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Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: repeated sonications with low focal temperatures

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Abstract

OBJECTIVE—The object of this study was to correlate lesion size with accumulated thermal dose (ATD) in transcranial MRI-guided focused ultrasound (MRgFUS) treatments of essential tremor with focal temperatures limited to 50°C–54°C.

METHODS—Seventy-five patients with medically refractory essential tremor underwent MRgFUS thalamotomy at the authors' institution. Intraoperative MR thermometry was performed to measure the induced temperature and thermal dose distributions (proton resonance frequency shift coefficient = −0.00909 ppm/°C). In 19 patients, it was not possible to raise the focal temperature above 54°C because of unfavorable skull characteristics and/or the pain associated with cranial heating. In this patient subset, sonications with focal temperatures between 50°C and 54°C were repeated (5.1 ± 1.5, mean ± standard deviation) to accumulate a sufficient thermal dose for lesion formation. The ATD profile sizes (17, 40, 100, 200, and 240 cumulative equivalent minutes at 43°C [CEM_{43}]) calculated by combining axial MR thermometry data from individual sonications were correlated with the corresponding lesion sizes measured on axial T1-weighted

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Disclosures

Dr. Hynynen is an inventor of intellectual property related to transcranial MRgFUS technology that is owned by Brigham and Women's Hospital and licensed to InSightec.

Previous Presentations

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(T1w) and T2-weighted (T2w) MR images acquired 1 day posttreatment. Manual corrections were applied to the MR thermometry data prior to thermal dose accumulation to compensate for off-resonance–induced spatial-shifting artifacts.

RESULTS—Mean lesion sizes measured on T2w MRI (5.0 ± 1.4 mm) were, on average, 28% larger than those measured on T1w MRI (3.9 ± 1.4 mm). The ATD thresholds found to provide the best correlation with lesion sizes measured on T2w and T1w MRI were 100 CEM (regression slope = 0.97, R^2 = 0.66) and 200 CEM_{43} (regression slope = 0.98, R = 0.89), respectively, consistent with data from a previous study of MRgFUS thalamotomy via repeated sonications at higher focal temperatures (≥ 55°C). Two-way linear mixed-effects analysis revealed that dominant tremor subscores on the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (CRST) were statistically different from baseline at 3 months and 1 year posttreatment in both low-temperature (50°C–54°C) and high-temperature (≥ 55°C) patient cohorts. No significant fixed effect on the dominant tremor scores was found for the temperature cohort factor.

CONCLUSIONS—In transcranial MRgFUS thalamotomy for essential tremor, repeated sonications with focal temperatures between 50°C and 54°C can accumulate a sufficient thermal dose to generate lesions for clinically relevant tremor suppression up to 1 year posttreatment, and the ATD can be used to predict the size of the resulting ablation zones measured on MRI. These data will serve to guide future clinical MRgFUS brain procedures, particularly those in which focal temperatures are limited to below 55°C.

Keywords

focused ultrasound; thalamotomy; MR thermometry; thermal ablation; thermal dose; functional neurosurgery

TRANSCRANIAL MRI-guided focused ultrasound (MRgFUS) is being clinically investigated for thermal ablation of tumors and functional neurosurgery applications.[32] To date, most of the clinical experience with MRgFUS in the brain has been obtained in treating essential tremor, one of the most prevalent movement disorders worldwide.[25] Subsequent to the previously developed radio frequency ablation[40] and deep brain stimulation approaches,[43] several groups have shown that unilateral lesioning in the ventral intermediate (VIM) nucleus of the thalamus via MRgFUS can lead to reduced contralateral hand tremor in patients suffering from essential tremor.[5,12,15,24] These pilot studies paved the way for a multicenter randomized controlled trial, which demonstrated that patients treated with MRgFUS thalamotomy had significantly improved tremor scores compared with those in sham controls and that the improvement was maintained at the 1-year follow-up.[13] A recent follow-up study reported that tremor suppression in this patient population was stably maintained at the 2-year time point.[4] The results of this landmark trial led to the procedure's approval by Health Canada and the US Food and Drug Administration in mid-2016.

A major source of treatment variability in MRgFUS brain procedures arises from the human skull's complex morphological and acoustical properties. Considerable inter and intrasubject variability in skull transmission efficiency has been observed during experimentation with ex vivo human skull samples,[14,26,35] and the acoustic energy required to produce lesions during clinical MRgFUS brain treatments varies commensurately.[24,38,41] Indeed, in some patients,

it is not possible to raise the focal temperature to within 55°C–60°C using the current transcranial MRgFUS system,[6,23] a range that is sufficient to produce lesions in brain tissue within a few seconds of exposure.[11,36] In addition to poor skull transmission efficiency, patient intolerance to the pain associated with substantial cranial heating[9,10] can also limit the focal temperatures that are achievable in practice. Furthermore, recent work has suggested that changes in the acoustical properties of human skull bone as a result of cranial heating[8] can cause beam de-focusing and concomitant reductions in treatment efficiency during MRgFUS brain procedures,[20] which may explain prior clinical observations.[2]

Given the aforementioned sources of treatment variability in transcranial MRgFUS procedures, the use of intraoperative MR thermometry[22,34] is essential for monitoring the temperature elevations induced within the brain to help ensure consistent clinical outcomes.[28,30] The current clinical MRgFUS brain systems perform 2D MR thermometry during each sonication, and spatial maps of any coagulation induced by a given exposure can be estimated[7,17] via calculation of the thermal dose.[11,36] MRgFUS thalamotomy procedures involve multiple independent sonications separated by lengthy off-times to allow for cooling of overlying tissues. The accumulated thermal dose (ATD) over multiple sonications, which accounts for off-resonance–induced spatial-shifting artifacts[16] to properly combine thermal dose data from successive exposures, has shown utility in predicting lesion sizes following MRgFUS thalamotomy with repeated sonications.[19] The ability to predict the ablation zone is important for determining treatment endpoints, as clinical experience has shown that proper placement of appropriately sized lesions is critical for durable tremor suppression,[31,37] whereas involvement of surrounding brain structures (e.g., internal capsule) can result in adverse effects.[3,13]

During transcranial MRgFUS patient treatments in which the focal temperature of individual sonications is limited (i.e., to 50°C–540°C, which may not be sufficient to induce thermal necrosis from a single sonication), the accumulated effects of repeated low-temperature sonications may result in sufficient thermal dose deposition to generate lesions. Therefore, investigation into the appropriate ATD thresholds for repeated low-temperature sonications is warranted to help guide this subset of case treatments. In this study, we retrospectively examined at our institution the clinical MRgFUS treatments of essential tremor with focal temperatures limited to below 55°C. ATD distributions were calculated offline with corrections[19] for off-resonance–induced spatial-shifting artifacts.[16] ATD profile sizes were compared to lesion size measurements made on follow-up T1-weighted (T1w) and T2-weighted (T2w) MR images to estimate the dose thresholds in cumulative equivalent minutes at 43°C (CEM_{43}) that best predict the resulting ablation zones. The ATD thresholds and clinical outcomes up to 1 year posttreatment from patients with repeated low-temperature sonications were compared with corresponding data from our institution in a prior study of MRgFUS thalamotomy with higher focal temperatures.[19]

Methods

Between July 2015 and July 2018, seventy-five patients with medically refractory essential tremor underwent unilateral thalamotomy at our institution (Sunnybrook Research Institute) using a commercial MRgFUS system (ExAblate 4000, InSightec Inc.; 650-kHz center

frequency, 1024 transducer elements) in a 3-T MRI scanner (MR750, GE Healthcare). All procedures were approved by Sunnybrook Health Sciences Centre's research ethics board. The treatment workflow has been described in detail in previous publications.[19,24] A subset of the data presented in this paper (high-temperature patient cohort from Huang et al.[19]) included patients who were enrolled in a clinical trial (clinical trial registration no.: NCT01827904; http://clinicaltrials.gov).

Intraoperative 2D MR thermometry was performed during each sonication to monitor the induced temperature elevation and thermal dose distributions (body coil; TR = 27.6 msec, TE = 12.8 msec, slice thickness = 3 mm, FOV = 28 × 28 cm, matrix size = 256 × 128 zero padded to 256 × 256, in-plane resolution = 1.1 mm, temporal resolution = 3.5 seconds, bandwidth = 44 Hz/pixel). The MRgFUS system software used a proton resonance frequency (PRF) shift coefficient of −0.00909 ppm/°C to calculate the temperature images. Initially, low-power and/or short-duration sonications (target focal temperature = 40°C–45°C) were applied to align the heating volume with the desired target based on MR thermometry feedback. The alignment process with the current MRgFUS system requires a minimum of three sonications performed with various combinations of imaging plane orientations (i.e., axial, coronal, sagittal) and frequency encoding directions to independently align the thermal focus along three orthogonal axes (i.e., left-right, anterior-posterior, and inferior-superior directions). The alignment process was subsequently repeated with higher-power and/or longer-duration sonications (target focal temperature = 45°C–50°C) to verify targeting while remaining at exposure levels below those required to produce a permanent lesion. Once targeting was verified, the applied acoustic power and/or sonication duration were further increased to reach exposures suitable for thermal coagulation (target focal temperature = 55°C–60°C).

In 19 patients it was not possible to raise the focal temperature (defined as a 3 × 3–pixel spatial average centered on the target pixel) above 54°C because of unfavorable skull characteristics or the pain associated with substantial skull heating. In this patient subset, low-temperature (50°C–54°C) sonications were repeated (5.1 ± 1.5, mean ± standard deviation) to accumulate a sufficient thermal dose to generate lesions. In this patient series, intraoperative MR thermometry was performed solely in the axial planes following target verification. From the time series of axial temperature maps, ATD distributions were calculated using the standard thermal dose model.[11,36] Following our previous work,[19] we applied corrections to compensate for off-resonance–induced spatial-shifting artifacts.[16] The corrections were applied independently for each sonication and were performed offline in MATLAB (The Math Works Inc.). In this study, temperature maps were interpolated down to a pixel size of 0.1 × 0.1 mm prior to spatial shift correction.

Axial ATD profile sizes at 17, 40, 100, 200, and 240 CEM_{43} were measured and compared with lesion sizes obtained from axial T1w (3D FSPGR [fast spoiled gradientecho], TR = 8.3 msec, TE = 3.3 msec, slice thickness = 1.2 mm) and T2w (FRFSE [fast recovery fast spin-echo], TR = 5200 msec, TE = 100 msec, slice thickness = 3 mm) MR images acquired 1 day posttreatment using an 8-channel head coil. The ATD profile and MRI lesion sizes represent maximal diameters, and both the left-right and anterior-posterior directions were measured independently for each patient (i.e., 44 total measurements). As previously described,[18,27,42]

the lesion patterns found on T2w MRI following MRgFUS thalamotomy consist of three concentric zones: a hypointense center (zone I, consistent with coagulative necrosis) surrounded by a strongly hyperintense region demarcated by a hypointense rim (zone II, consistent with cytotoxic edema) with a diffuse and weakly hyperintense periphery (zone III, consistent with vasogenic edema). MRI lesion sizes were assessed based on the extent of the hypointense regions on T1w scans and on regions of thermal coagulation (i.e., zone I) and cytotoxic edema (i.e., zone II) on T2w scans. Regions of vasogenic edema (i.e., zone III) were excluded from the T2w size measurements as this type of brain edema resolves over time.[18,42] The MRI lesion sizes were evaluated by two investigators (S.K. and Y.H.) who were unblinded to the experimental cohort (i.e., low or high temperature).

For each dose threshold investigated, linear regression analysis (slope and correlation coefficient calculation; y-intercept fixed at origin) was performed to compare the ATD profile size (dependent variable) with different MRI size measurements (independent variable). Logarithm fits were applied to the linear regression slopes to determine the dose thresholds that provided the best correlation with the different MRI size measurements. Paired t-tests with null hypotheses that various ATD profile sizes were equivalent to the lesion sizes measured on T1w and T2w MR images were also evaluated. Bland-Altman analysis was used to evaluate the agreement between ATD profile sizes and different MRI size measurements, with limits of agreement defined as the mean bias ± 1.96 standard deviations.[1]

The dominant tremor subscores (maximum value of 32) of the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (CRST)[39] measured at baseline, 3 months posttreatment, and 1 year posttreatment were compiled for patients with repeated sonications at focal temperatures of 50°C–54°C (low-temperature cohort, 19 patients) and for the subset of patients from our previous clinical study[19] with focal temperatures ≥ 55°C (high-temperature cohort, 30 patients). The CRST subscores were evaluated by two investigators (N.S. and M.L.S.) who were blinded to the experimental cohort (i.e., low or high temperature). Differences in mean dominant tremor scores were assessed using a two-way (i.e., temperature cohort and time point as factors) linear mixed-effects model (Geisser-Greenhouse correction, significance level = 0.05), followed by post hoc Tukey multiple comparison testing. All statistical testing was performed in GraphPad Prism (version 8.0.1, GraphPad Software).

Results

In all 19 patients, repeated sonications with focal temperatures between 50°C and 54°C accumulated a sufficient thermal dose to generate lesions. MRI and ATD data from a representative patient are provided in Fig. 1. Axial T1w and T2w MR images acquired 1 day following MRgFUS thalamotomy depicted the ablation zone in the VIM nucleus, and corresponding ATD profiles at the various dose thresholds tested are provided for comparison. Across all 19 patients, the lesion sizes (mean ± standard deviation) measured on T2w MRI (5.0 ± 1.4 mm) were, on average, 28% larger than corresponding measurements on the T1w scans (3.9 ± 1.4 mm).

Linear regression analysis revealed that, of the dose thresholds tested, ATD values of 100 and 200 CEM_{43} provided the best correlation (i.e., linear regression slope closest to unity) with the lesion sizes measured on T2w (regression slope = 0.97, R^2 = 0.66) and T1w (regression slope = 0.98, R^2 = 0.89) MRI, respectively (Fig. 2). A summary of the paired t-test analysis is provided in Table 1. Paired t-tests failed to reject the null hypotheses that ATD profile sizes of 100 and 200 CEM_{43} were equivalent to the lesion sizes measured on T2w and T1w MRI at a confidence level of 95% (p = 0.54 and 0.39, respectively). For all other combinations of dose thresholds and MRI sequence types (i.e., 17, 40, 100, and 240 CEM_{43} vs T1w MRI; 17, 40, 200, and 240 CEM_{43} vs T2w MRI), paired t-tests rejected the null hypothesis of equivalence with a $p < 0.0001$. At the “optimal” thresholds (i.e., 100 CEM_{43} for T2w MRI, 200 CEM_{43} for T1w MRI), the ATD and lesion size measurements showed good agreement (Fig. 3).

The baseline dominant tremor CRST subscores (Fig. 4) were 20.5 ± 5.8 and 20.3 ± 5.0 in the low and high temperature cohorts, respectively. The dominant tremor scores of the low and high-temperature cohorts were improved by 53% ± 32% and 51% ± 22% at 3 months posttreatment, respectively; at the 1-year time point the corresponding reductions were 45% ± 55% and 44% ± 22%. The two-way linear mixed-effects model revealed a significant fixed effect on the dominant tremor scores for the time point factor (Fquent post hoc analysis showed dominant tremor scores to 1.680, 67.20 = 99.31, $p < 0.0001$). Subsebe significantly different from baseline at both 3 months and 1 year posttreatment in each patient cohort, with no statistical difference between the 3-month and 1-year time points in either group. There was no significant fixed effect on the dominant tremor scores for the temperature cohort factor ($F_{1, 47}$ = 0.1098, p = 0.7418), and there was no statistical interaction between the two factors (F2, 80 = 0.2177, p = 0.8049).

Discussion

The ATD thresholds found to provide the best correlation with MRI-based size measurements of lesions generated from repeated low-temperature (50°C–54°C) sonications were in agreement with previously reported clinical data on MRgFUS patient treatments with repeated high temperature exposures (≥ 55°1C).[19] It is worth noting that the values obtained from these two clinical studies (i.e., 100 CEM for T2w MRI, 200 CEM considerably higher than that in early preclinical work in the in vivo rabbit brain, which demonstrated a 17.5 CEM_{43} thermal dose threshold for ablation.[29] The dominant factor causing this discrepancy is thought to be the different PRF shift coefficients employed (i.e., −0.00909 ppm/°C clinical vs −0.011 ppm/°C preclinical).[19] Indeed, this difference in PRF shift coefficients leads to a 20% increase in the temperatures calculated in the clinical studies relative to those in the preclinical study, making a “clinical dose” of 200 CEM_{43} equivalent to a “preclinical dose” of 18 CEM_{43}. If the PRF shift coefficient used in the MRgFUS system is changed in the future, target temperature and thermal dose levels will need to be modified accordingly.

MRI-based size measurements following repeated low temperature sonications suggested that lesions were, on average, 28% larger on T2w images than on corresponding T1w images, which is consistent with our clinical experience of repeated exposures at higher

focal temperatures.[19] Earlier preclinical work has shown that signal changes on T2w MRI are correlated with the lesion's central necrotic region and surrounding edema,[33] whereas signal changes on T1w MRI depict the vascular necrosis caused by thermal coagulation.[21] Therefore, the observed difference in MRI-based lesion sizes (i.e., T1w vs T2w) may reflect a requirement of higher thermal exposures to induce such vascular effects.

The T2w and T1w MRI lesion sizes (5.0 ± 1.4 mm and 3.9 ± 1.4 mm, respectively) obtained from MRgFUS thalamotomy with repeated low-temperature sonications were 19% and 26% smaller, respectively, than corresponding data from a previous clinical study at our institution (6.2 ± 1.3 mm and 5.3 ± 1.2 mm, respectively) on repeated exposures with higher focal temperatures.[19] This size mismatch is a result of the lengthy off-times required following high-energy sonications to allow for skull cooling between successive sonications (e.g., approximately 20 minutes at 40 kJ of applied energy), which places a limit on the number of exposures that are feasible in a reasonable clinical timeframe. In our experience, sonications with a focal temperature of 50°C (30- to 50-second duration) need to be repeated 4–5 times to accumulate a sufficient thermal dose to generate lesions with a size of 3–5 mm. In this study, the procedural time between the initial and final sonications for patients in the low-temperature cohort (115 ± 34 minutes, 19 patients) was 26% longer than for patients in the high-temperature cohort (91 ± 33 minutes, 30 patients) on average. Note that these estimates do not include the times associated with the patient preparation (approximately 90 minutes), patient setup, and pretreatment MR imaging (approximately 30 minutes) that take place prior to the initial sonication. In the absence of such practical constraints, additional low-temperature sonications should be performed in future treatments with limited focal temperatures to further accumulate thermal dose and increase the resulting lesion size, with a view toward ensuring durable clinical outcomes.[31,37] Intraprocedural calculation of the ATD will be particularly useful in helping to guide this subset of MRgFUS cases.

The lesions generated by MRgFUS via repeated low temperature sonications led to a significant reduction in the dominant tremor score up to 1 year posttreatment. A statistical comparison of this cohort with a subset of patients from our previous clinical study[19] in which we employed higher-temperature sonications suggested that a similar level of tremor suppression was obtained in both cases up to this time point. Nevertheless, given the smaller lesion sizes in the low-temperature cohort and the fact that larger lesions have been associated with increased durability of tremor suppression,[31,37] long-term follow-ups are needed to fully evaluate this ablation approach. Therefore, further examinations of the safety and efficacy profiles of repeated low-temperature sonications for MRgFUS thalamotomy are warranted.

Limitations of this study include potential errors in MR thermometry, inaccuracies in the off-resonance–induced shift corrections, uncertainty regarding the PRF shift coefficient for human brain tissue, the use of only one time point for measuring lesion size (i.e., 1 day posttreatment), and the small sample size of the low-temperature cohort at the latest time point for which clinical outcomes were compared (i.e., 1 year posttreatment). We anticipate that further improvements to the MRgFUS system (e.g., higher signal/noise ratio in MR thermometry with integrated imaging coils, 3D thermometry for more accurate delineation

of the heating volume) will reduce the variability of thermal dose measurements in future studies.

Conclusions

In transcranial MRgFUS thalamotomy procedures for which focal temperatures are limited to below 55°C, repeated low-temperature (50°C–54°C) sonications can accumulate a sufficient thermal dose to generate lesions for clinically relevant tremor suppression up to 1 year posttreatment, and the ATD can be used to predict the size of the resulting ablation zones measured on MRI. These data will help to predict lesion sizes and define treatment endpoints during future MRgFUS procedures, particularly those in which the achievable focal temperatures are limited to below 55°C.

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ABBREVIATIONS

ATD	accumulated thermal dose
CEM_{43}	cumulative equivalent minutes at 43°C
CRST	Fahn-Tolosa-Marin Clinical Rating Scale for Tremor
MRgFUS	MRI-guided focused ultrasound
PRF	proton resonance frequency
T1w	T1-weighted
T2w	T2-weighted
VIM	ventral intermediate

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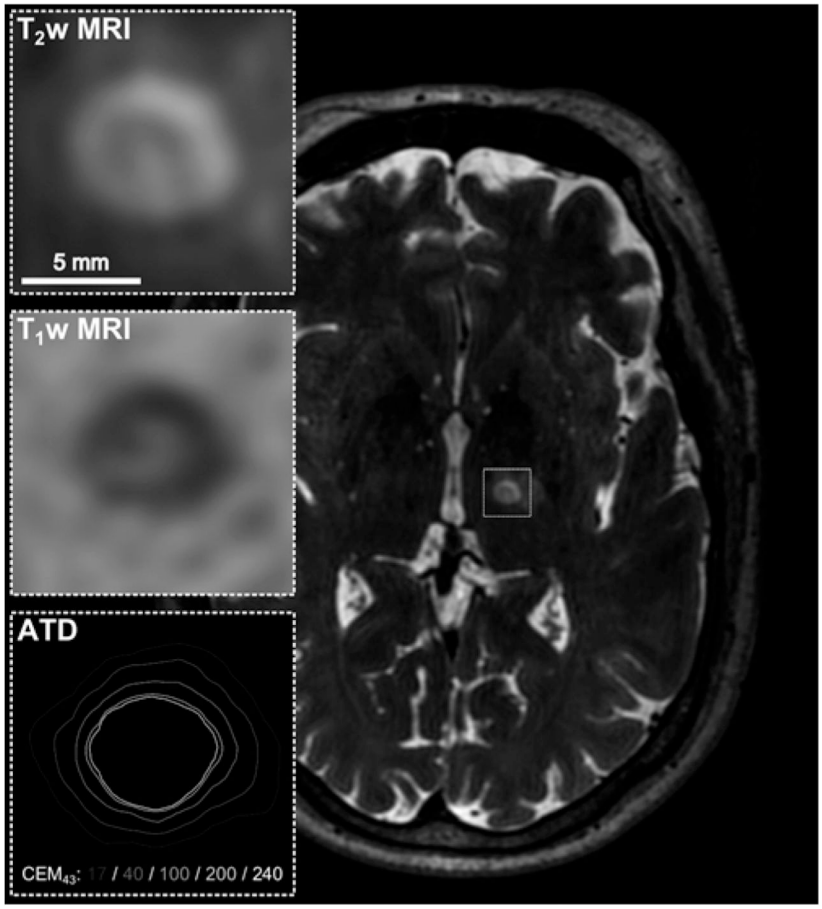

FIG. 1.

Axial T2w MR images acquired 1 day posttreatment showing a unilateral thalamotomy in the VIM nucleus (*dashed square*). **Insets:** Magnified views of the same patient's T2w MRI, T1w MRI, and ATD profiles, respectively (17, 40, 100, 200, and 240 CEM_{43}) (FOV = 12 × 12 mm). In this patient, six sonications with focal temperatures between 50°C and 54°C (duration range = 15–45 seconds) were applied to generate a lesion.

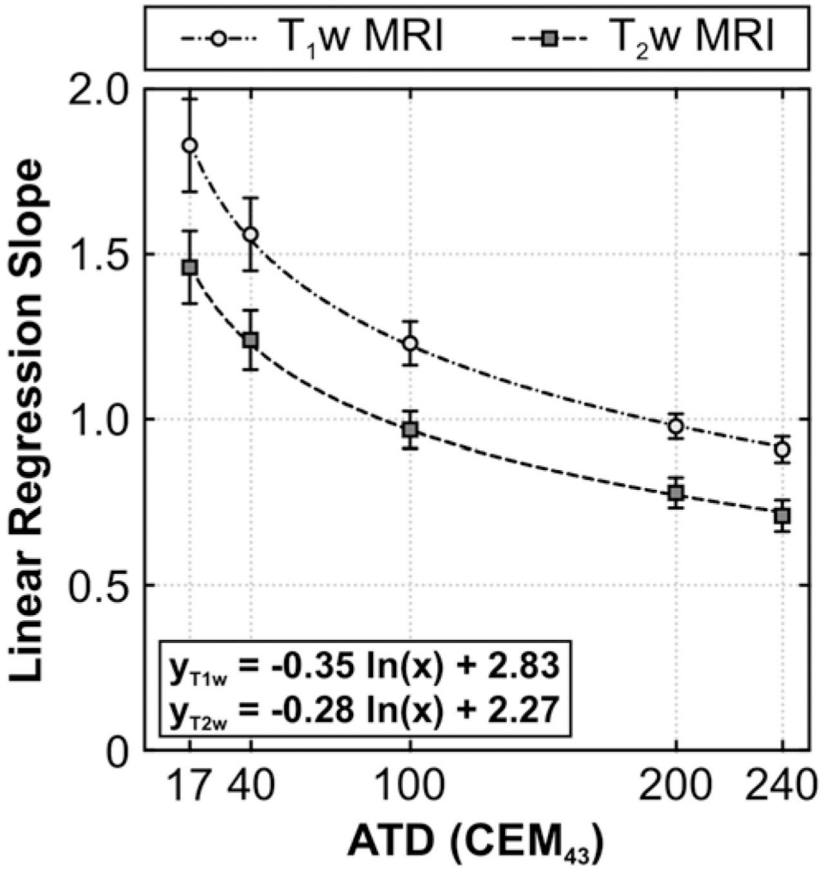

FIG. 2.

Slopes of linear regressions between the ATD profile size (17, 40, 100, 200, and 240 CEM_{43}) and the lesion size measured on T1w and T2w MR images acquired 1 day posttreatment. *Error bars* represent 95% confidence intervals (± 1.96 SDs). Logarithmic fits were applied to the data and added to the plots.

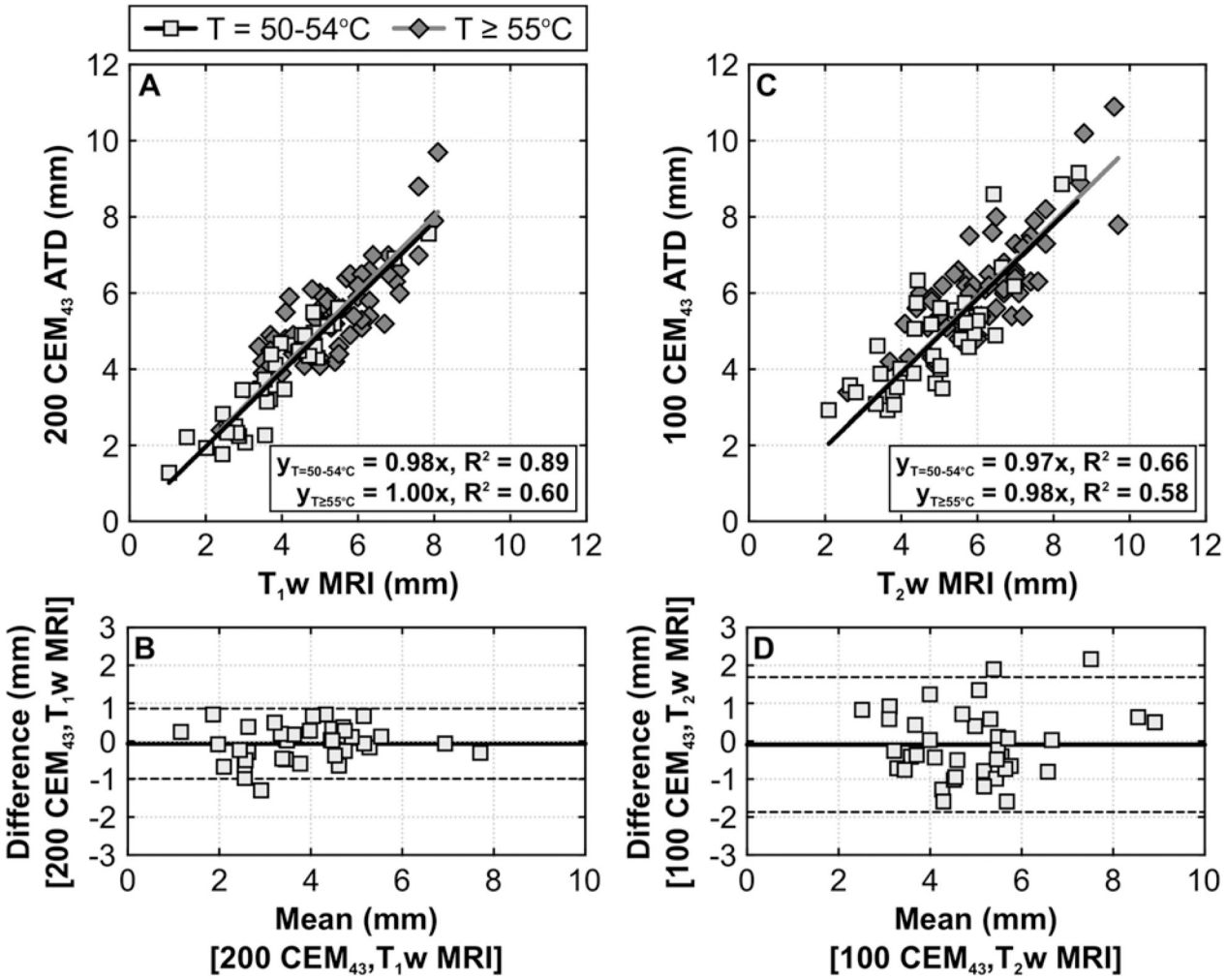

FIG. 3.

Scatterplots (**A and C**) and Bland-Altman plots (**B and D**) [difference(x, y) = x − y, mean(x, y) = (x + y)/2] of the comparison of lesion diameters estimated via ATD profile size with those measured via MRI acquired 1 day posttreatment. Comparison of the 200 CEM_{43} ATD profile size with the lesion size measured on T1w MRI (A and B). Comparison of the 100 CEM_{43} ATD profile size with the lesion size measured on T2w MRI (C and D). *Solid lines* (A and C) represent linear regressions, and data from a previous clinical study with repeated sonications at higher focal temperatures (≥ 55°C)[19] are plotted for comparison. *Solid* and *dashed lines* (B and D) represent the mean bias and limits of agreement (mean bias ± 1.96 standard deviations), respectively. T = temperature.

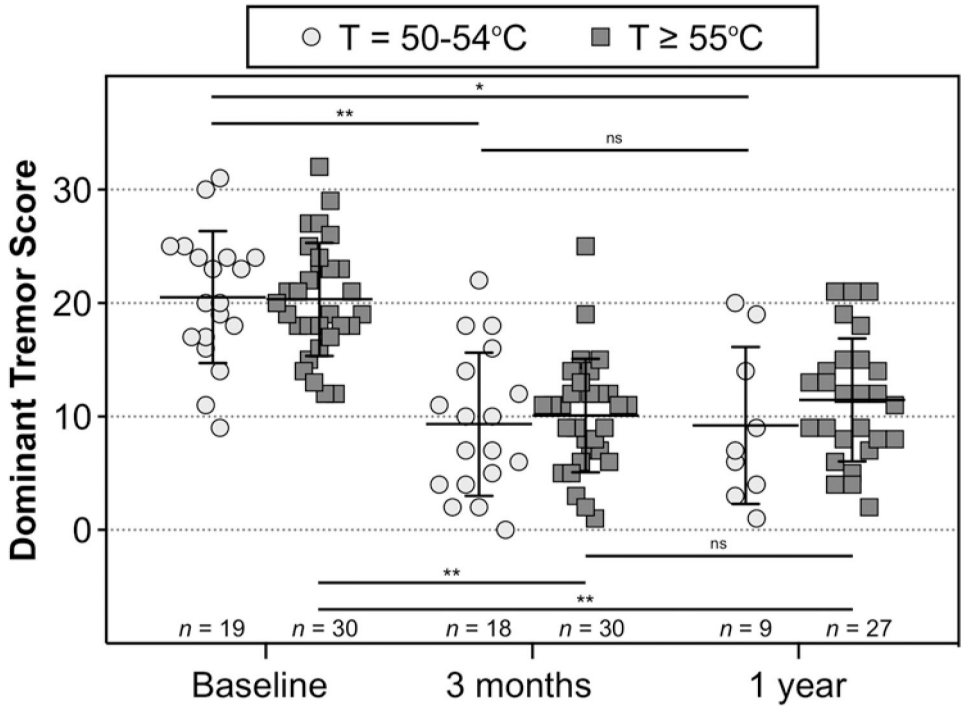

FIG. 4.

Scatterplots of dominant tremor CRST subscores at baseline, 3 months posttreatment, and 1 year posttreatment for both the low and high-temperature cohorts. Statistical analysis was performed on both cohorts: *$p < 0.05$ and **$p < 0.0001$ (ns = not significant, $p > 0.05$) on post hoc Tukey multiple comparison testing (adjusted p values). *Horizontal lines* and *error bars* represent mean and standard deviation values, respectively. The number of patients who completed each follow-up examination (n) is listed for each group.

TABLE 1.

Summary of analyses comparing MRI lesion diameters with ATD profile sizes in patients with repeated low-temperature sonications

ATD in CEM_{43}	Regression Slope	Regression R^2	Mean [difference(ATD, lesion size)] in mm	SD [difference(ATD, lesion size)] in mm	t-test p Value	95% CI, Lower Bound in mm	95% CI, Upper Bound in mm
T1w							
17	1.83	0.33	3.56	1.50	<0.0001	3.07	4.06
40	1.56	0.51	2.38	1.29	<0.0001	1.95	2.80
100	1.23	0.72	0.99	0.76	<0.0001	0.74	1.24
200	0.98	0.89	−0.07	0.47	0.39	−0.22	0.09
240	0.91	0.88	−0.40	0.48	<0.0001	−0.56	−0.25
T2w							
17	1.46	0.35	2.48	1.61	<0.0001	1.95	3.01
40	1.24	0.50	1.30	1.39	<0.0001	0.84	1.75
100	0.97	0.66	−0.09	0.91	0.54	−0.39	0.21
200	0.78	0.73	−1.15	0.75	<0.0001	−1.39	−0.90
240	0.71	0.71	−1.48	0.76	<0.0001	−1.73	−1.23

Difference(x, y) = x − y; R^2 = coefficient of determination; SD = standard deviation.