ExAblate device. The ventralis intermedius region of the thalamus must be apparent on magnetic resonance images such that targeting can be performed with either direct visualization or by measurement from a line connecting the anterior and posterior commissures of the brain.
6. Ability to communicate sensations during the ExAblate magnetic resonance imaging-guided focused ultrasound treatment.
7. Postural or intention tremor severity score ≥2 in the dominant hand/arm as measured by the Clinical Rating Scale for Tremors (CRST).
8. Stable doses of all medications for 30 d before study entry and for the duration of the study.
9. Bilateral appendicular tremor.
10. Significant disability caused by essential tremor despite medical treatment (CRST score ≥2 on any one of items 16–23 from the Disability subsection of the CRST: speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working and social activities).
11. Agreement on inclusion and exclusion criteria by two members of the medical team.

range 8 to 13 Hz. The frequencies used in the wavelet analyses of mu activity were determined individually for each patient as their dominant peak frequency within the mu frequency range. For evoked activity, the baseline correction was conducted from 1600 to 1500 ms before movement onset, and we assessed the maximum amplitude within the time window between 300 ms before and 300 ms after movement onset. Total activity was measured at the peak latency of its corresponding evoked activity to investigate the existence of phase resetting (Min et al. 2007). This time window was selected based on the grand averages and individual variances. These measures were assessed on the five individually dominant MEG channels around the left motor cortex (region of interest; approximately compatible to the C3 position in electroencephalography). Owing to individual variances, all measures were normalized to the percentage relative to the individual values before MRgHIFU treatment. The averaged values across these five channels were analyzed using non-parametric Wilcoxon signed-rank tests for two related samples to evaluate differences between the values measured before and after the operation, as well as differences in the CRST (Fahn et al. 1993) scores over time. The primary effectiveness of the MRgHIFU treatment on patients' performance was evaluated using the CRST for patients with ET. We also determined whether the MRgHIFU-mediated reduction in MEG mu power of patients with ET was statistically similar to the level observed in age/sex-matched non-operated healthy volunteers, using non-parametric Mann–Whitney *U*-tests for two independent samples. In addition, to provide intra-subject control data, the MEG mu power in the ipsilateral (task-irrelevant) counterpart is provided in Table 2 as a comparison for the contralateral (task-relevant) MEG activity.

MRgHIFU sonication setup

All MRgHIFU procedures were conducted using ExAblate4000 (InSightec, Tirat Carmel, Israel), which was integrated with a 3-T MR scanner (GE Medical Systems, Milwaukee, WI, USA) (Fig. 1). ExAblate embeds a sonication process wherein FUS destroys tissues by focusing a high-energy beam on the ventralis intermedius nucleus (Vim) of the thalamus and raising its temperature from 56°C to 60°C. Multiple sonications were necessary to ablate a specific tissue area. MR images were acquired after head-frame fixation, and the images were transferred to an ExAblate workstation (InSightec). The MRI system provides high-resolution 3-D images of the target location (*i.e.*, Vim). The imaging sequences used include diffusion-weighted imaging (echo time [TE] = 85.2 ms, repetition time [TR] = 9000.0 ms), pre- and post-gadolinium-enhanced T1-weighted fast spin echo imaging (TE = 3.3 ms, TR = 8.6 ms) and T2-weighted fast spin echo imaging (TE = 81.4 ms, TR = 4941.0 ms). The points for multiple sonications were chosen along the three axes.

At the initial planning stage, the Vim nucleus (14–15 mm from midline, 6–7 mm anterior to the posterior commissure and at the line of the intercommissural line) was identified. Then, we measured the distances from the initial coordinates to the wall of the third ventricle (optimal distance: 11–11.5 mm) and to the region around the lateral border of the thalamus (optimal distance: 2 mm), because this is the recommended target for gamma knife thalamotomy (Ohye 2006; Ohye et al. 2012). Several low-power sonications below the ablation threshold were then applied for 10–20 s to induce peak temperatures of 40°C–42°C. These sonications allowed us to assess the exact position and size of the thermal spot and to determine the overall safety profile of the applied sonication parameters. Next, high-power sonications were applied under the guidance of MRI and MR thermometry, with stepwise increases in acoustic power and energy to achieve a peak target temperature of 55°C–62°C.

The initial values for Vim localization were 13–14 mm lateral to the midline, and 25%–28.5% anterior to the posterior commissure in the inter-commissural

Table 2. Parameters used in magnetic resonance imaging-guided high-intensity focused ultrasound treatment and MEG data

									Evoked mu power (fT^2)				Total mu power (fT^2)			
									Pre-operation		Post-operation		Pre-operation		Post-operation	
ID	Sex	Age	Number of sonications	Sonication power (W)	Sonication time (min)	Maximum thermal rise (°C)	Treatment result	MEG artifact rejection rate (%)	Left-M	Right-M	Left-M	Right-M	Left-M	Right-M	Left-M	Right-M
Patients with essential tremor																
1	M	78	16	1100	15	55	Success	33.02*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	M	63	16	1000	16	54	Success	42.77*								
3	M	68	27	775	32	55	Success	7.86	230.69	31.59	96.31	50.02	867.98	331.34	522.45	342.40
4	F	76	8	750	10	42	Failure†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5	M	61	19	850	20	55	Success	5.97	231.42	52.00	77.41	16.86	1036.81	393.07	638.82	411.94
6	M	61	18	1000	16	55	Success	11.01	63.22	22.36	40.32	3.41	377.26	502.70	1195.51	460.88
7	M	55	15	750	12	40	Failure‡	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	M	53	25	1200	16	43	Failure‡									
9	M	67	13	650	15	62	Success	11.95	111.14	34.66	12.72	3.86	644.09	320.83	213.96	148.44
10	M	68	14	850	18	57	Success	9.43	108.90	10.99	21.23	16.77	458.41	224.31	584.66	335.04
Healthy controls																
1	M	70	N/A	N/A	N/A	N/A	N/A	6.29	79.74	40.25	N/A	N/A	546.00	330.52	N/A	N/A
2	M	64						3.14	42.84	24.77			575.25	539.46		
3	M	68						10.06	36.31	6.05			413.02	279.21		
4	M	61						5.35	14.91	4.85			265.68	133.78		
5	M	70						15.41	13.96	5.92			262.62	129.06		
6	M	59						5.03	81.61	16.06			468.16	173.84		
7	M	67						15.41	32.65	1.03			260.64	150.40		

MEG = magnetoencephalography; Left-M = left motor cortical area (*i.e.*, contralateral to movement of the right hand); Right-M = right motor cortical area (*i.e.*, ipsilateral to movement of the right hand).
* Because of the high magnetoencephalography artifact rejection rates, two patients were excluded from the MEG analyses.
† Because of a cardiovascular problem.
‡ Because of no increase in temperature.

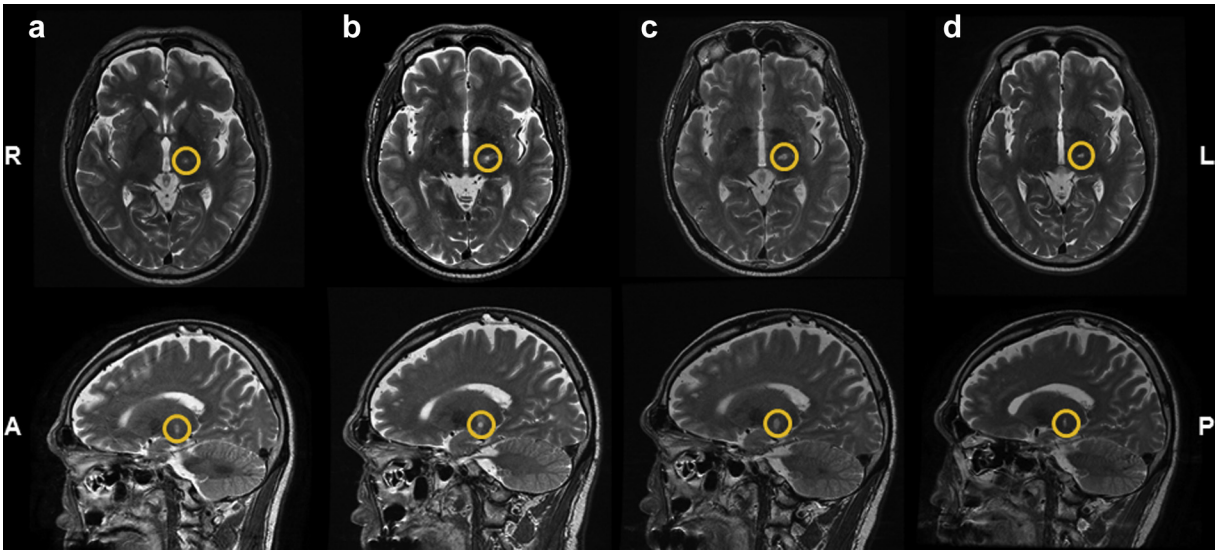

Fig. 1. Images from a 3-T magnetic resonance imaging scanner (T2-weighted sequences) in a patient with essential tremor after sonication treatment. The patient was treated with transcranial magnetic resonance imaging-guided high-intensity focused ultrasound to create a lesion in the ventralis intermedius nucleus of the left thalamus (highlighted with *yellow circles*). (a) Immediately after magnetic resonance imaging-guided high-intensity focused ultrasound thalamotomy, (b) 1 wk post-operation, (c) 1 mo post-operation, (d) 3 mo post-operation. In the upper row are horizontal images (L = left; R = right), and in the lower row are the corresponding sagittal images (A = anterior, P = posterior).

plane. HIFU pulses were generated using a hemispherical 1024-element phased-array transducer operating at a frequency of 650 kHz. The sonication power used in this study ranged from 25 to 1050 W, with a total exposure duration of 10–32 s. The focal spot generated by the transducer was previously measured to be 4–6 mm wide and 5–8 mm long. The MRI system also provided real-time temperature feedback that indicated the degree of tissue heating. Simultaneously, detailed neurologic examinations, including examinations for motor function, sensory function and the treatment's effect on tremors, were evaluated. Therefore, the integration of FUS with MRI serves as a "closed-loop therapy and feedback system" that enables the physician to control the treatment by adjusting its parameters to ensure optimal tolerability and efficacy levels.

RESULTS

As illustrated in Figure 2, we observed significantly improved movement control in patients with ET as assessed with CRST Part B (drawing and writing with the right hand) 1 wk after thalamic MRgHIFU treatment ($Z = -2.041$, $p < 0.05$, 80.88% improvement in CRST scores). We also found that thalamic MRgHIFU yielded significantly reduced evoked mu power compared with that before treatment ($Z = -2.023$, $p < 0.05$, 66.73% reduction) (Table 2 and Fig. 3). The level of post-operational evoked mu power of patients with ET was statistically similar to that of non-operated healthy controls ($Z = -0.081$, not significant). Compared with the pronounced post-operational reductions in contralateral motor-cortical evoked mu power in patients with ET, relatively small decreases (or sometimes increases) in ipsilateral evoked mu power were observed (Table 2). In addition, no significant differences in total mu power around movement onset ($Z = -0.405$, not significant) were observed after MRgHIFU treatment. Thalamic MRgHIFU either decreased or increased movement-related total mu power at the latencies of their peak-evoked mu activities. Notably, before thalamic MRgHIFU treatment, patients with ET exhibited insufficiently suppressed evoked mu rhythm compared with that during normal skillful movement, whereas all five patients had, on average, a 66.73% reduction (ranging from 36% to 89%) of evoked mu power after thalamic MRgHIFU treatment. In contrast to these observations, we found no significant differences in total mu activity at the same latencies of the peak-evoked activity. Irrespective of the enhanced or decreased total mu activity at the latencies of its movement-related evoked peak, the consistent enhancement of movement-related evoked mu activity before sonication treatment might indicate abnormal hyper-phase resetting of mu activity in patients with ET.

As outlined in Table 2, we also observed that the contralateral evoked mu power was significantly higher than the ipsilateral evoked mu power in both healthy

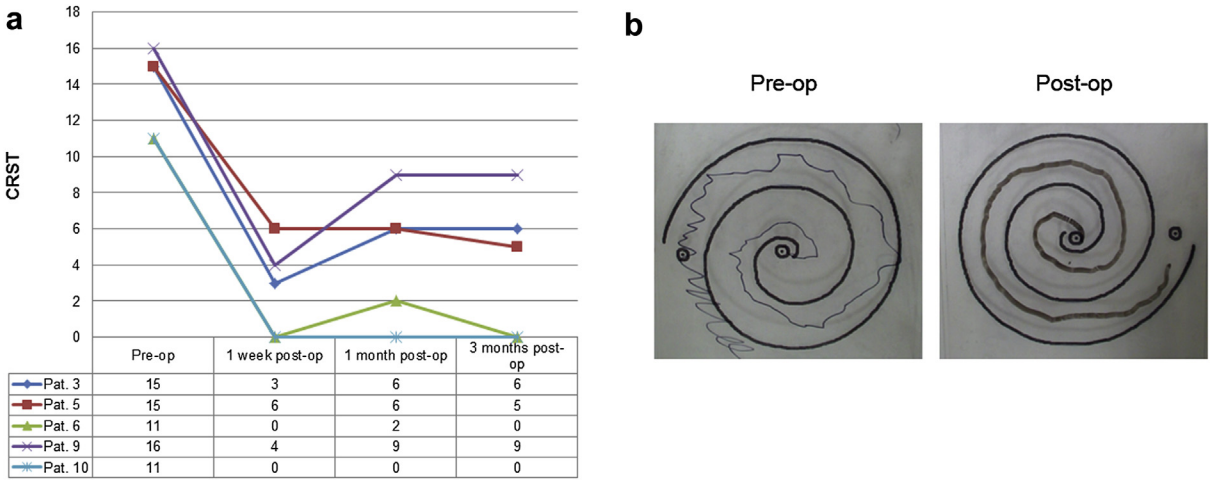

Fig. 2. (a) Improvement in the Clinical Rating Scale for Tremors (CRST), Part B (drawing and writing with the right hand) scores of the five patients. CRST scores were markedly decreased 1 wk after thalamic magnetic resonance imaging-guided high-intensity focused ultrasound and remained low 1 to 3 mo post-operation, which indicates a persistent therapeutic effect on the impaired motor control of patients with essential tremor. (b) Sample of the improved hand drawing of a concentric circle before (pre-op) and after (post-op) thalamic magnetic resonance imaging-guided high-intensity focused ultrasound treatment. Note that the skill level of hand movements significantly improved after the thalamic magnetic resonance imaging-guided high-intensity focused ultrasound operation.

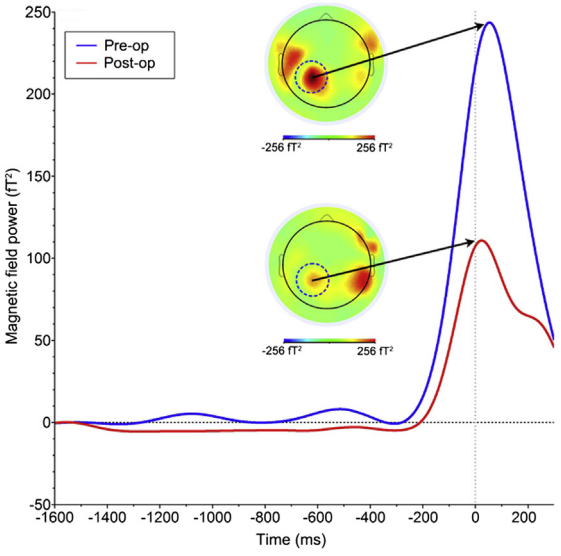

Fig. 3. Time courses of magnetoencephalography-evoked mu activity on the channel above the corresponding motor cortex (refer to the area within the *blue dotted circle*) contralateral to the site of movement (*i.e.*, the right hand) and each topographic distribution (averaged from 50 ms before movement onset to 150 ms after movement onset) before (pre-op, noted as the upper topography and the *blue line*) and after (post-op, noted as the lower topography and the *red line*) thalamic magnetic resonance imaging-guided high-intensity focused ultrasound treatment of a patient with essential tremor. All views of topographies are from the vertex, and the upside is nasal. The *dotted blue circles* indicate the left motor cortical area corresponding to movement of the right hand.

controls ($Z = -2.366$, $p < 0.05$; contralateral = 43.15 fT^2, ipsilateral = 14.13 fT^2) and patients with ET ($Z = -2.023$, $p < 0.05$; contralateral = 149.07 fT^2, ipsilateral = 30.32 fT^2 for pre-operation; $Z = -2.023$, $p < 0.05$; contralateral = 49.60 fT^2, ipsilateral = 18.18 fT^2 for post-operation). The same trends were detected for total mu power in healthy controls ($Z = -2.366$, $p < 0.05$; contralateral = 398.77 fT^2, ipsilateral = 248.04 fT^2). Although for patients with ET there were no significant differences in total mu power between the contralateral and ipsilateral sides before thalamic MRgHIFU treatment ($Z = -1.753$, not significant), the contralateral total mu power was significantly higher than the ipsilateral total mu power after thalamic MRgHIFU treatment ($Z = -2.023$, $p < 0.05$; contralateral = 631.08 fT^2, ipsilateral = 339.74 fT^2). These results are consistent with the intrasubject control data that reflected left-sided dominance of motor cortical activity in response to movement of the right hand (*i.e.*, cerebral contralateral regulation of the body).

DISCUSSION

As mentioned earlier, the level of the rolandic mu rhythm is a neurophysiologic correlate of the progressing extent of movement. A reduction in the corresponding mu rhythm and a return to normal skillful performance were observed in patients with ET after MRgHIFU treatment, as evidenced by the similar level of evoked mu power in

sonication-treated patients and age/sex-matched healthy controls. This may imply that the abnormally hyperactivated mu rhythm event-related synchronization in patients' contralateral motor cortex recovers to the normal level after sonication treatment. Notably, mu rhythms are thought to be produced by thalamocortical circuits and reflect cortical inhibition in the motor cortex (Niedermeyer 1999). Additionally, motor cortex activity is controlled by inhibitory innervations of the thalamic structures (Ando et al. 1995; Behrens et al. 2003). Collectively, these data suggest that thalamic MRgHIFU might exert its therapeutic influence on abnormal thalamic inhibitory controls to the motor cortex in patients with ET.

Another possible etiologic account for ET is the involvement of abnormal cerebellothalamocortical signaling (Louis and Vonsattel 2008); 80% of autopsied brains from patients with ET exhibited changes in the cerebellar γ-aminobutyric acidergic inhibitory neurons (Louis et al. 2007). Because the thalamus is also regulated by γ-aminobutyric acidergic inhibitory circuits (Min 2010), we surmise that thalamic MRgHIFU treatment might interrupt the imbalanced inhibitory signaling across the thalamus and cerebellum, which eventually controls the motor cortex. In other words, thalamic MRgHIFU treatment might contribute to releasing the motor cortex from abnormal thalamic inhibitory controls. Presumably, MRgHIFU-mediated disinhibition of the abnormal thalamic suppression on the motor cortex seems to be required to return to intact movement performance. Subsequently, thalamic MRgHIFU treatment resulted in a return to the significantly reduced level of movement-related evoked rolandic mu rhythm, which may reflect cortical inhibition in the motor cortex (Niedermeyer 1999). This interpretation of the thalamic therapeutic effect on ET symptoms is consistent with that of anti-epileptic medications (*e.g.*, primidone) used to treat ET symptoms (Zesiewicz et al. 2011), as well as other anti-epileptic effects of direct thalamic sonication (Min et al. 2011). A potential explanation for this observation is sonication-mediated regulation of thalamic γ-aminobutyric acidergic inhibitory neurons, because thalamic γ-aminobutyric acidergic inhibitory synapses are regarded as a critical control point for regulating thalamocortical network activity such as epileptic seizures (Schofield et al. 2009).

CONCLUSION

We observed that MRgHIFU treatment potently alleviated ET symptoms in a non-invasive way by measuring the MEG correlates. Because an enhanced reduction in evoked mu rhythm of MEG signals was observed around the corresponding motor cortex after this treatment, the thalamic MRgHIFU might exert its therapeutic influence on abnormal thalamic inhibitory controls to the motor cortex in patients with ET. However, the present study has some implicational constraints that are worth mentioning. First, our inclusion criteria for patients with tremor did not extend to other types of tremor including Parkinson's disease. Thus, further exploration of this treatment on other types of tremor is needed to determine the extent of its clinical applications. Second, although a larger sample size could guarantee a higher statistical power, it is not easy to acquire sufficient ultrasonic thalamotomy data from patients with ET. Instead, the comparison analysis between patients with ET and healthy controls supports that MRgHIFU-mediated thalamotomy may contribute to the reduction of abnormal hyperexcitable activity in the motor cortex of patients with ET, which results in normalized behavioral activity after sonication treatment. Compared with other surgical interventions, including thalamotomy and deep brain stimulation (Schuurman et al. 2000; Zesiewicz et al. 2005; Rana 2010), thalamic MRgHIFU is a non-invasive and spatially accurate therapeutic technology that has many potential clinical applications in the treatment of neurologic disorders.

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