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SCIENTIFIC PAPER

Memory enhancement by transcranial radiofrequency wave treatment occurs without appreciably increasing brain temperature

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Abstract

We have previously shown in small studies that full brain Transcranial Radiofrequency Wave Treatment (TRFT) to subjects with Alzheimer's Disease could stop and reverse their cognitive decline. An 8-emitter head device, the "MemorEM", was used in these studies to provide TRFT at 915 MHz frequency and power level of 1.6 W/kg Specific Absorption Rate (SAR) during daily 1-hour treatments. Although no deleterious side effects during up to 2.5 years of treatment were reported, it is important to rule out the possibility that brain heating will occur during TRFT in humans at a higher power level of 4.0 W/kg SAR, which is anticipated for future clinical testing in order to increase treatment intensity/efficacy to deep sub-cortical areas. To examine if brain heating occurs during a single 1-hour treatment at 4 W/kg SAR, a hollow human head phantom filled with brain-analogous gel and with an attached MemorEM head device was utilized. Brain temperatures were taken at 64 specific coordinates within the brain gel before and immediately following one-hour of TRFT. Results revealed none of the 64 sites having a temperature increase after TRFT of 1 °C or more. Indeed, 45 of the 64 sites exhibited a temperature rise of less than 0.5 °C, with just three sites exhibiting an increase between 0.75 and 0.9 °C. These results demonstrate that TRFT in a human head phantom that mimics the electromagnetic properties of the human head, does not appreciably increase brain temperature (i.e., is non-thermal) at 915 MHz frequency and 4 W/kg SAR power level. Thus, TRFT would appear to be safe at 4 W/kg for long-term daily treatments.

Keywords Memory · Transcranial radiofrequency waves · Alzheimer's treatment, brain temperature · Non-thermal

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease that causes progressive cognitive impairment and primarily affects individuals over 65 years of age [1]. Currently there are over 400 million people worldwide with AD dementia, prodromal AD, or preclinical AD (22% of all persons over 50 years of age) [2]. Over a 2–10 year period, AD causes the loss or dysfunction of neurons in cognitively important brain areas such as the cerebral cortex and hippocampus. An effective AD therapy is needed because there is no drug that has been shown to prevent, stop, or reverse the progressive cognitive decline of AD. In that regard, the ability of the U.S. FDA's newly-approved monoclonal antibodies (Lecanumab and Donanemab) to slow AD cognitive decline has been questioned [3]. Because of the failure of drugs against AD for over two decades now, neuromodulatory (non-pharmacologic) approaches have emerged and are currently being clinically evaluated in AD subjects.

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Neuromodulatory approaches against AD include transcranial magnetic stimulation (tMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), LED light photo/auditory stimulation (LAS), and transcranial ultrasound (tUS) [4–6]. All of these neuromodulatory approaches appear to induce their effects on the brain largely through modulation of neuronal activity. tMS involves the in-clinic application of large magnetics to the head surface to induce magnetic fields that generally extend no deeper than the cerebral cortex. In applying direct current directly onto the forehead, tDCS has only been given clinically to AD subjects for short periods of only a few weeks and any cognitive benefits are temporary. DBS involves neurosurgical permanent placement of electrodes deep within the brain to directly activate small brain areas. Aside from being invasive and expensive, DBS simply stimulates dysfunctional brain circuitry and only a small minority of AD families would even consider this therapy. LAS only accesses the human brain through visual and auditory afferents and has thus far not shown any cognitive benefits through 3 months of treatment. Transcranial ultrasound involves invasive injection of gas bubbles into the vasculature to vibrate/open the blood/brain barrier. Many "focused" US treatments are needed per session in a hospital setting, with no clinical benefits against AD having been reported so far. In contrast to the novel neuromodulatory approach of the present study, none of these other neuromodulatory approaches have yet clinically demonstrated: (1) long-term cognitive stabilization/improvement in AD subjects, (2) the ability to treat all forebrain regions affected in AD, or (3) the ability to modify AD markers in the brain or blood of AD subjects [4–6].

To address the immense unmet need of an effective therapeutic against AD, we have developed a new bioengineering-based technology against AD – Transcranial Radiofrequency Wave Treatment (TRFT). Through a head device called the MemorEM, radiofrequency (RF) waves are administered non-invasively to the entire human brain. These RF waves easily penetrate the bony cranium to then enter all neurons of the human forebrain. In small studies, 2-months of daily TRFT has been shown to reverse AD cognitive impairment [7] and TRFT stops AD cognitive decline over a 2.5 year period [8] – this, with beneficial effects on multiple AD/inflammatory markers in both brain and blood. Because RF waves provided by the MemorEM device have no difficulty going through the skull and into all neurons of the human forebrain, the diverse brain areas affected by AD can all be treated through TRFT's "disease-modifying" mechanisms of action such as disaggregation of toxic β-amyloid (Aβ) and p-tau oligomers, mitochondrial enhancement, and reduction in brain inflammation (see Discussion). By contrast, pharmacologic interventions such as monoclonal antibodies against Aβ have difficulty getting into the brain and almost no ability to get into the brain's neurons. Even if they could do so, they don't target what most researchers now believe are the primary culprits in AD– soluble oligomeric of β-amyloid and p-tau, low energy production, and inflammation.

Regarding TRFT given clinically, no deleterious side effects were reported by subjects/caregivers or observed in clinical visits for the 915 MHz frequency and 1.6 W/kg Specific Absorption Rate (SAR) power level utilized [7, 8]. However it is important to be confident that TRFT and the MemorEM device are safe in not providing any unseen damage to the brain for a higher "4.0 W/kg" power level anticipated for future TRFT clinical studies. This higher power level should achieve greater treatment distribution/intensity to deeper brain areas involved in AD. Regarding use of this higher 4.0 W/kg power level, any deleterious effects due to TRFT would involve induction of increased brain temperature [9]. Indeed, targeted RF ablation in the brain to kill cells within gliomas occurs through focal heat generation (increased tissue temperature) [10].

Given the aforementioned potential of RF waves to damage/destroy brain tissue via hyperthermia, it would be desirable to measure brain temperature of human subjects before and immediately following a standard 1-hour TRFT administration via MemorEM devices to determine the degree to which a higher power (4.0 W/kg) TRFT affects brain temperature. Presently, the most direct non-invasive way to measure TRFT effects on human "brain" temperature would be through MR chemical shift thermometry [11]. However, this approach is impractical for TRFT because: (1) back-to-back scans would need to be done before and after treatment, thus involving over two hours of immobility, and (2) metal components within the MemorEM device on the subjects head would interfere with any MR-based scan. As such, direct measurement of any brain temperature effects of TRFT in human subjects is impractical.

Despite the aforementioned impracticality of direct brain temperature measurement with TRFT/RF wave exposure, a number of studies have utilized the Finite-Difference Time-Domain (FDTD) "computer simulation" method to approximate the change in brain temperature during RF wave treatment at 900 MHz and near 1.6 W/kg SAR (i.e., the MemorEM device's parameters). In their human head computer model, Wessapan et al. [12] showed that a very minimal 0.1°-0.2 °C increase in brain temperature occurred. Wang [13], as well Van Leeuwen et al. [14], also calculated brain temperature in their FDTD computer simulation studies involving around 900 MHz exposure and found no more than a 0.1° C rise in brain temperature. Similarly, Zhao et al. [15] investigated brain temperature at various brain depths in an FDTD model and reported a very minimal increase of 0.02 °C or less at various depths. In all of these FDTD

computer simulation studies, the degree of brain heating at 900 MHz and near 1.6 W/kg SAR is predicted to be insufficient to induce any deleterious biological effects.

Since any potential health problems due to radiofrequency field exposure are linked to temperature increases of at least 2°–3° C [16, 17], the very minimal increases in brain temperature calculated in the FDTD studies [12–15] suggest that the presently-used power level (1.6 W/kg) of the TRFT device is highly unlikely to have any thermally-induced health hazards associated with its use. However, no study has yet focused RF treatment to the entire human brain, much less at the 4.0 W/kg SAR power level that we wish to use in our future clinical studies to achieve greater treatment distribution/intensity to deep brain areas involved in AD. To avoid any potential for brain damage with use of higher power levels clinically (e.g., 4.0 W/kg SAR), the present paper firstly utilizes a human head computer simulation to show the deep/penetrating SAR and electric field distribution within the simulated head at both 1.6 and 4.0 W/kg SAR for an RF emitter on the head surface. We then use a first-of-its kind in situ human head model to directly determine RF effects at 4 W/kg SAR from the MemorEM head device on temperature at dozens of sites within the model's brain-analogous gel before and after the typical 1-hour period of TRFT administration [7, 8]. Results from this in situ human head model indicate only minimal increases in brain temperature of less than 1 °C induced by TRFT at 4 W/kg. These results are then considered in the Discussion relevant to brain temperature increases necessary to induce thermal damage to the human brain, with the conclusion that the minimal RF-induced temperature increases observed are below threshold for inducing any deleterious physiologic/behavioral effects [18].

Methods

Investigational device

The MemorEM device has been designed for in-home daily treatment, allowing for complete mobility in performing most daily activities during treatment. The device has a custom-engineered circuit board and a rechargeable battery inside the box housing, as well as a control panel on the outside of the housing for treatment control. The box is worn on the upper arm and wired via a cable to eight emitters within a two-layered head cap (Fig. 1a, b). Emitters are activated sequentially at 217 Hz such that only one emitter is active at any given time. When active, an emitter projects radiofrequency waves into the brain at 915 MHz and 1.6 W/kg power level. The selection of 915 MHz frequency was based on our pre-clinical work in AD transgenic mice wherein we showed a reversal of cognitive impairment and AD marker changes at that frequency, while selection of 1.6 W/kg power level was based on that SAR level being the maximal power level allowed by FCC in the U.S for mobile phones.

In 2017, the MemorEM device was approved as "non-significant risk" (NSR) by the Western Institutional Review Board (WIRB; Study #1176697). This approval was based upon the device design, bench testing data, pre-clinical test data, clinical test data, and the design of an initial Phase I clinical study. In 2020, the device was designated by the FDA as its first *"Breakthrough Device"* for the treatment of AD cognitive impairment (FDA reference Q151058/S001) [19].

As a first step in comparing the penetration ability of 1.6 W/kg vs. 4.0 W/kg SAR power levels at 915 MHz, computation of SAR and electric field in the head was performed following the 62704-1-2017 - IEC/IEEE International

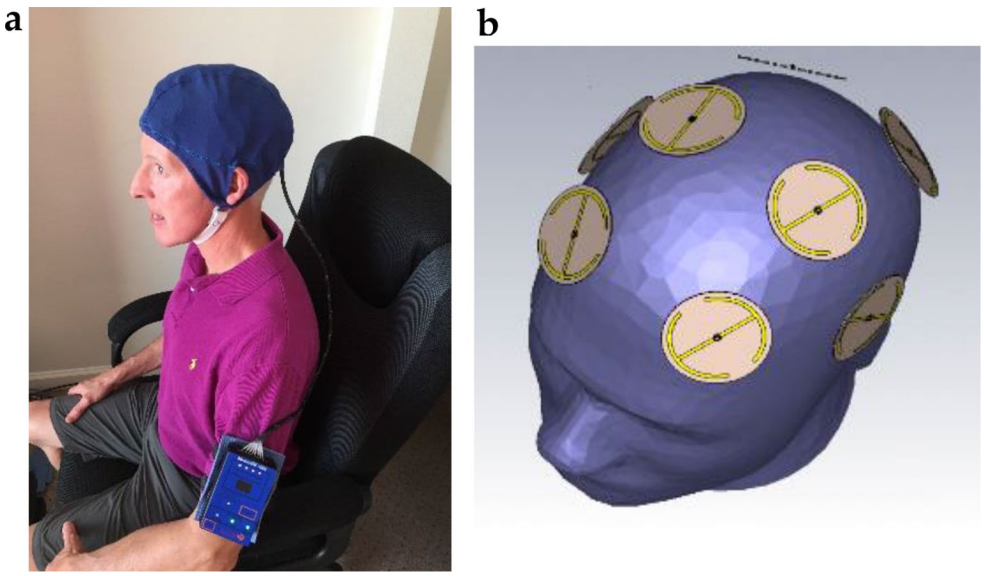

Fig. 1 **a** A MemorEM head device being worn by a subject sitting down. The in-home device allows for near-complete movement during treatment. **b** Head positions of the eight radiofrequency wave emitters embedded between the device's two-layered head cap. Emitters are activated sequentially at 217 Hz to collectively provide full forebrain TRFT

Standard utilizing the commercial finite-element method (FEM) High-Frequency Structure Simulation (HFSS) from ANSYS Corporation. This standard identifies families of human head models for use in SAR and electric field determinations, which are important to distinguish between. SAR is a measure of the rate at which a body or body part (i.e., brain) absorbs RF energy in watts per kilogram (W/kg). More specifically, SAR expresses the energy absorption rate of an RF field impinging on human body tissue as defined by the time derivative (i.e., the speed) of the energy absorbed by a given portion of tissue mass. In practice, SAR is calculated by determining (by direct measurement or simulations) the electric field (E) inside the human tissue (in volts/meter) and using the relationship $SAR = \sigma \times E^2 / p$ where "σ" is the sample's electrical conductivity and "p" is the sample's density. SAR is a measure of power dissipation (as a surrogate for temperature rise) in a given volume. Regulations limit how much power (SAR) can be dissipated in a given volume. The electric field is the main contributor to tissue heating because its intensity decreases with distance (r) following a (1/r) relationship. Thus, the closer the source of the electric field, the stronger will be the heating effect on tissue, with power decaying as ($1/r^2$). Power is the square of the electric field. Efficacy is proportional to the electric field (according to the Lorentz force).

When the SAR calculations are to be compared with temperature measurements, a specific anthropomorphic mannequin (SAM) model is appropriate and therefore used in this work, as described in Sect. 2.2.

In situ set-up

In order to mimic as closely as possible the RF field provided by the MemorEM device to human subjects (without the vascular thermoregulatory mechanisms present in a human's brain), an in situ set-up was created. Temperature measurements were accomplished using a Speag V10 Phantom Head filled with brain-analogous gel – a model that is generally considered acceptable for Radio Frequency Measurements. This SAM head model has been developed through measurement of many adult human males of military age.

The SAM model consists of a 2 mm boundary layer composed of dielectric having the same electrical properties as human skin. The SAM cranial shell is filled with brine solution representative homogeneous brain tissue. The parameters of the brine solution/gel yield equivalent permeability and permittivity measures as in the living human brain. Such SAM models defined by this standard are routinely used for compliance temperatures measurements, as has been done in the present study.

Temperature measurements performed capture thermal changes in the brain-analogous brine solution/gel immediately after a typical 1-hour clinical treatment, with a MemorEM device's 8 emitters attached appropriately to the Phantom's outer wall (Fig. 2a-c). Thus, temperature measurements simulate the heating of the human head tissue due to RF exposure during a typical MemorEM use session. A block diagram of the in situ setup's components and connectivity is shown in Fig. 3.

Temperature measurement locations

The diagramed grid in Fig. 4a shows the top view of planar (x, y) measurement locations used for the temperature determinations. The locations are separated by no more than 2" point to point, and they follow the contours of the Speag V10 Phantom. The physical implementation of this grid is shown in Fig. 4b. The images in Fig. 4c and d show how the Phantom Head and measurement grid are integrated to obtain location consistency. The Top surface of the phantom is 1.75" above the body analog gel and the top measurement location is 0.25" into body analog gel.

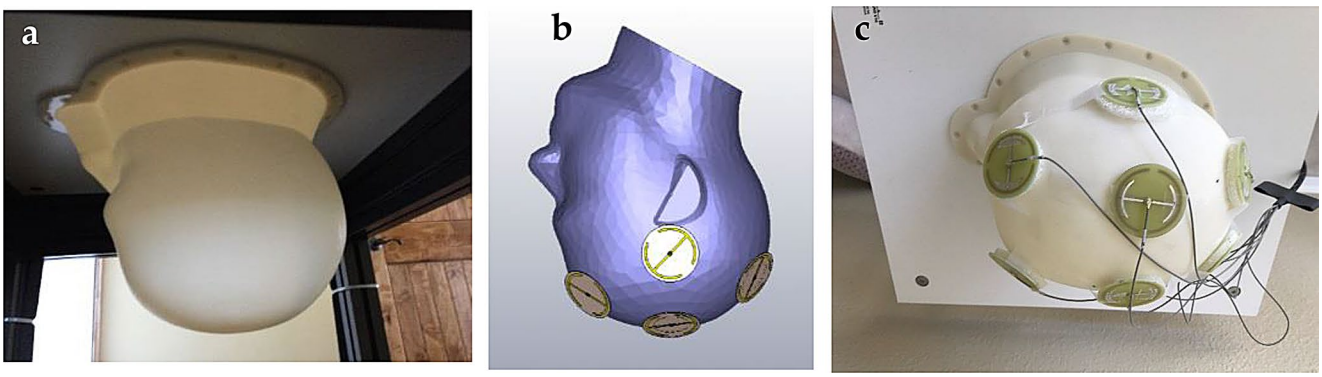

Fig. 2 **a** The inverted Speag phantom head filled with brain-analogous gel as pictured from below the custom table. **b** Diagramed location of the four RF wave emitters on the right side of the head for orientation with the phantom head. **c** The actual experimental set-up, showing Egyptian Axe RF wave emitters wired to RF switching box (not shown). Note 5 mm thick foam spacer underneath each RF emitter

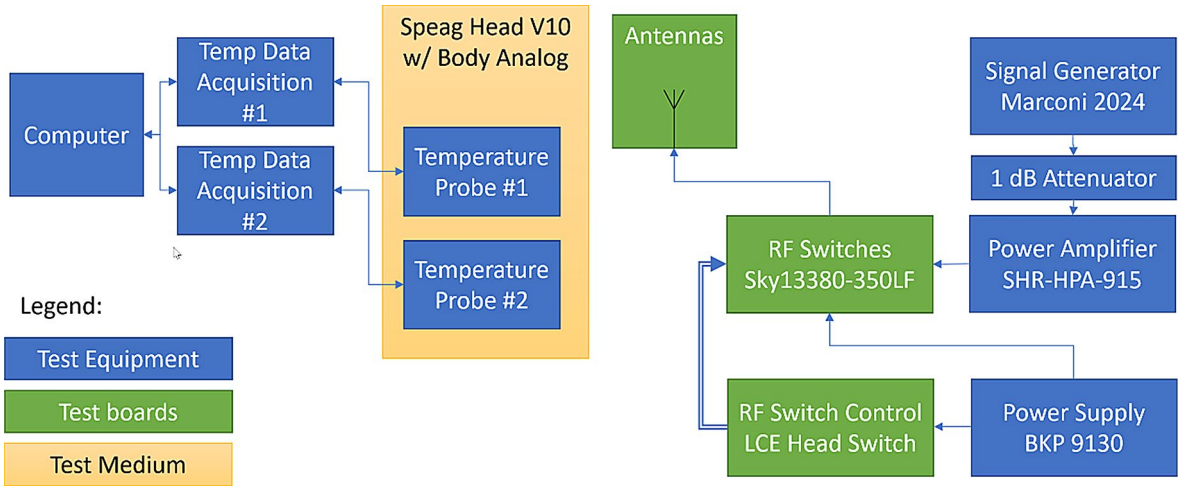

Fig. 3 The in situ setup's components and connectivity shown in a block diagram

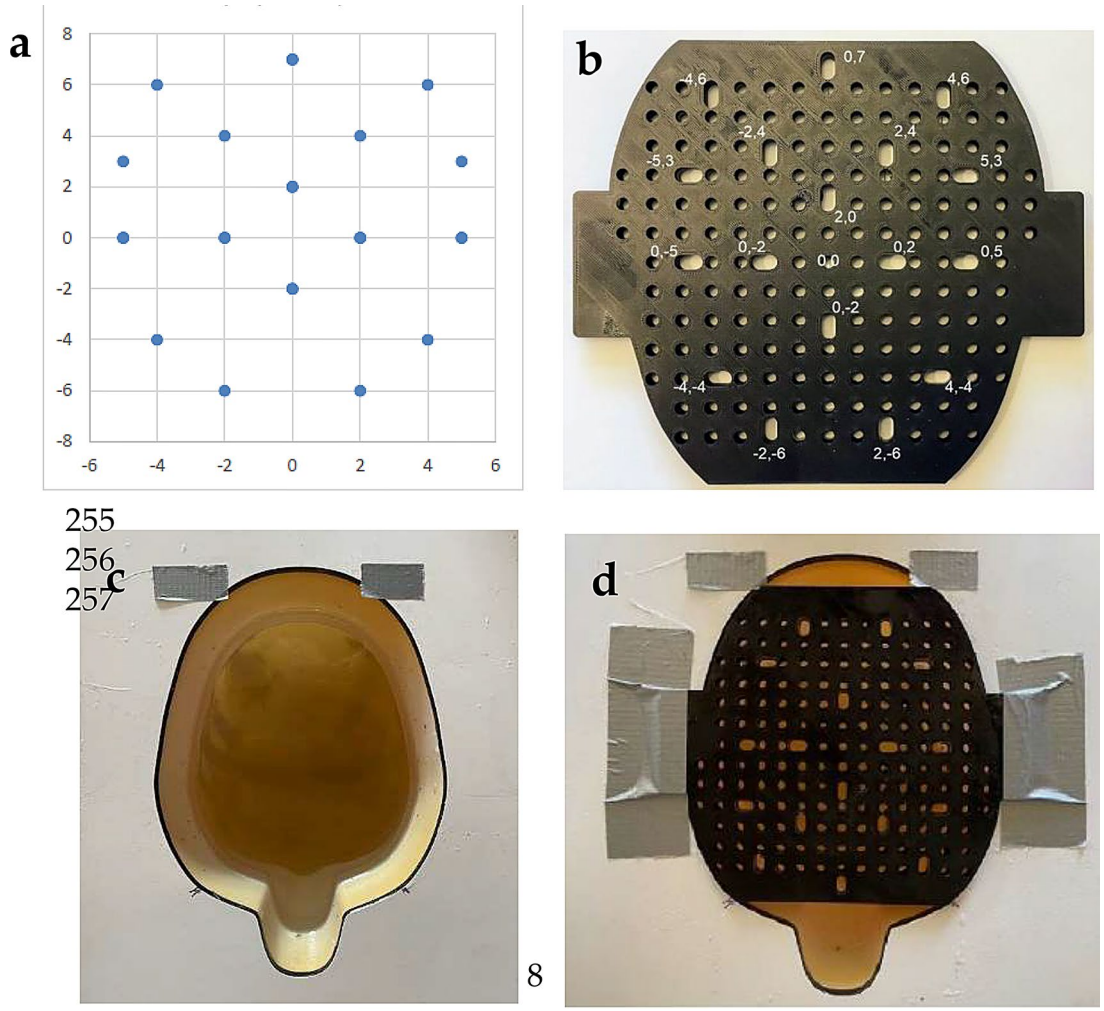

Fig. 4 **a** Top view of the diagramed grid showing planar measurement locations used for temperature determinations. **b** The actual 3D alignment grid based on (A). **c** The hollow Speag head phantom from above which is normally filled with brain analogous gel for measurements. Note that this head is inverted, where the bottom of the phantom corresponds with the top of the head. **d** Integration of the phantom head and grid, which provides planar location consistency

Temperature collection

Left and right sides of the head were done in separate tests because of the length of time required for measurement and to prevent gel cool down. Measurements were done after RF completion so that the probe did not influence RF patterns and vice-versa. The temperature probe used in the testing was the Dracal RTD-PT100-SIL. Initial experiments showed that the temperatures measured with this probe would be offset in the presence of RF, which meant measurements could not be performed during the RF treatment. More importantly, there was concern that being close to the phantom during RF treatment could influence the antennas and change the overall radiation pattern incident to the gel. To reduce that risk, the setup and area around it was left static and still during the one-hour RF treatment, which precluded taking measurements during the treatment time.

For the *pre-exposure* measure at any given planar (x, y) site, the temperature probe was initially positioned at the top of the gel, then lowered for temperature readings (z coordinate) at the following measurement depths: 0.25", 2.25", 4.25", and 6.25" (or 5.75" or 5.25" depending on the contour of the Speag Head). The probe was maintained in a position until the temperature reading settled, defined by temperature reading changes of less than 0.001 C per second. This settling typically took over 60 s per measurement location. To prevent stirring of the gel during probe movement, positions were changed slowly; on the order of a few seconds per location. This, with the number of sample points collected, meant that collecting the data for half the head would take a considerable amount of time.

For RF treatment at 4.0 W/kg via the MemorEM device's 8 emitters attached to the Speag Head, the RF power on the signal generator was enabled and power amplifier turned on. After one hour of RF treatment, the signal generator's power was turned off. For *post-exposure* temperature measures, the same procedure was utilized as for pre-exposure measurements. All measurements for one side of the head were collected within 60 min. The entire procedure was then repeated for the other side of the head phantom. For determination of change in temperature induced by the one-hour RF treatment at each site, the difference between pre-exposure and post-exposure temperature was calculated.

Results

TRFT effects in human head computer simulations

At 915 MHz and a power level of either 1.6–4.0 W/kg SAR, ANSYS High Frequency Structure Simulator (HPSS) human head computer simulations show that the eight emitters within a MemorEM device collectively provide penetrating TRFT to the human forebrain, including the cerebral cortex, underlying structures, and both superficial and deep cerebral vessels, as shown in Fig. 5 for both SAR and electric field penetration of RF waves from a single emitter in an HPSS human head computer simulation.

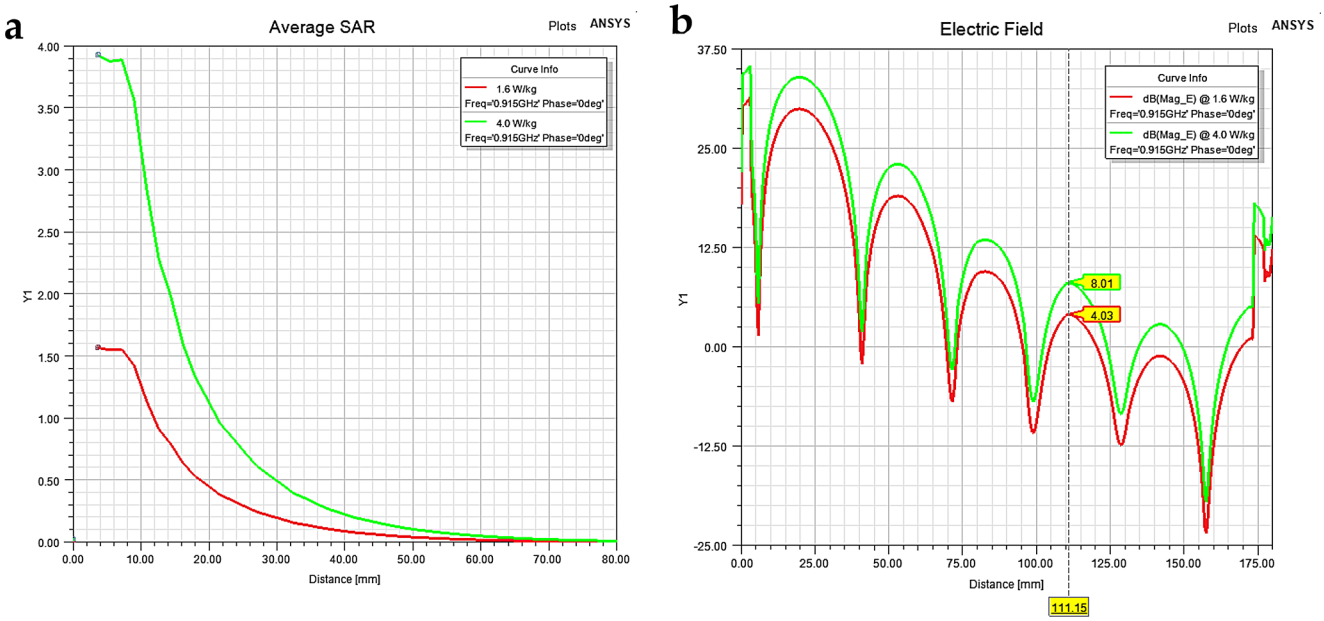

Fig. 5 Electromagnetic penetration for one of the eight emitters (above the ear) of the SAM head model when the emitter is in the "ON" position. **a** SAR (W/kg) vs. penetration distance/depth for transmitter power levels yielding a maximum 1.6 W/kg and 4.0 W/kg (NOTE: model's brain center is at 70–75 mm) and **b** Electric field magnitude (dBV/m) vs. penetration distance/depth for transmitter power levels yielding a maximum 1.6 W/kg and 4.0 W/kg. Note that the electric field is still substantial at the center of the brain.

Figure 5a shows the penetrating SAR resulting from a single emitter (above the ear) in the "ON" position at either 1.6 or 4.0 power level, while 5**b** depicts the associated electric field penetration for both power levels. SAR continually decreases with brain depth for both power levels to reach near zero at the center of the brain (approximately 70–75 mm). Electric field, while also decreasing with brain depth, is still sizable at the center of the brain. Although the higher power level of 4.0 W/kg SAR increased the electric field (treatment intensity) to deep sub-cortical areas compared to 1.6 W/kg, both power levels resulted in electric fields within the brain at any distance from the RF emitted on the head surface. It should be noted that operating at a SAR of 4.0 W/kg results in a 4 dBV/m increase in electric field strength vs. 1.6 W/kg at any depth and across the entire head width.

TRFT effects on temperature in a human phantom head model

The diagram in Fig. 6 provides a three-dimensional representation of the collected temperature data. Each of the 64 sites is represented by a sphere indicating the difference in temperature between before and immediately following a 1-hour treatment with a MemorEM device's 8 emitters sequentially operating on the phantom head at 217 Hz. The ranges of temperature increases are represented by different color markers. The data in this view is looking down through the inside of the Phantom Head shown in Fig. 5c.

As shown in Fig. 6; Table 1, none of the 64 sites exhibited an increase of 1 °C or high (highest increase was 0.87 °C). For temperatures taken before and immediately after the 1-hour TRFT, 29 sites exhibited a temperature increase less than 0.25 °C, 16 sites had a temperature increase between 0.25 and 0.50 °C, 16 sites showed a temperature increase between 0.50 and 0.75 °C, while only 3 sites had a temperature increase of 0.75–1.0 °C. All 3 sites in this latter category were located in the brain gel immediately below the two temporal emitters (above the ears). All 16 of the sites having an increase between 0.50 and 0.75 °C were located in brain gel just below the cranium to a depth of around 5 cm – volumetric areas occupied by cerebral cortex gray and white matter.

Discussion

We have previously treated mild/moderate AD subjects for periods of up to 2.5 years with TRFT, a new bioengineered technology that has been shown to stop and reverse the cognitive decline of AD subjects, albeit in relatively small clinical studies [7, 8]. TRFT was administered through use of an in-home and self-contained head device called the MemorEM, which provided RF wave treatment to the entire human forebrain at 915 MHz and 1.6 W/kg power level. Although there were no safety issues raised by subjects/caregivers or observed in clinical visits with such long-term treatments at 1.6 W/kg power level, our future clinical trials at a higher 4.0 W/kg power level require a more definitively

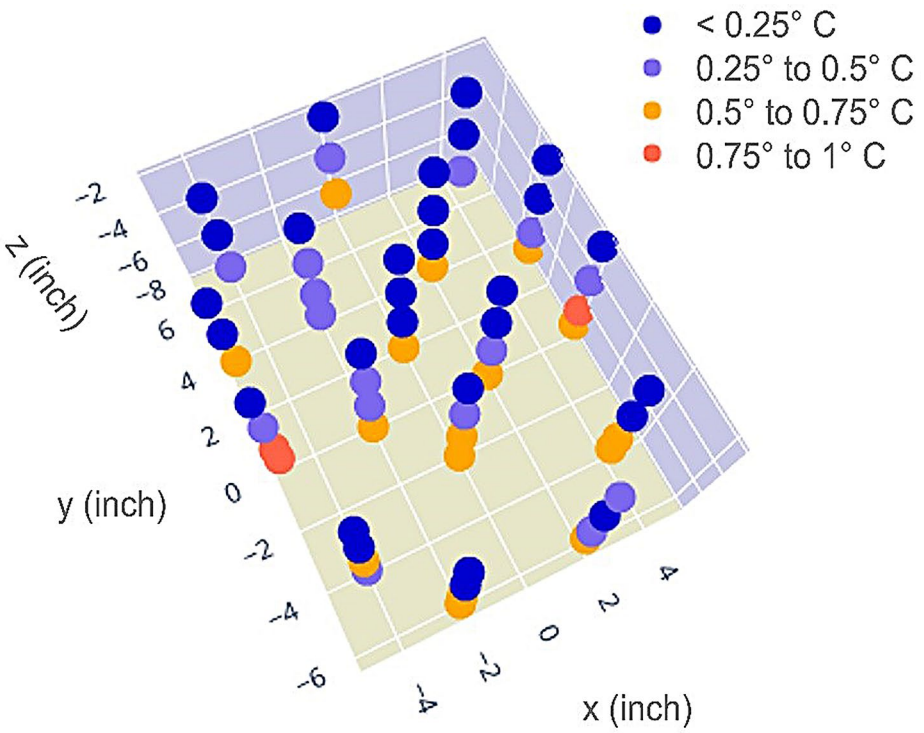

Fig. 6 A diagram providing three-dimensional representation of collected temperature change data from each of the 64 measurement sites (spheres). Each colored sphere represents the difference between pre-treatment and post-treatment temperature at that site. The data in this view are looking from above and down into the inverted phantom head shown in Fig. 4c, where the deepest measurements correspond to the top of the inverted head (Crown of Head at z = -8, nose at 0,-8). The four ranges of temperature change are represented by different colored spheres. Actual values are listed in Table 1

Table 1 64 Recording sites (x, y, and z coordinates in inches) and temperature data. For each of the 64 sites, the change in temperature (Δ) is indicated, both exactly and within one of the four temperature ranges in Fig. 6

x (in)	y (in)	z (in)	Exact Δ	Δ within a range
-5	0	0.25	0.131°	<0.25 °C
-5	0	-0.25	0.432°	0.25 to 0.5 °C
-5	0	4.25	0.874°	0.75 to 1 °C
-5	0	-5.25	0.804°	0.75 to 1 °C
-2	4	-0.25	0.121°	< 0.25 °C
-2	4	-2.25	0.301°	0.25 to 0.5 °C
-2	4	-4.25	0.462°	0.25 to 0.5 °C
-2	4	-5.75	0.482°	0.25 to 0.5 °C
-4	-4	-0.25	-0.020°	< 0.25 °C
-4	-4	-2.25	0.248°	< 0.25 °C
-4	-4	4.25	0.625°	0.5 to 0.75 °C
-4	-4	5.75	0.434°	0.25 to 0.5 °C
-5	3	0.25	0.041°	< 0.25 °C
-5	3	2.25	0.158°	< 0.25 °C
-5	3	4.25	0.583°	0.5 to 0.75 °C
-2	-6	-0.25	-0.020°	< 0.25 °C
-2	-6	-2.25	0.178°	< 0.25 °C
-2	-6	-4.25	0.523°	0.5 to 0.75 °C
-2	-6	-5.75	0.512°	0.5 to 0.75 °C
-2	0	-0.25	0.030°	< 0.25 °C
-2	0	-2.25	0.271°	0.25 to 0.5 °C
-2	0	-4.25	0.412°	0.25 to 0.5 °C
-2	0	-6.25	0.522°	0.5 to 0.75 °C
0	2	-0.25	-0.171°	< 0.25 °C
0	2	-2.25	-0.251°	< 0.25 °C
0	2	-4.25	0.010°	< 0.25 °C
0	2	-6.25	0.673°	0.5 to 0.75 °C
-4	6	-0.25	-0.070°	< 0.25 °C
-4	6	-2.25	0.080°	< 0.25 °C
-4	6	-4.25	0.342°	0.25 to 0.5 °C
0	7	-0.25	0.241°	< 0.25 °C
0	7	-2.25	0.301°	0.25 to 0.5 °C
0	7	-4.25	0.603°	0.5 to 0.75 °C
4	6	-0.25	0.221°	< 0.25 °C
4	6	-2.25	0.221°	< 0.25 °C
4	6	-4.25	0.452°	0.25 to 0.5 °C
2	-6	-0.25	0.296°	0.25 to 0.5 °C
2	-6	-2.25	0.188°	< 0.25 °C
2	-6	-4.25	0.405°	0.25 to 0.5 °C
2	-6	-5.25	0.538°	0.5 to 0.75 °C
2	4	-0.25	-0.059°	< 0.25 °C
2	4	-2.25	-0.049°	< 0.25 °C
2	4	-4.25	0.227°	< 0.25 °C
2	4	-5.75	0.563°	0.5 to 0.75 °C
4	-4	-0.25	-0.059°	< 0.25 °C
4	-4	-2.25	0.197°	< 0.25 °C
4	-4	-4.25	0.504°	0.5 to 0.75 °C
4	-4	-5.25	0.622°	0.5 to 0.75 °C
5	3	-0.25	0.242°	< 0.25 °C
5	3	-2.25	0.201°	< 0.25 °C
5	3	-4.25	0.442°	0.25 to 0.5 °C
5	3	-5.25	0.603°	0.5 to 0.75 °C
0	-2	-0.25	0.128°	< 0.25 °C
0	-2	-2.25	0.296°	0.25 to 0.5 °C
0	-2	-4.25	0.563°	0.5 to 0.75 °C
0	-2	-6.25	0.612°	0.5 to 0.75 °C
2	0	-0.25	-0.089°	< 0.25 °C
2	0	-2.25	0.188°	< 0.25 °C
2	0	-4.25	0.385°	0.25 to 0.5 °C
2	0	-6.25	0.622°	0.5 to 0.75 °C
5	0	-0.25	-0.128°	< 0.25 °C
5	0	-2.25	0.424°	0.25 to 0.5 °C
5	0	-4.25	0.819°	0.75 to 1 °C
5	0	-5.25	0.622°	0.5 to 0.75 °C

determination if any damage to brain tissue may occur at that higher power level. Any deleterious effects or damage to brain tissue through RF waves would necessitate a brain temperature rise (hyperthermia) of at least 2–3° Celsius [20]. Since the present study found only a minimal (< 1 °C) brain temperature rise with TRFT/MemorEM at 4.0 W/kg in an in situ human brain model, it would seem to be safe at 4.0 W/kg for long-term daily treatments clinically.

The current study's unique in situ set-up was designed specifically with the MemorEM device in mind through a human head phantom and brain gel that closely mimics cranial and brain radiofrequency properties of the human head/brain. The device's 8-emitters were "ON" one at a time at power levels that provide an average of 4.0 W/kg and in a sequence which was repeated 217 times per second to provide the first full forebrain RF wave treatment to humans. The heat distribution profile across the entire phantom brain for the MemorEM device was as expected (e.g., no site having a temperature increase greater than 1 °C). Specifically, half of the 64 sites had a very minimal/no increase (< 0.50 °C) in temperature and were located primarily in and around the central core of the brain and furthest from the 8 emitters. All 16 of the sites registering a temperature increase between 0.50 and 0.75 °C were located more superficially within the cerebral cortex, closer to the emitters located on the cranium. The remaining 3 sites showing a temperature increase of 0.75–1.0 °C were located immediately below the two temporal lobe emitters (above the ears).

The present study's 4.0 W/kg SAR exposure is well below the brain exposure SAR limit of 8.0 W/kg established by the FCC for occupational exposure or with training [18] – the latter is the case for TRFT since the subject or caregiver are provided with full training on use of the MemorEM device in advance of treatment. The occupational limit has been established with the criteria that a person's exposure time per day be limited, as it is with TRFT's once or twice daily 1-hour treatments. Prior to the present study,

brain temperature effects of RF wave exposure exclusively to the human "brain" had only been investigated in FDTD computer simulations [12–15], wherein a power level of 1.6 W/kg induced increases in brain temperature of 0.2 °C or less [12/15]. As well, both acute and long-term mouse studies measuring brain temperature indirectly via a temporal muscle probe found only a 0.1–0.3 °C increase in brain temperature after one-hour RF at 1.6 W/kg [21, 22]. In view of these prior studies involving human brain computer simulations or mice, the current study's in situ set-up provides a more direct and accurate system for determining RF wave treatment effects on temperature within the entire human forebrain's simulated brain tissue.

Numerous clinical studies have determined that short- or long-term human exposure to radiofrequency waves similar to those provided by the TRFT device (900 MHz RF, 1.6 W/kg power level) do not have deleterious effects on general health, subjective symptoms, cognitive function, or a variety of physiologic measures [23]. Moreover, such radiofrequency wave exposure has been shown not to increase the risk of any type of cancer in human epidemiologic studies [23, 24]. Rather, beneficial effects of radiofrequency waves of around 900 MHz RF have been reported on brain physiology, such as enhanced cortical excitability, increased alpha-wave EEG activity, and enhanced brain energy metabolism (glucose utilization) [25–27] – this, in addition to stoppage and/or reversal of Alzheimer's Disease cognitive decline as reported in our prior studies [7, 8]. Indeed, most AD subjects in our 2.5 year study received around 600 one-hour treatments over that period, with cognitive stability and no safety issues.

The human brain represents only around 2% of body weight, yet it accounts for around 20% of a human's total energy consumption at rest [28, 29]. Thus, the heat continuously being generated by the brain needs to be removed by the cerebral circulation through homeostatic thermoregulation. There is a temperature differential between cooler arterial blood flowing into the brain and warmer brain tissue, which results in dissipation of excess heat in brain tissue via outflowing blood from the brain [29]. As such, one drawback to the presently-used in situ head-analogous set-up is its inability to mimic the brain's substantial thermoregulatory system that maintains brain temperature – thus the currently modeled RF-induced temperature rises were not "buffered". Fortunately, RF-induced temperature rises were so small (< 1 °C) as to make any homeostatic vascular system actions either unnecessary or minimally important when the MemorEM device is being used on the head of a human at 4.0 W/kg power level. Thus, the 4.0 W/kg power level should not result in any rise in body temperatures. Supportive of this notion are our small AD clinical trials involving 2 months [7] or 2.5 year periods [8] of TRFT treatment at 1.6 W/kg power level. Any "unbuffered" increase in brain temperature during any given 1-hour treatment would have likely been picked up as an increase in body temperature during or immediately following that treatment. However, body temperature readings taken before, during, and immediately following all 1-hour treatments by caregivers showed no pattern of increased body temperature during or following TRFT [7, 8].

A second drawback to the current model is that there are potential non-thermal, physical effects of TRFT to the human brain that may become manifest at this higher power level and that our model cannot predict because it does not contain the actual parenchyma and blood vessels of the human brain. Specifically for AD, the insoluble, deposited β-amyloid (Aβ) in both cerebrovascular blood vessels and brain parenchyma may be dislodged/disaggregated at the higher 4 W/kg power levels. This could have some deleterious effects on neuronal function, cerebrovascular blood flow, and/or on occurrence of cerebrovascular blood clots. Although we consider these potential complications to have low likelihood, only human clinical trials with TRFT at the higher power level will unequivocally confirm its safety.

Brain cells are exceptionally sensitive to heat, with some irreversible damage starting to occur about 3 °C above normal baseline and progressing with even slight increases above this level [16, 17]. The only known mechanism that RF waves have for damaging living tissue is through heating. Normal "average" brain temperature is 38.5 °C, with it fluctuating by about one degree with daily activities [30]. Along this line, direct measurements from healthy human volunteers suggest that their brain temperatures reach 39.5–40.0 °C during a 30-min bicycle exercise [31, 32]. Yet the physical and mental states of these volunteers at these higher temperatures remained within the normal range. Thus, the less than 1 °C increase in temperature induced by the MemorEM device at 4 W/kg power level within brain gel of the present human head model would be insufficient to damage brain tissue – especially since the brain's thermoregulatory system is not considered in this set-up.

Although the present human head model appears to be the first *"in situ"* model (i.e., physical human head) capable of assessing thermal effects of RF on the human brain, one earlier FDTD computer simulation study would appear to be the closest analogy for assessing thermal effects of RF waves on the human brain [33]. The study investigated the potential heat generated by one or eight silicon chips on the surface of an anatomically-detailed human head mesh, with each chip simulating emission of RF waves at a brain machine interface. The investigators used calculated SAR values generated at each chip alone or collectively and used those SAR values to predict peak temperature changes in the head using the two-dimensional bio-heat equation.

Although utilizing a much lower power level (10 mW of power absorption per chip) than in the current study, their results indicated minimal brain heating of only 0.018–0.06 degrees at frequencies up to 5.8 GHz – including 1 GHz (very near the present study's 915 MHz). Thus, results from this closest FDTD simulation study to our in situ study are consistent with the present paper's findings.

Any thermal effects of radiofrequency waves would be due to the temperature rise in the brain caused by energy absorption from oscillating electric fields [30]. It is the electric fields induced by RF waves (not induced magnetic fields) that are responsible for any RF wave clinical benefits. As shown in the HPSS human head computer simulations of the present study comparing 1.6 W/kg vs. 4.0 W/kg power levels, the greater electric field at any given brain depth with 4.0 W/kg should provide greater clinical benefits. Nonetheless, TRFT at even 1.6 W/kg has multiple established mechanisms that target AD in humans: (1) disaggregation of toxic Aβ and tau aggregates/oligomers within neurons, (2) mitochondrial enhancement within neurons, and (3) a "re-balancing" of the immune system in both brain and body/blood that results in a dramatic decrease in both brain and body inflammation [7, 8, 21, 22, 34–36]. Most recently, our clinical studies have revealed a fourth mechanism of TRFT action, which is to increase the CSF drainage/clearance of toxins (e.g., Aβ, tau) from the brain and into the blood [37]. Given the current understanding of AD pathogenesis, all of these mechanisms are "disease-modifying". Moreover, with the present study's findings of minimal temperature increase with TRFT at 4.0 W/kg, these multiple mechanisms of TRFT action are apparently non-thermal in nature. It should be noted that, in addition to AD, there are many other neurodegenerative diseases (e.g., Parkinson's Disease, Frontotemporal Lobe Dementia, Amyotrophic Lateral Sclerosis) that share the same pathologic process of toxic protein aggregation, decreased mitochondrial function, and/or an imbalanced immune system in brain/body [36]. Therefore, TRFT at 4 W/kg could be a safe and effective preventative or therapeutic intervention against multiple neurodegenerative diseases.

There are a number of current limitations of TRFT, both clinically and practically. First, as a new clinical approach to treating neurodegenerative diseases such as AD, the best set of TRFT parameters (i.e., frequency, power level, duration of treatment) has yet to be identified for AD. Moreover, no TRFT clinical trials have been even initiated in any other neurologic condition despite the aforementioned multiple "disease-modifying" mechanisms of action that TRFT has. From a practical limitation standpoint, there is presently a strong bias in the scientific community against non-pharmacologic interventions against neurologic disease. This is in part because clinicians do not know much or anything about such interventions and because of the broad influence of Big Pharma to only investigate drugs in clinical research. Nonetheless, the most substantive present need is for controlled clinical trials to be done with TRFT in AD subjects, followed by controlled trials in other neurologic conditions. Attaining the funding for TRFT controlled clinical trials and achieving positive clinical data therein would go a long way in exciting clinicians about TRFT technology to possibly address multiple unmet needs in neurologic disorders.

Conclusions

Long-term clinical TRFT treatment at 1.6 W/kg SAR power level through the MemorEM head device has resulted in no deleterious side effects reported either by subjects/caregivers or during clinical visits, suggesting the treatment and device are safe at that power level. The present human head phantom study extends this safety by showing that human TRFT administration at least up to 4.0 W/kg SAR should induce only minimal human brain heating of less than 1 °C. This nominal increase is too low to induce any damage to brain tissue by itself and would be easily buffered through the brain's vascular thermoregulatory mechanisms. As such, future TRFT clinical administration should be safe at least up to the 4 W/kg power level, which should provide for greater distribution and greater treatment efficacy.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The University of South Florida (USF) and Left Coast Engineering have a financial interest in NeuroEM Therapeutics. The interest of USF has been reviewed and managed in accordance with its Institutional Conflict of Interest policy. Dr. Arendash has a financial interest in NeuroEM Therapeutics as a common shareholder and has previously received a salary at times as CEO or CSO of the company. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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