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Thalamic deep brain stimulation in traumatic brain injury: a phase 1, randomized feasibility study

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Supplemental Material

Study design considerations

Our study design was guided by prior experience in a feasibility clinical trial of DBS targeting CL using standard methods of stereotactic functional neurosurgery in a more severely injured population of post traumatic brain injury subjects [28,67-69]. In this prior study, the most important observations that guided our present design were those of strong carry-over effects of CL-DBS leading to marked 'wash-in' and wash-out' effects that continued into 30-day blocks of ON/OFF cross-over periods[28,64]. Statistical modeling of these effects (see Figure 4 of [64]) demonstrated that carry-over effects lasting up to 14-days could confound a cross-over design limiting testing effects of CL DBS (see [70] for review). In addition, very limited exposure to DBS of only 28 hours was demonstrated to result in marked and enduring improvement in some behavioral scales during initial titration testing (see Figure 2 of [28]).

These constraints guided the design of the present trial, along with an additional requirement to limit the participants' exposures to test materials to avoid practice effects. We chose comparison of the pre-surgical baseline and performance at the fourth timepoint – after 3 months of DBS – as the predetermined outcome measure to contrast no exposure to DBS to maximum exposure, rather than the second or third timepoint (see Extended Figure 8). The timing of these intermediate assessments was more variable, and the amount of DBS exposure was less controlled. Further, the intermediate timepoints, particularly the second timepoint, might have confounds related to the surgery itself as has been shown in prior studies. These considerations guided both the discussions with the FDA and the formalization of outcome measure testing with the NIH program staff who administered our milestone driven contractual agreement. This measurement has the further strength of its *a priori* selection.

The design considerations also recognized the utility of two measurements with continuous bilateral DBS exposure, one after initial titration (to catch fast responses as seen in [28]), and another at end of the treatment period (to look at differences over time). This design feature allowed characterization of variations in the dynamics of initial response to DBS. It was anticipated that some participants might show significant initial effects with only ~96-110 hours of exposure to bilateral DBS prior to the treatment start measurements (as seen for both P5 and P6, see Extended Figure 8).

We note that several lines of evidence that the changes observed on our primary outcome measure are unlikely to reflect practice effects: 1) Our study design used time intervals that

would not be expected to lead to practice effects, 2) as noted above, improvements were paralleled by objective and subjective quality of life measures, 3) three of the patients in our study (P3, P5, and P6, Extended Figure 2) had abrupt improvements following the initial exposure to continuous DBS, a finding inconsistent with the magnitude of previous practice effects. Specifically, several prior studies indicate that our design of (4 time points spread over six months) should not result in significant practice effects. Feinkohl et al.[71], for example, demonstrated that healthy older controls tested with 3 TMT test periods over three months, organized similarly to the period between post-surgical baseline and Treatment end measurements in our study, showed stable performance. In their study, two tests were administered 7 days apart followed by a third three months later; there were no improvements across the measurements. The range of separation for the 4 time points across participants in our study is quite comparable to this report: Baseline to Post-Surgery (range 55-91 days), Post-Surgery to Treatment Start (7-33 days) and Treatment Start to Treatment End (89-107 days). It would be unlikely then that the addition of a single TMT exposure two to three months prior to the post-surgical measurements would have resulted in a far different experience for our cohort of chronically brain-injured subjects.

Underscoring the implausibility that the Treatment End measurements reflect test practice, studies of high-functioning normal controls show no changes across a six-month interval. Bartels et al.[72] studied 36 high functioning (mean IQ 127), highly motivated subjects (with no study drop out data) for 7 high-frequency testing sessions over 1 year. In their study significant practice effects were present if subjects took weekly tests but there were no practice effects across a six-month interval.

Ethical considerations and consent mechanisms

An ethical justification for the CENTURY-S (CENtral Thalamic Deep Brain Stimulation for the Treatment of Traumatic Brain InjURY-Stimulation using the Medtronic PC+S) study was developed in tandem with the scientific rationale for this work over the past 25 years[73,74].

The population for the CENTURY-S study (post msTBI GOS-E 5-7 outcome level subjects) was deemed ethically proportionate after earlier investigative work demonstrated the safety and efficacy of DBS in the minimally conscious state (MCS) following traumatic brain injury[28,75]. In this prior work, DBS targeting CL was shown to restore elements of motor executive function, spoken language, and control of swallowing in MCS in a single subject. The MCS level of recovery was deemed an ethically appropriate first target population with a proportionate risk-

benefit ratio: studies had suggested the possibility of a hypothetical therapeutic benefit while the risk of incremental harm was less than for individuals with higher functional status given the lack of prior testing in conscious subjects.

The CENTURY-S study follows in this scientific and normative lineage following the demonstration of the safety and proof of principle of CL/DTTm-DBS in post-traumatic MCS. The present study differs in that participants were required to be able to function independently in and outside of the home and provide autonomous informed consent, unlike the MCS study where participants were fully dependent on others and surrogate consent was obtained. In the MCS study consent was obtained from a legally authorized representative (LAR) with the proviso the subject would be reconsented should decision-making capacity be restored. While neuromodulation did restore elements of agency[76] for assent and dissent, autonomous decision-making capacity was not achieved at the level of consent and refusal[77].

Because of the history of severe brain injury and prior cognitive impairment in the study population, care was taken to ensure that CENTURY-S participants had regained decision-making capacity and were able to provide autonomous consent. An independent attending consultation-liaison psychiatrist evaluated all potential participants for their decision-making capacity, including their ability to understand the risks, benefits, and alternatives. In addition, care was taken to ensure that potential participants understood that the study was investigational and did not suffer from a therapeutic misconception[78] falsely believing that the intervention was a vetted therapy. This was evaluated by the consultation-liaison psychiatrist and confirmed in a parallel BRAIN Initiative funded study in which in-depth interviews were conducted with participants, their friends, and family members[36]. These narratives indicate that while participants hoped for benefit they understood the investigational nature of the study[79].

Efforts were also undertaken to ensure that decisions about the assumption of surgical risk were made by the participant and not surrogate decisionmakers accustomed to a decision-making role while participants lacked decision-making capacity as patients. How former surrogates ceded the decision-making role to participants and appreciated the dignity of that assumption of risk was a major theme in the narrative study[80,81].

Supplemental material for detailed descriptions of study phases.

Pre-screening evaluation – To determine potential eligibility for the study, participants were pre-screened by telephone or in-person using a structured interview to screen for historical inclusion and exclusion criteria. Pre-screening evaluation was conducted following self-referral and prior

to consent at the study's contracted call center. If no exclusion criteria were identified after discussion with study team, the individual was forwarded to the clinical study site coordinator for in-depth phone screening. If no exclusion criteria were identified, a consent meeting was scheduled. The participant was informed that study eligibility would not be finalized until all screening criteria had been reviewed and all pre-operative tests and procedures completed.

Consent meeting – If no exclusion criteria were identified during the pre-screening interview, the investigator/coordinator sent the informed consent form to the candidate for review. The coordinator arranged a consent meeting with the candidate and study neurosurgeon. Caregivers were encouraged to attend this meeting. The informed consent was thoroughly reviewed during this meeting to ensure understanding of all study procedures, risks, potential benefits, alternative therapies, if available. The study neurosurgeon answered any questions the candidate may have had regarding the study. Consent for release of medical records was obtained during the consent meeting to acquire additional information and medical records related to study eligibility. The candidate was reminded that study eligibility would not be finalized until all inclusion/exclusion criteria were met and pre-operative tests and procedures had been completed.

Assessment of decision-making capacity – A capacity assessment was conducted by an independent consultation-liaison psychiatrist (Dr. Maldonado) who remained sequestered from other study activities to ensure that each participant had decision-making capacity to understand the risks, benefits, and alternatives associated with the study. In addition, all participants were assessed for a therapeutic misconception to ensure that they understood the investigative nature of the study. This evaluation also assessed their ability to manage the activities associated with trial participation.

Screening and pre-operative baseline evaluation – 1 month before DBS implant surgery (with 1 month defined as 30 days ± 3 days), participants completed physical and neurological screening examinations and completed laboratory studies to ensure study eligibility and suitability for surgery. Participants then underwent a pre-operative multi-dimensional baseline assessment using a battery of cognitive (e.g., attention, memory, information processing speed, executive functions), psychological health (e.g., depression, anxiety), functional status (e.g., employment level), and quality of life (e.g., satisfaction with life) measures (see **Description of outcome measures** below). A structured interview was also conducted to obtain additional background information and determine pre- injury levels of academic, vocational, and social function.

Randomization to multiple baseline conditions – Following hospital discharge (post-op day 5), participants were randomly assigned to one of three baseline conditions lasting 30 (short), 44 (intermediate), or 58 (long) days. Two participants were assigned per condition. The staggered baseline schedule was designed to detect potential acute CL/DTTm-DBS effects within individual participants and between participant pairs following stimulator activation.

Post-surgical washout and baseline assessment – Participants entered the 30 day post-surgical washout phase following hospital discharge. At the end of the surgical washout period (Day 65 [with a ±3 day assessment window]), the multi-dimensional outcome assessment battery that was administered during the pre-surgical baseline phase was repeated to measure any significant changes in performance before CL/DTTm-DBS was switched on (see **Description of outcome measures** below). After the post-operative baseline assessment, two participants entered the DBS Titration/Optimization Phase while the other four participants waited either two or four more weeks (depending on the baseline condition to which he/she was randomized) before the DBS Titration/Optimization Phase began. The purpose of this phase of the design was two-fold: to provide a 30-day surgical washout for resolution of any transient physiological or behavioral effects of surgery, and to detect the temporal onset of the stimulation effects for each subject, should these have occurred. Electrophysiologic measures were also sampled during this phase.

DBS stimulation titration/optimization – On completion of the postoperative baseline phase, DBS was turned on for the first time (beginning day 66, 80, or 94, depending on cohort) to initiate the stimulation titration phase. During this phase, which lasted 14 days for all participants, an array of stimulation parameters were assessed to optimize the settings that were used during the treatment phase. Optimization relied on acute observable changes in cognitive-behavioral test performance and subjective report of favorable (cognitive, emotional) and unfavorable (adverse effects) symptoms. If no acute favorable effects were noted, we set chronic stimulation for the unblinded treatment phase (see below) at 80% of the amplitude that consistently produced adverse effects.

Unblinded treatment phase – After DBS titration/optimization was complete, participants entered the unblinded 90-day treatment phase during which DBS remained on for 12 hours per day (with start time chosen individually by each participant). Participants underwent re-assessment on the multi-dimensional outcome assessment battery at the beginning (day 80, 94, or 108, depending on cohort [with a +3 day assessment window]) and end (day 169, 183, or 197, depending on cohort [with a -3 day assessment window]) of the unblinded treatment phase.

Randomized double-blinded treatment withdrawal phase – At the time of enrollment, each participant was randomly assigned to a treatment withdrawal or continuation condition. Neither the investigator nor the participant had knowledge or was apprised as to whether DBS was on or off during this period. Even though we were concerned that DBS activation might cause a discernible physiological effect that would limit the feasibility of a double-blinded treatment phase, we anticipated that it would be feasible to conduct a blinded withdrawal phase due to adaptation to these discernible effects over a 90-day period. For participants assigned to the treatment withdrawal condition, DBS was switched off for 21 days (on days 170, 184, and 198 for cohorts 1-3, respectively) immediately after completing the 90-day unblinded treatment phase. Participants randomized to the continuation condition continued to receive stimulation 12 hours per day over the same 21-day period. Upon conclusion of the 21-day treatment withdrawal phase, participants underwent a final re- assessment on the multi-dimensional outcome assessment battery and on the electrophysiologic measures (on day 190, 204, and 218, depending on cohort [with a -3 day assessment window]). The purpose of this follow-up visit was to determine if there was evidence of loss of effect in those assigned to the treatment withdrawal condition, and to evaluate the influence of intervening factors on the effectiveness of DBS. The trial was considered complete at the end of the treatment withdrawal phase (see below).

Open label phase – Participants had the option to continue receiving CL/DTTm-DBS after study completion if there were no medical contraindications or other concerns that could pose a risk to safety or quality of life. Participants who elected to engage in the open label phase were monitored using an IRB-approved individualized battery of measures selected by the investigators on the basis of sensitivity to effect and input from the participant.

Surgical targeting and implantation

The MRI containing the optimized lead locations was imported into the StealthStation neuronavigational system (Medtronic Inc., Minneapolis, MN, USA), where it was merged with isotropic T2 CUBE, white-matter-nulled and contrast-enhanced T1 data sets. The trajectory was then modified as needed based on anatomic constraints, including the local vasculature surrounding the entry point dorsal to the thalamus. All trajectories took an intraventricular course, as this provided the optimal trajectory to the CL thalamus and DTTm.

Leads were placed via a frameless technique using the Nexframe platform (Medtronic, Inc.)[82,83]. In the first five patients, microelectrode recording was performed to investigate target site

physiology and to guide implantation. In these five patients, postoperative imaging revealed a discrepancy in the planned vs. actual trajectory on the second side, felt to be due to brain shift due to CSF loss related to the lengthy recording procedure and the intraventricular trajectory. Therefore, in the sixth patient, the decision was made to perform the procedure with intraoperative image guidance using the O-arm intraoperative imaging system (Medtronic, Inc.) to verify lead location.

Following target verification, deep brain stimulation leads (model 3387, Medtronic, Inc.) were placed at the target bilaterally, and tunneled subcutaneously to the retroauricular region. The participant was then repositioned, and the pulse generator was placed in the right infraclavicular region. Extensions were tunneled from the retroauricular site to the chest, and all connections verified with an intraoperative impedance check. Due to device availability, only participants P1 and P2 received an Activa PC+S sensing neurostimulator (investigational device, Medtronic, Inc.); participants P3-P5 received an Activa PC (model 37601, Medtronic, Inc.), and participant P6 received a Percept (model B35200, Medtronic, Inc.). Participants were admitted for 1-3 days following the surgical procedure and discharged when stable and ambulatory.

Thalamic modeling

For each subject we acquired white-matter-nulled magnetization-prepared rapid acquisition gradient echo (WMn-MPRAGE or WMn for short)[84] and diffusion weighted imaging (DWI) MRI data for use in the surgical planning pipeline (see Supplementary Figure 1A-F and Methods for details). In brief, we processed each patient's WMn images using the THOMAS (**T**halamus **O**ptimized **M**ulti **A**tlas **S**egmentation) automated thalamic segmentation algorithm[62] (see Methods), which produced patient-specific 3D boundaries of a standardized set of thalamic nuclei. Because the THOMAS algorithm did not include the central lateral nucleus as one of these nuclei, we further identified the CL boundary using a novel single-atlas segmentation method. This employed a CL atlas derived by manual segmentation by an expert neuroradiologist from the THOMAS template, an extremely high quality WMn image volume formed by non-linear registration and averaging of 20 WMn volumes. We prevented this CL segmentation from overlapping with THOMAS nuclei by giving priority to the latter; the choice of a THOMAS prioritized CL volume provided a deliberately conservative estimate of the boundaries of CL. The DWI data was processed using DSI Studio (https://dsi-studio.labsolver.org/) to perform tensor reconstruction and generate deterministic tractography models for fibers emanating from CL and from other neighboring thalamic nuclei generated by the THOMAS algorithm (Supplementary Figure 1). We used finite element models and

biophysical modeling of fiber activation to model electrode placement, considering safe entry points, blood vessel anatomy, and proximity to areas of target activation and avoidance. We adjusted lead and electrode placement to simultaneously maximize activation of the CL/DTTm fiber tract and minimize activation of off-target fibers (Figure 3).

A synthetic atlas was created by warping all individual image volumes to a common template using Advanced Normalization Tools software (ANTs, **http://stnava.github.io/ANTs/**), followed by averaging the warped volumes together. More specifically, white matter-nulled MRI image volumes from each of the five participants were combined using nonlinear registration to produce a template or synthetic atlas volume, representative of all participants. The spatial transforms produced as a result of this process allowed for the electrode contacts, segmented nuclei, and tractography to be similarly warped, visualized and analyzed in the synthetic atlas space.

Titration phase

Approach to titration phase

We employed a systematic and staged approach to titrating the stimulation parameters used for each participant: 1) we began the initial assessment by testing for acute effects of single contact activations applying increasingly larger, radially symmetric, activation fields around individual contacts using the implantable pulse generator as anode ('cathodal survey' in monopolar stimulation mode). The cathodal survey determined the amplitude boundaries of current or voltage associated with non-target or adverse effects (see below). We tested each contact to correlate the modeling of effective activation of the CL/DTTm target utilizing our post-operative patient specific models and assessed effects linked to off target pathways (See Supplementary Figures 20-24. This phase of assessment typically required one half-day or a full day of testing depending on the complexity of subject responses. 2) once we determined the boundaries of adverse effects for individual contact activation, we used the models of fiber activation and avoidance boundaries to guide the selection of a small set of contact geometries for testing utilizing bilateral simultaneous stimulation. During these assessments we tested a short battery of neuropsychological tests customized for each subject based on individual performance during test sessions. We compared performance ON and OFF testing to guide assessment of parameters (see below). This phase varied in duration of time spent on different electrode contact geometries if side effects emerged, particularly if after long delays which varied considerably. In some instances subjects reported side effects within 15 to 30 minutes of

remaining on one setting, in other instances only hours after continuous testing for more than an hour with a parameter set after completing a day of titration; 3) we then chose the most promising sets of stimulation parameters to leave ON for the duration of the 12-hour day cycle to test tolerance either overnight or over three nights (Friday afternoon evening and 12 hours per day for each day of weekend) at the end of the first week of testing.

Overall, our approach was strongly guided by our prior experience with systematic testing of stimulation parameters of CL stimulation in humans[28], non-human primates[19,29,64] and rodents[24,25,62] and key references from the literature[43,44,61] Briefly, our approach was organized by recognizing that electrode geometry is the primary determinant of effect (with cathode/anode configuration, amplitude of voltage/current, and pulse width setting the relevant activation field, see [85]). Exhaustive testing of frequency variations in the non-human primate did not reveal clear differences for frequencies in the range 150-225Hz on performance of executive attention tasks but a reliable shortening of reaction times was seen in one experimental animal with use of 150 Hz and we based our initial frequency testing at 150Hz on this prior observation. Prior efforts to differentiate frequency effects in all species have shown that high-frequencies of 100Hz or greater are associated with stronger driving of frontal cortical and striatal neuronal populations in wakeful states. Nonetheless, we made limited efforts during the titration period to examine frequency differences once electrode geometries and intensities of stimulation had been chosen in each subject; in one participant (P3) a subjective preference for stimulation at 185Hz guided selection of this frequency for the trial. No other participant noted objective or subjective changes associated with frequency when tested with electrode geometries free of side effects.

Cathode survey

Thirty to sixty-one days following surgery (depending on randomization cohort), participants began the DBS titration process. Impedances were tested for each of the eight DBS electrode contacts; in most cases impedance remained in the range ~1-1.5kΩ, although in P4 the top right sided electrode contact appeared to be shorted [>40kΩ] in the ventricular cerebral spinal fluid – see Extended Figure 4 – and no further testing was done. For each subject we carried out a cathode survey for each of the individual contacts with acceptable impedance using a monopolar cathodal stimulation employing the implantable pulse generator (IPG) as the anodal return.

Stimulation parameters of pulse width (60-90us) and frequency (150-160Hz) were kept constant as the stimulation amplitude was slowly ramped up at 0.1V increments, from 0 up to 5V in participants P1, P3, P4 and P5 (using either the PC+S or PC device), or at 0.1mA increments,

participants P1, P3, P4 and P5 (using either the PC+S or PC device), or at 0.1mA increments, from 0 up to 4mA in participant P6 (using the Percept device). The 30-day post-operative activation histograms (see Figure 3 and Extended Data Figures 3-7) for the ON and OFF target fiber pathways were used as a guide for anticipated side effects. If side effects were verbalized by the patient, the voltage/milliamp levels were noted. An experienced DBS programmer carried out all cathode surveys and tested each subjective observation by blinded threshold testing and OFF stimulation assessments.

Side effect profiles showed consistency with the post-operative histogram estimates of activation of CL/DTTm fibers and off-target fibers from CM, MD, although specific adverse effects differed for each participant (Supplementary Figures 20-24). P1 reported dysarthria with activation of the lowest contact of electrodes in both hemispheres, with contact R2 of the right hemisphere eliciting the strongest effect (Supplementary Figure 20). This observation is consistent with the histograms shown in Extended Data Figures 3B and 3E which reveal a consistent contribution of CM fibers to all amplitudes on lowest contacts (L1, R1). Afferents carrying jaw-closing muscle proprioception are known to innervate CM homolog regions in rodents[86], consistent with these findings reflecting CM fiber activation. P3 similarly noted an abnormality of jaw sensation with activation of the lowest left sided contact in monopolar mode (Supplementary Figure 21) which also correlated with a predominance of predicted CM fiber activation on the lower contacts of both electrode placements (Extended Data Figures 4B 4E). Other transient adverse effects associated with both monopolar and multi-contact cathode activation are summarized in Supplementary Figures 20-24. In addition to transient jaw-related side effects in P1 and P3, a variety of sensorimotor side effects were noted several subjects during the titration testing, typically with activations of lower electrode contacts; prominently, impersistent lower extremity sensory side effects were present for both left and right sided contacts of P4 (Supplementary Figure 22) that appeared at different thresholds and could not be correlated with modeling (which showed CM activation on all but top left electrode contact; right sided modeling confounded by the combination of shift in electrode placement and failure to model CL/DTTm fibers on this side, see Supplementary Figures 4 and 5). P4 showed strong sensitivity to multipolar configurations and akathisia at high stimulation amplitudes (see below) and the observations may reflect a form fruste of the frank akathisia observed with bilateral stimulation. P5 demonstrated several of the same side effects with evidence of jaw tingling on the R2 contact, lower extremity sensations on several contacts, and immediate changes in a sense of alertness for lower contacts on the left hemisphere (Supplementary Figure 23). Acute effects in P6 were limited to changes in subjective mood, most prominent with the left lowest L1 contact (Supplementary Figure 24).

Testing of selected stimulation parameter combinations

Following the cathode survey in each subject, a small set of stimulation parameters underwent detailed assessment using a battery of motor and cognitive testing, participant observation by investigators and participant subjective reports. The choices of stimulation parameter sets for each participant were based on the results of the cathode survey (primarily avoiding any contacts with identified side effects) and the guidance of biophysical modeling results for each of the DBS contacts:

1. Electrode geometries (monopolar versus bipolar, number of cathodes) and pulse width were chosen in each individual subject to a) maximize activation of DTTm fibers as estimated by the post-operative histogram model of tract activation, and b) avoid all subject reported changes in sensory, motor, or emotional valence to reduce likelihood of activation of (Vc, Cm-Pf, or MD fiber tracts).
2. Once sets of electrode geometries were chosen for testing, patients underwent stimulation sessions of varying length using variations of time on stimulation, intensity of stimulation (voltage or current amplitude), and frequency of stimulation. Typically, this phase of titration elapsed over 4 days of testing (3 days during one week and fourth day after a weekend of continuous stimulation) with approximately one hour per set of stimulation parameters with frequent changes made within a single session if side effects emerged over longer exposure to stimulation.

While a standardized battery of brief neuropsychological tests formed the basis of formal aspects of testing during this phase of titration, each subject demonstrated performance variations on only a small set of test items and evaluations were customized per subject for purpose of investigator assessments of tolerance of stimulation. Side effects emerged within 15-30 minutes of testing in several participant's testing sessions (e.g. jaw sensations, akathisia) leading to adjustment of contact geometries (e.g. shift from monopolar to bipolar contact configurations and narrowing of pulse width bilaterally in P4 electrodes). For all subjects tested, once a combination of tolerated contact geometry, stimulation intensity and estimated maximal coverage of modeled CL/DTTm fibers was achieved, subjects reported no regional sensory phenomenon associated with the DBS ON phase.

At the onset of each participant's period of stimulation testing, an OFF stimulation pre-titration baseline was obtained for each behavioral test. During these periods of assessment, combinations of bilateral stimulation were used employing activation of 1-3 cathodes per

electrode in each hemisphere. Observation periods and behavioral testing varied from ~30-90 minutes based on the results of the testing. In some participants, evident side effects at lower contacts with cathodes in monopolar mode led to longer testing of the chosen combined configurations with adjustments of the number of cathodes, bipolar modes of stimulation and independent adjustments of other parameters of stimulation (pulse width and amplitude) to reshape the applied field to find combinations that were tolerated without side effects. In P4, a rollover effects of increased arousal and akathisia required a tight restriction of both left and right hemisphere fields leading to use of bipolar configurations on both sides and 60 microsecond pulse widths (see Supplementary Table 12). After each testing day, a well-tolerated set of parameters was chosen for continuous stimulation, and the stimulator was programmed for a 12 hour on / 12 hour off duty cycle. Based on the reports obtained from participants on the next testing day (either overnight or over a weekend), revisions of the stimulation parameter set were tested and the process repeated. This titration of the final stimulation parameter set typically required 4-5 days of testing in each subject.

The stimulation settings used during the treatment phase for each participant are listed in Supplementary Table 12. Contact numbering for the Activa PC+S, Activa PC, and Percept follow the convention left four electrodes from bottom to top: E0, E1, E2, E3; right four electrodes from bottom to top: E8, E9, E10, E11. Cathodes are denoted “C”, anodes denoted “A”. For the final stimulation parameters shown in Supplementary Table 12, maximum charge density ranged from 3.3 to 5.1uC/cm2/phase, per contact.

Blinded withdrawal phase

Only three participants completed the planned blinded withdrawal phase of the study; two participants declined to participate. P1 experienced an unplanned withdrawal of stimulation during the treatment phase, attributed in retrospect to passing through a magnetic theft detector system while shopping. P1 noted a sharp decline in function over a 2-3 week period before alerting study investigators and undergoing a system interrogation which revealed an unexplained deactivation. Based on this experience, P1 withdrew consent for the blinded withdrawal component of the study. P5 also withdrew consent to participate in the withdrawal phase of the study. All participants were issued a hand-held programmer to allow them to deactivate the system in case of any concerning side effects. P5 experimented with this programmer and noted worsening of function with deactivation of the neurostimulator. He thus declined to participate in the withdrawal phase.

Of the three participants completing the blinded withdrawal, P3 demonstrated a 34.1% decline in TMT-B performance (condition off), P4 demonstrated a 10.6% decline in TMT-B performance (condition on), and P6 demonstrated a 13.8% improvement in TMT-B performance (condition on), see Supplementary Table 7. Of note, interrogation of the implantable pulse generator in P4 at the end of the withdrawal period revealed that a phase reversal in 12-hour cycling occurred at the time of blinding. This period was subjectively noted by the subject to have been marked by insomnia and daytime sleepiness.

Post-trial narrative interviews of study participants and family members

All participants and their families were interviewed in a semi-structured format as a part of a parallel study, "Cognitive Restoration: Neuroethics and Disability Rights", funded by the NIH BRAIN Initiative [1RF1MH12378-01] to analyze the narrative responses of subjects and families participating in the “Central Thalamic Stimulation for Traumatic Brain Injury” (CENTURY-S) study. [UH3 NS095554, NCT 02881151]. Transcribed interviews were conducted preoperatively and following the treatment end phase of the stimulation trial. Responses were coded both inductively and deductively using qualitative data analysis software. Separate IRB approval for this study was obtained at Weill Cornell Medical College and Stanford University. Interviews were conducted preoperatively and following the stimulation trial. Pre-operative narratives (participants 69K word count, families 74.5K word count) revealed consistent themes demonstrating chronic and disabling cognitive impairments associated with the original injuries[36]. Post treatment end narrative data (participants 56.8K word count, families 67.4K word count) revealed improved cognitive/executive function, emotional regulation, interpersonal relationships, and reports of improved quality of life associated with CL/DTTm DBS as excerpted in Supplementary Table 8 which notes reports of functional improvements linked to executive functions (quotations excerpted from [37]). These observations parallel the changes on both self-report measures (Figure 2C) and global functioning (see Supplementary Tables 2-6). As shown in Supplementary Table 8, in post-trial interviews both participants and their family members reported functional improvements in cognitive/executive function, emotional regulation, and interpersonal relationships (Fins et al. in press[37]).

Supplementary analysis of data from Dikmen et al.[5]

We obtained deidentified TMT A and B scores from 118 subjects collected as part of a longitudinal study of outcomes from moderate to severe traumatic brain injuries, all studied at one year and 3-5 year time points, from Drs. Sureyya Dikmen and Nancy Temkin (Dikmen et al.

2003)[5]. Neuropsychological outcomes of this subject cohort have been published previously. In this cohort, approximately 40% of subjects recovered to preinjury level of cognitive competence, demonstrating a significant overall long-term morbidity as a group[5]. This cohort of subjects was predominantly male (82%) with average age of 36 years at time of injury and thus comparable to our reported sample of five subjects (80% male, average age 35.8 years), although our cohort averaged 8.8 years following injury at the time of study. The Dikmen et al.[5] cohort all had a qualifying injury of at least one of the following characteristics: immediate onset post-traumatic seizures, depressed skull fracture, penetrating brain injury, CT evidence of cortical contusion, or subdural, epidural, or intracerebral hemorrhage. In addition to comparison of the Dikmen et al.[5] cohort TMT-B scores with our five subjects (Figure 2B). We also tested both TMT-A (Supplementary Figure 18) and TMT B-A (Supplementary Figure 19) scores from both groups to examine the likelihood that the test-retest performances seen with CL/DTTm stimulation could have been obtained in the Dikmen et al. data[5] demonstrating spontaneous recovery.

As with TMT-B, the uniform improvements we observed in TMT-A were in marked contrast to those observed from the two cohorts examined from the Dikmen study.[5] TMT-A completion times were 21 to 47% faster in our sample, representing an average T-score improvement of 13.4 points (>1 SD). This was significantly better than first Dikmen et al.[5] cohort [146 subjects; 6 months to year], average test-retest change, 11% faster (K-S test, $p<0.002$ [.0103], Suppl Fig. 18A), and the second Dikmen et al.[5] cohort [118 subjects; 1 year to 3-5 years], average test-retest change, 6% slower (K-S test, $p<0.001$ [.00057], Suppl Fig. 18B). In addition, the derived measure (TMT-B) –(TMT-A), which probes executive control[34] showed an improvement of 35% for our cohort but a worsening of 2% for both Dikmen et al.[5] cohorts (K-S test, $p\sim0.08$ [.0812] for first cohort Suppl Fig. 19A, $p<0.05$ [.0443] for second cohort, Suppl Fig. 19B).

CL/DTTm multi-dimensional outcome assessment battery

Description of CL/DTTm-DBS multi-dimensional outcome assessment battery

The CL/DTTm-DBS Outcome Assessment Battery is comprised of patient-reported, performance-based and interview measures. It was designed to assess multiple outcome domains, including physical symptoms, cognition, psychological health, quality of life and functional status. The primary (i.e., Trail Making Test)[87] and secondary outcome measures were intended to capture the anticipated cognitive and behavioral effects of CL/DTTm-DBS, which relate to processing speed, vigilance, sustained attention and behavioral persistence and a

range of more global variables (described below). Where possible, we selected measures designated as TBI Common Data Elements for research by NINDS[88] and supplemented the battery with additional measures to address the specific aims of the study. The duration of the battery was approximately 55 minutes.

Performance-based measures

Trail Making Test (Primary Outcome Measure)[87] – The TMT is a measure of attention, speed, and mental flexibility. It also tests spatial organization, visual pursuits, recall, and recognition. Part A requires the individual to draw lines to connect 25 encircled numbers distributed randomly on a page. Part A tests visual scanning, numeric sequencing, and visuomotor speed. Part B is believed to be more difficult and takes longer to complete as it adds a cognitive load by requiring the respondent to connect the circles by alternating between numbers and letters. Part B tests cognitive processing speed, vigilance, and mental flexibility. Both parts are timed and the score represents the amount of time required to complete the task.

Ruff 2 & 7 Selective Attention Test[89] – The Ruff 2 & 7 Test was developed to measure two aspects of visual attention: sustained attention (ability to maintain consistent performance level over time) and selective attention (ability to select relevant stimuli while ignoring distractors). The test consists of a series of 20 trials of a visual search and cancellation task. The respondent detects and marks through all occurrences of two target digits: “2″ and “7”. In the 10 Automatic Detection trials, the target digits are embedded among alphabetical letters that serve as distractors. In the 10 Controlled Search trials, the target digits are embedded among other numbers that serve as distractors. The respondent is instructed to switch from one trial to the next after a fixed 15-second interval has elapsed. Correct hits and errors are counted for each trial and serve as the basis for scoring the test. Speed scores reflect the total number of correctly identified targets (hits). Accuracy scores evaluate the number of targets identified in relation to the number of possible targets.

Self-report measures

Rivermead Post-Concussion Symptom Questionnaire (RPQ)[90-92] – The Rivermead PCS Questionnaire (RPQ) measures the severity of symptoms that are commonly associated with mild TBI. It consists of 16 post-concussion symptoms including headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed/tearful, feeling frustrated/ impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. In the original version of

the RPQ, respondents are asked to rate the degree (on a scale of 0 to 4) to which a particular symptom has been absent or a mild, moderate or severe problem over the previous 24 hours compared with premorbid levels. For purposes of this study, symptom ratings were anchored to "the last 7 days." A score of 0 (i.e., "not experienced) means the symptom was not previously experienced and is currently not a problem. A score of 1 (i.e., "no more of a problem") indicates that a symptom that was present before the injury has not worsened since the current injury. Scores of 2, 3 and 4 (i.e., "mild," "moderate," and "severe" problem) imply that there has been a mild, moderate or severe worsening of a symptom that was present before the current injury.

Patient Health Questionnaire-9 (PHQ-9)[93-95] – The Participant Health Questionnaire 9 is a 9-item standardized assessment instrument designed to screen, diagnose, monitor, and measure the severity of depression.

Columbia Suicide Severity Rating Scale (C-SSRS)[96] – The C-SSRS is a standardized questionnaire that comprehensively assesses suicidal behavior and ideation to determine the presence and severity of suicidality, identify those at risk, and track response to treatment. It has three main sections that evaluate suicidal ideation, the intensity of ideation and suicidal behavior. The first section, suicidal ideation, assesses risk ranging from a death wish or unspecific suicidal thoughts to active ideation with specific plans. In the second section the severity of ideation is evaluated and takes into account the frequency, duration and controllability of suicidal thoughts as well as environmental and cultural deterrents and reasons for suicidal ideation. The third section evaluates actual suicidal behavior and asks if there was an actual attempt, interrupted attempt, aborted attempt or preparatory acts of behavior. It also asks whether there was active suicidal behavior at the time of assessment and, finally, if suicide was completed. A fourth section, administered only when there is evidence of suicidal attempts, measures the lethality and potential lethality of each suicidal attempt. The CCSRS is a widely-used instrument and is currently being utilized in other first-in-man DBS clinical trials. The C-SSRS was administered during the pre-surgery baseline assessment and then at any follow-up visit triggered by a score ≥ 1 on question 9 of the PHQ-9.

Traumatic Brain Injury Quality of Life (TBI-QOL)[97] – The TBI-QOL was developed as a comprehensive patient-reported outcomes (PRO) measurement system specifically for individuals with TBI. It consists of 20 independent calibrated item banks and 2 uncalibrated scales that measure physical, emotional, cognitive, and social aspects of health-related quality of life. We administered the short form (6-10 questions each) of the TBI-QOL Fatigue,

Attention/Concentration, and Executive Function subscales. The TBI-QoL Fatigue subscale served as our secondary outcome measure.

Glasgow Outcome Scale – Extended (GOSE)[33,98] – The Glasgow Outcome Scale – Extended (GOSE) is the most widely-used instrument for assessment of global outcome after severe TBI. The GOSE relies on a structured interview that classifies responses hierarchically into 8 discrete outcome categories- dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery. For purposes of this study, we used the GOS-E-TBI scoring system in which GOS-E ratings reflect disability specifically caused by the effects of the brain injury (versus the consequences of both brain and peripheral bodily injuries).

Participant interview

The Participant Interview was administered to all participants at the time of study enrollment, at the beginning and end of the treatment phase and at the 6-month continuation visit. The Interview (adapted from the TRACK-TBI Patient Interview[99], with permission) includes questions that address the participant's current living situation, academic pursuits, employment level, substance use, health service utilization, satisfaction with support from others and income level.

Data acquisition procedure

Participants were assessed in-person at four time points: Pre-surgery Baseline (Day 1), Post-surgical Baseline (Day 65), Treatment Phase Start (Day 80, 94, or 108 depending on cohort assignment), and Treatment Phase End (Day 169, 183, or 197 depending on cohort assignment). Assessment measures were administered and scored according to the corresponding user manual or instruction sheet. Measures were administered in a standard order and the full battery was expected to be completed within 3 days of the target date. If a participant was unable to complete the test battery in person, the Participant Interview and self-report measures were administered via telephone. For each measure, guidelines were provided for managing unexpected interruptions. A Test Completion Code (TCC) was assigned to each measure to indicate whether the measure was completed and valid, completed but invalid, attempted but not completed, or not attempted. Specific TCCs were used to designate the reason a test was not attempted, not completed or completed but invalid (see TCC Code List).

Data curation

Where indicated, examiners identified and recorded confounding factors that they believed may have invalidated test administration, scoring, and/or ratings (e.g., new illness or injury, emotional lability, errors in test administration, etc.). Senior investigators reviewed confounding factors on a case-by-case basis and excluded data that was determined to be invalid. Review of cognitive testing responses and case report forms was conducted by study personnel not involved in data collection to ensure accuracy of scoring, consistency of responses (e.g., consistent employment information on GOSE and Participant Interview), and completeness of data entry.

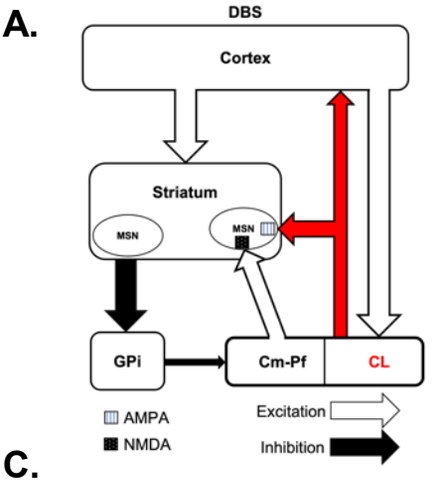
Test completion codes (TCCs).

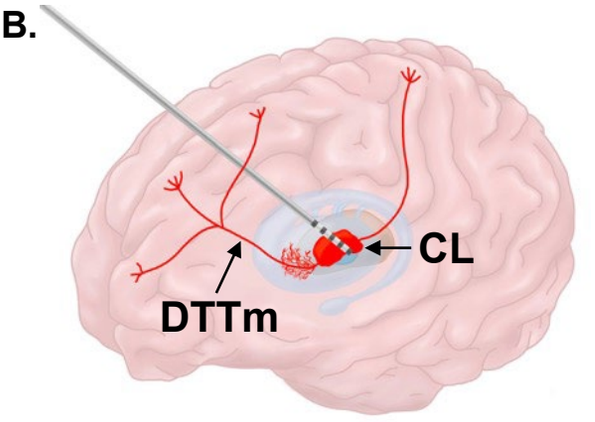
Test Attempted and completed	
1.0	Test completed in full, in person- results valid
1.1	Non-standard administration – a measure normally requiring an oral response, allowed a written response, results valid
1.2	Non-standard administration –Other (specify):_____
1.3	Test Completed, valid administration done over the phone
Test Attempted but NOT completed	
2.1	Test attempted but not completed due to cognitive/neurological reason
2.2	Test attempted but not completed due to non-neurological/physical reasons
2.3	Test attempted but not completed - participant cognitively intact enough to respond but poor effort, random responding, rote response, not cooperative, refusal, intoxication
2.4	Test attempted but not completed due to major problems with English language proficiency (and/or Spanish language proficiency if the site can also enroll Spanish speaking subjects)
2.5	Test attempted but not completed due to test interrupted by illness and test could not be completed later
2.6	Test attempted but not completed due to logistical reasons, other reasons – site specific
Test not attempted	
3.1	Test not attempted due to severity of cognitive/neurological deficits
3.2	Test not attempted due to non-neurological/physical reasons

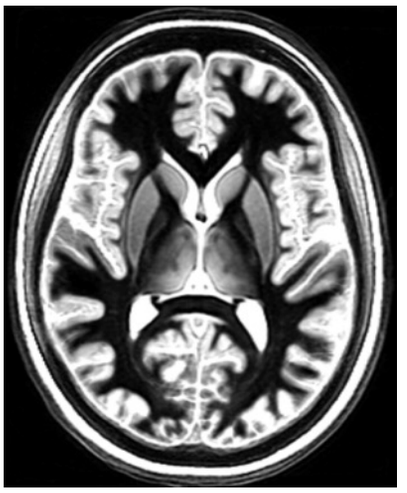
3.3	Test not attempted - participant can respond appropriately but poor effort, not cooperative, refusal, intoxication
3.4	Test not attempted due to major problems with English language proficiency (and/or Spanish language proficiency if the site can also enroll Spanish speaking subjects)
3.5	Test not attempted due to participant illness and test could not be completed later
3.6	Test not attempted due to logistical reasons, other reasons – site specific
4.0	Test not attempted, completed or valid due to examiner error
5.0	Other (specify:_____)

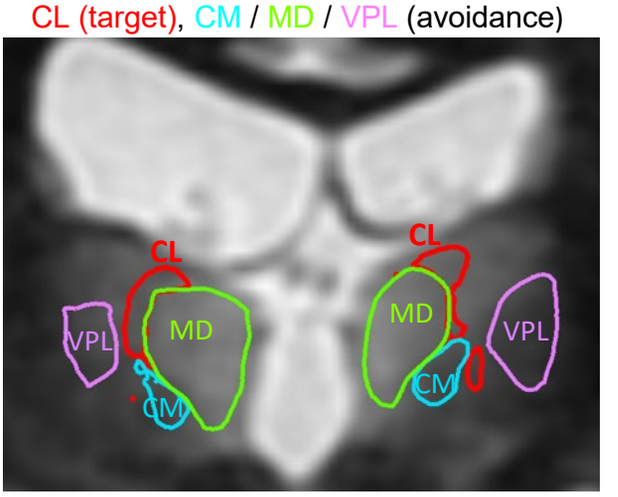
1730

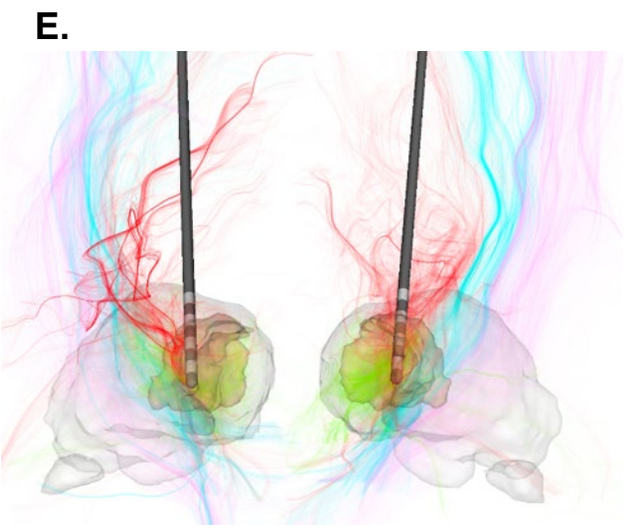
Suppl Figure 1.

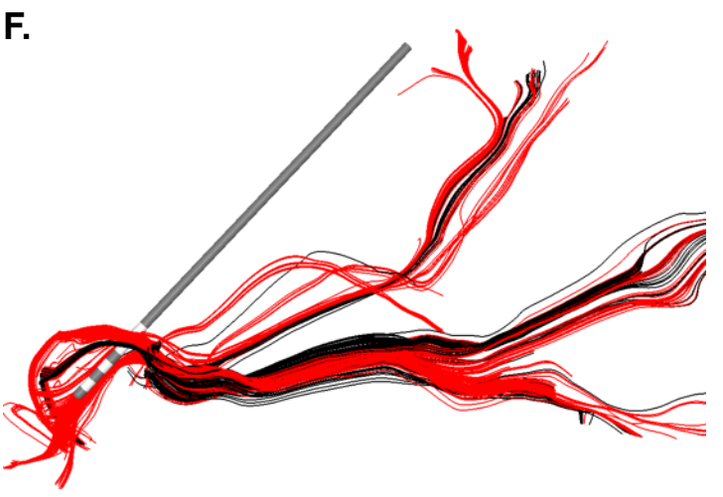












Supplementary Figure 1. Pre-surgical planning pipeline for targeting of the central lateral thalamic nucleus (CL) and its associated dorsal tegmental tract medial (DTTm) fiber bundle: theory, imaging techniques, and surgical planning.

1. **Theoretical foundation for CL/DTTm deep brain stimulation for msTBI.** The central lateral thalamic nucleus (CL) is proposed to play a key role in determining outcomes of traumatic brain injuries on the basis of its dual properties of 1) widespread anatomical connectivity across frontal and parietal cortices and the striatum[21,27,36,39-41], and 2) functional contributions to forebrain arousal via activation of frontostriatal neurons[19,20,25,27]. The broad anatomical connectivity of CL is proposed to underlie graded degeneration of inputs to CL with worsening severity of injury[27]. In human, a prior study demonstrated that bilateral DBS of CL produced enduring recovery of spoken language and executive motor control in a subject in minimally conscious state (MCS) with stable deficits after six years[28]. Partial deafferentation of CL afferents in msTBI is proposed here to underlie impaired arousal regulation of the anterior forebrain and consequent impaired executive function. Compared to healthy controls msTBI subjects are expected to have baseline decreases of long-range excitatory neurotransmission that through direct effects on cortical excitability and indirect effects via cortico-striatopallidal loops reduce overall thalamocortical activation[27]; CL/DTTm DBS is predicted to restore long-range excitatory tone and reduce excess pallidal inhibition of the thalamus arising from reduced background activity (Extended Figure 1).
2. **Graphical illustration of DBS targeting of CL/DTTm.** Cartoon rendering of single DBS electrode (grey), brain surface (pink), thalamus (silver), CL nucleus and fibers emanating from CL (red).

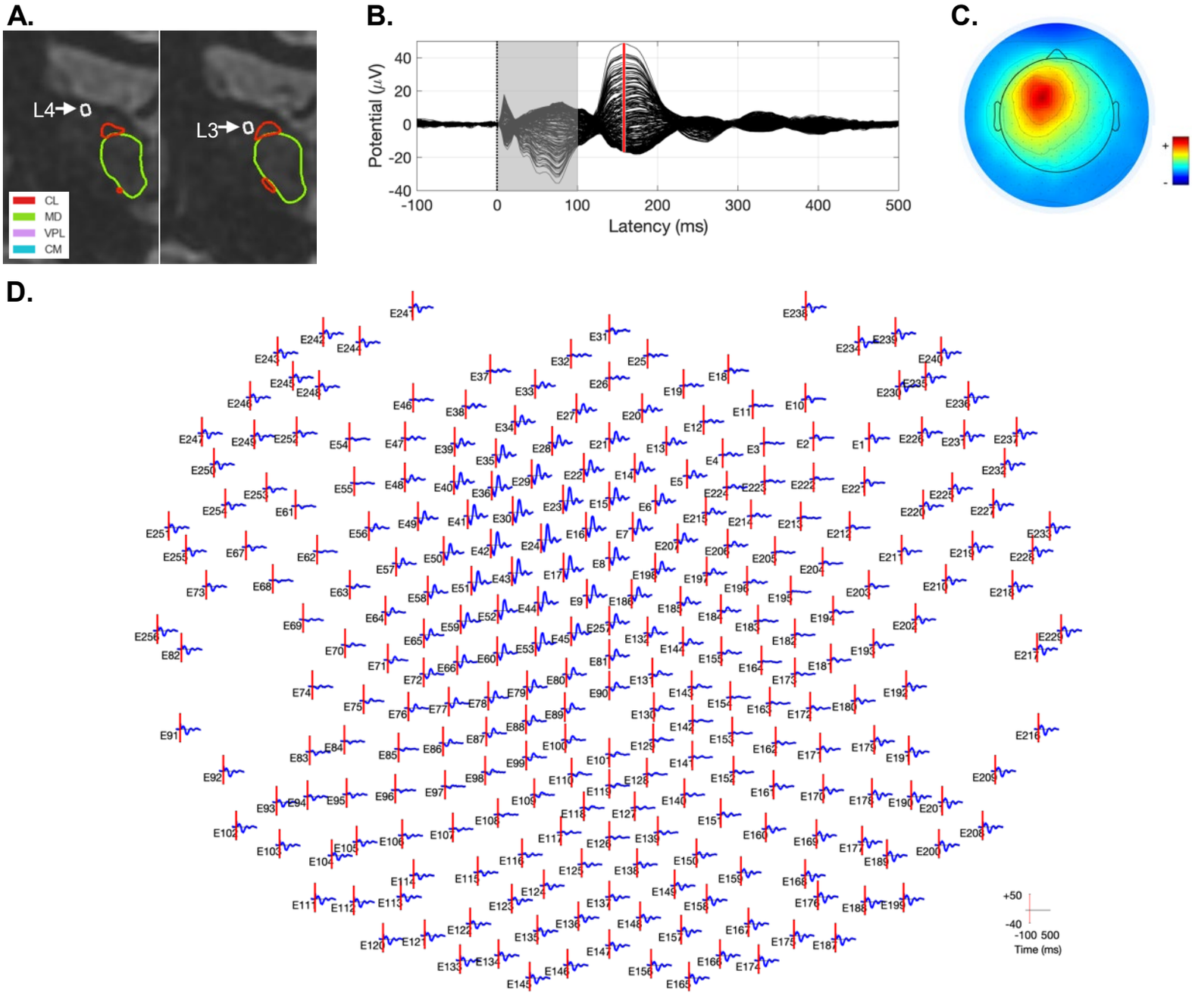
3. **WMn imaging.** White-matter-nulled (WMn) imaging was used as input to the THOMAS thalamic segmentation method[56]. WMn imaging is based on the 3D magnetization-prepared rapid acquisition gradient echo (3D MPRAGE) pulse sequence, in which the inversion time is adjusted to null white matter (conventional MPRAGE uses CSF suppression which results in good WM and GM signal but poor intra-thalamic contrast). WMn imaging produces the highest intra-thalamic (i.e. inter-nuclear) as well as thalamic-WM contrast[84] with excellent signal-to-noise characteristics. This sequence was installed on a GE 3T scanner, and WMn images were acquired with 1mm isotropic voxels covering the whole brain. Panel B shows an example axial slice at the mid-thalamus level from a whole-brain WMn volume. Scan parameters were: 3D MPRAGE sequence, coronal orientation, TE 4.7ms, TR 11.1ms, TI 500ms, TS 5000ms, views per segment 240, FA: 8°, RBW +/-11.9kHz, spatial resolution 1mm isotropic, 220 slices per volume, k-space ordering; 2D radial fanbeam, ARC parallel imaging acceleration: 1.1x1.1, scan time <8min.
4. **THOMAS segmentation.** Automated segmentation of thalamic subnuclei utilized WMn images and the THOMAS segmentation algorithm[56]. Relevant to the present work, a subset of the most important THOMAS nuclei are shown as colored boundaries overlaid onto a zoomed WMn coronal slice. Labeled subnuclei include: central lateral, CL (red); median dorsalis, MD (green), centromedian, Cm (cyan), ventral posterior lateral VPL (purple). The DBS lead was targeted to CL as well as the DTTm fiber tract, but our pre-surgical planning procedure also involved modeling of fiber activation from these neighboring nuclei and optimizing lead placement to minimize activation of those “avoidance” fiber tracts.
5. **Tractography and fiber modeling.** Fiber modeling utilized the relevant THOMAS-derived thalamic nuclei segmentations as seeds regions, followed by tensor reconstruction and deterministic tractography from the DWI data using DSI Studio

(https://dsi-studio.labsolver.org/). Panel shows an example of one such fiber tract that was constrained to pass through the CL volume – this is our model of the DTTm fiber tract to be used in subsequent biophysical modeling steps.

6. **Biophysical modeling.** Using a biophysical model of the DBS lead and driving the chosen active electrodes, we modeled the activation of relevant nerve fibers. One outcome of this biophysical modeling was the generation of fiber activation profiles, showing the proportion of a given fiber bundle that is activated by the combination of active electrodes and stimulation settings (voltage or current applied to those electrodes). Here the CL/DTTm fiber tract is split into red (activated) and black (non-activated) fibers. The outcome of biophysical modeling of this type, applied to all relevant thalamic nuclei, was the generation of fiber activation histograms for each of left and right hemispheres and for each participant in the study (see Figure 3).

Supplementary Figure 2.

Participant 1 (P1). Left Hemisphere



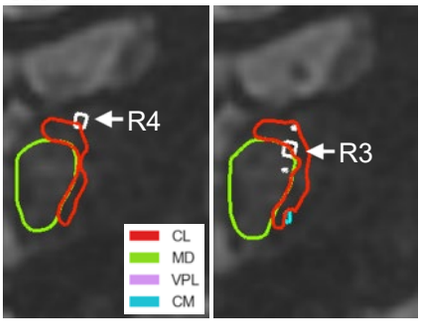
Supplementary Figure 2. Cortical evoked response patterns elicited by active contacts left hemisphere P1.

A. Placement of active contacts (L4, L3) for P1 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). Response pattern demonstrates a dominantly ipsilateral response over frontal and midline channels with modest activation of contralateral frontal midline changes. **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (50 μV to -40 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 3.

Participant 1 (P1). Right Hemisphere

A.



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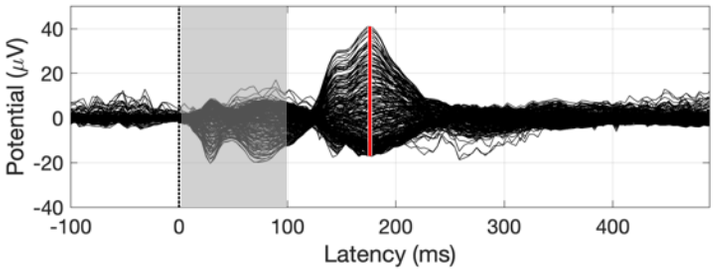

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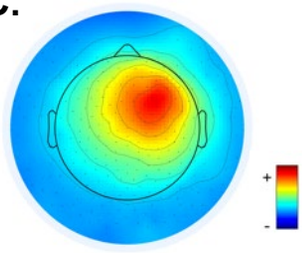

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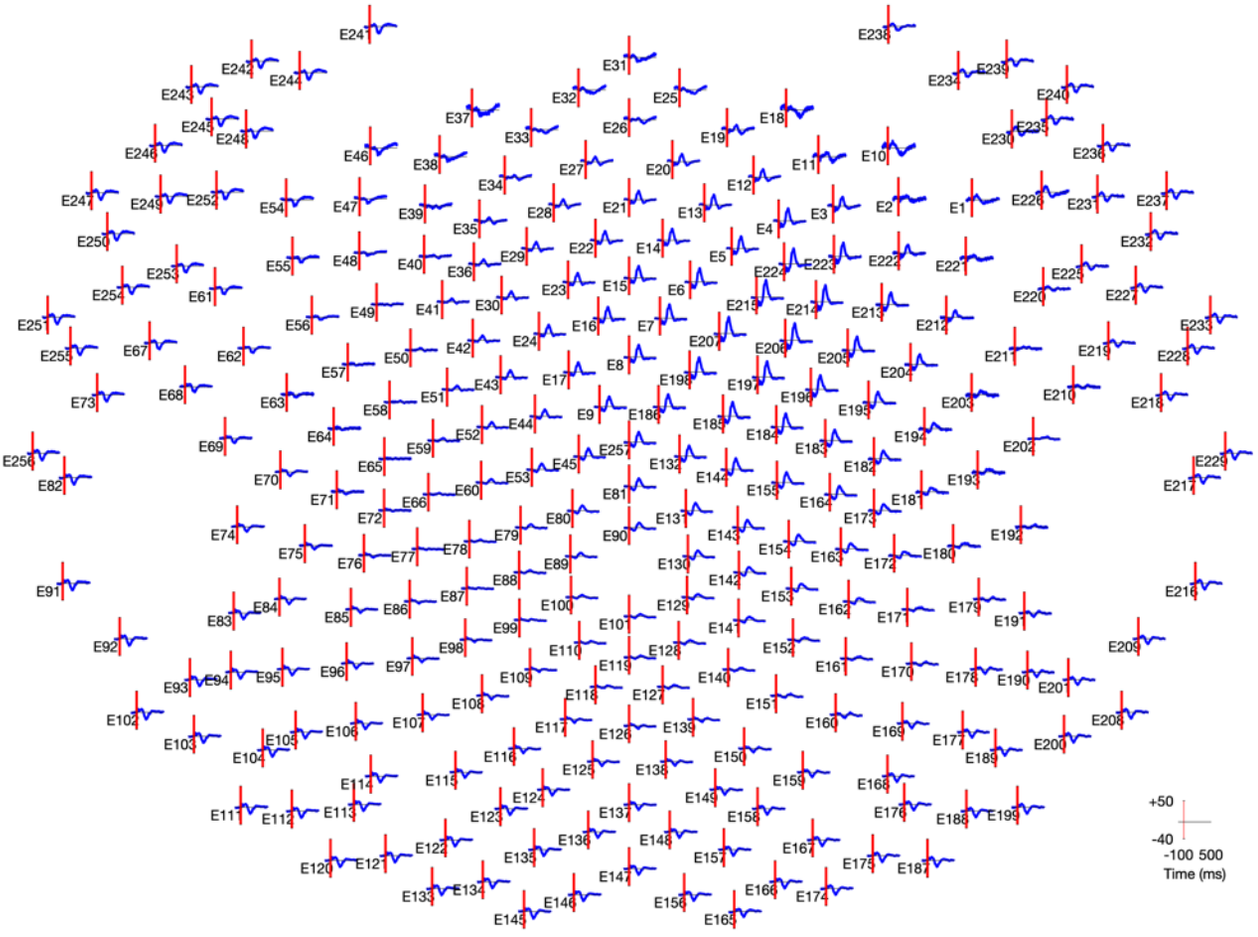
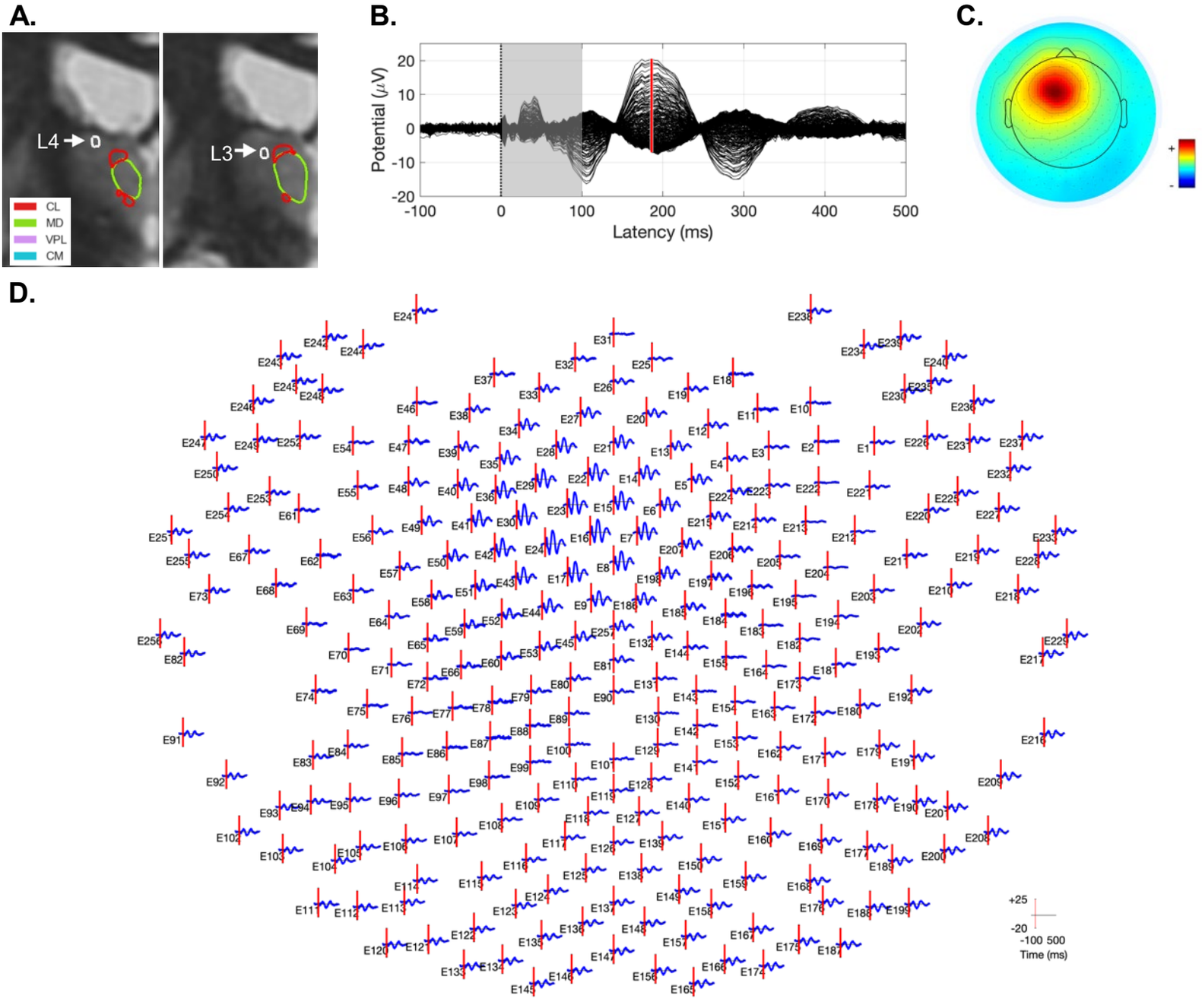


Supplementary Figure 3. Cortical evoked response patterns elicited by active contacts right hemisphere P1.

A. Placement of active contacts (R4, R3) for P1 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). Response pattern demonstrates a dominantly ipsilateral response over frontal and midline channels with modest activation of contralateral frontal midline changes. **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (50 μV to -40 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 4.

Participant 3 (P3). Left Hemisphere



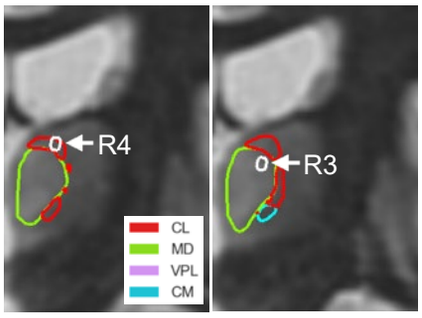
Supplementary Figure 4. Cortical evoked response patterns elicited by active contacts left hemisphere P3.

A. Placement of active contacts (L4, L3) for P3 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). Response pattern demonstrates a dominantly ipsilateral response over frontal and midline channels with modest activation of contralateral frontal midline changes. **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (25 μV to -20 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 5.

Participant 3 (P3). Right Hemisphere

A.



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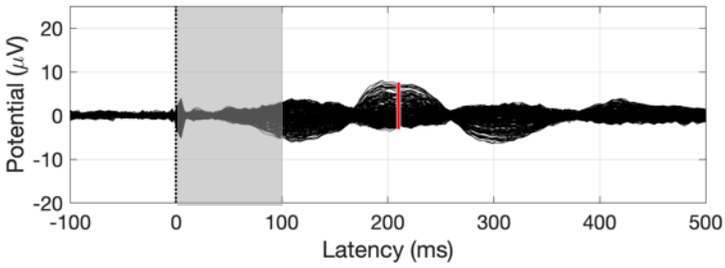

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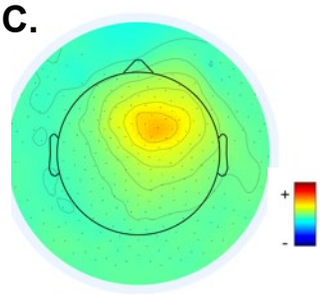

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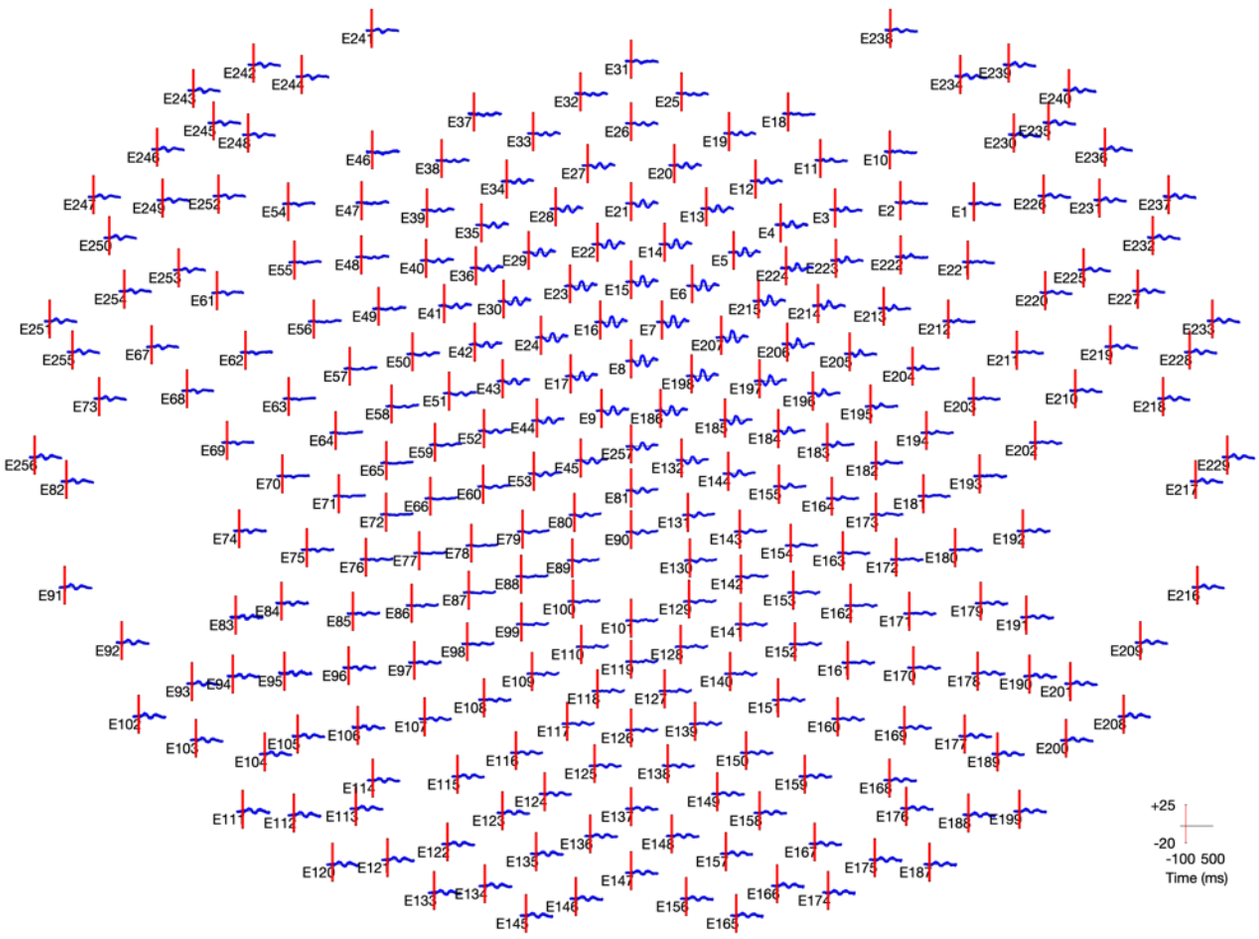


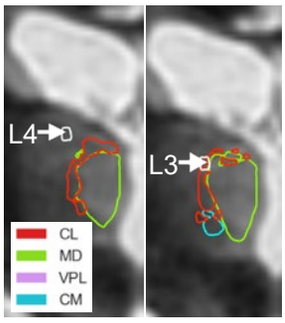
Supplementary Figure 5. Cortical evoked response patterns elicited by active contacts right hemisphere P3.

A. Placement of active contacts (R4, R3) for P3 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). Response pattern demonstrates a dominantly ipsilateral response over frontal and midline channels with modest activation of contralateral frontal midline changes, note responses diminished compared with left hemisphere activation (Supplementary Fig 9). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (25 μV to -20 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 6.

Participant 4 (P4). Left Hemisphere

A.



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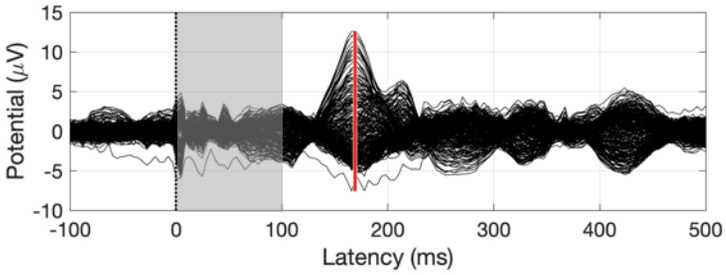

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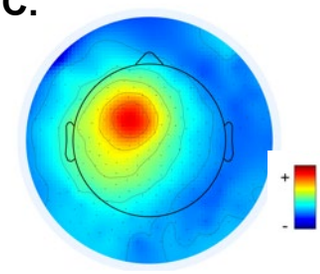

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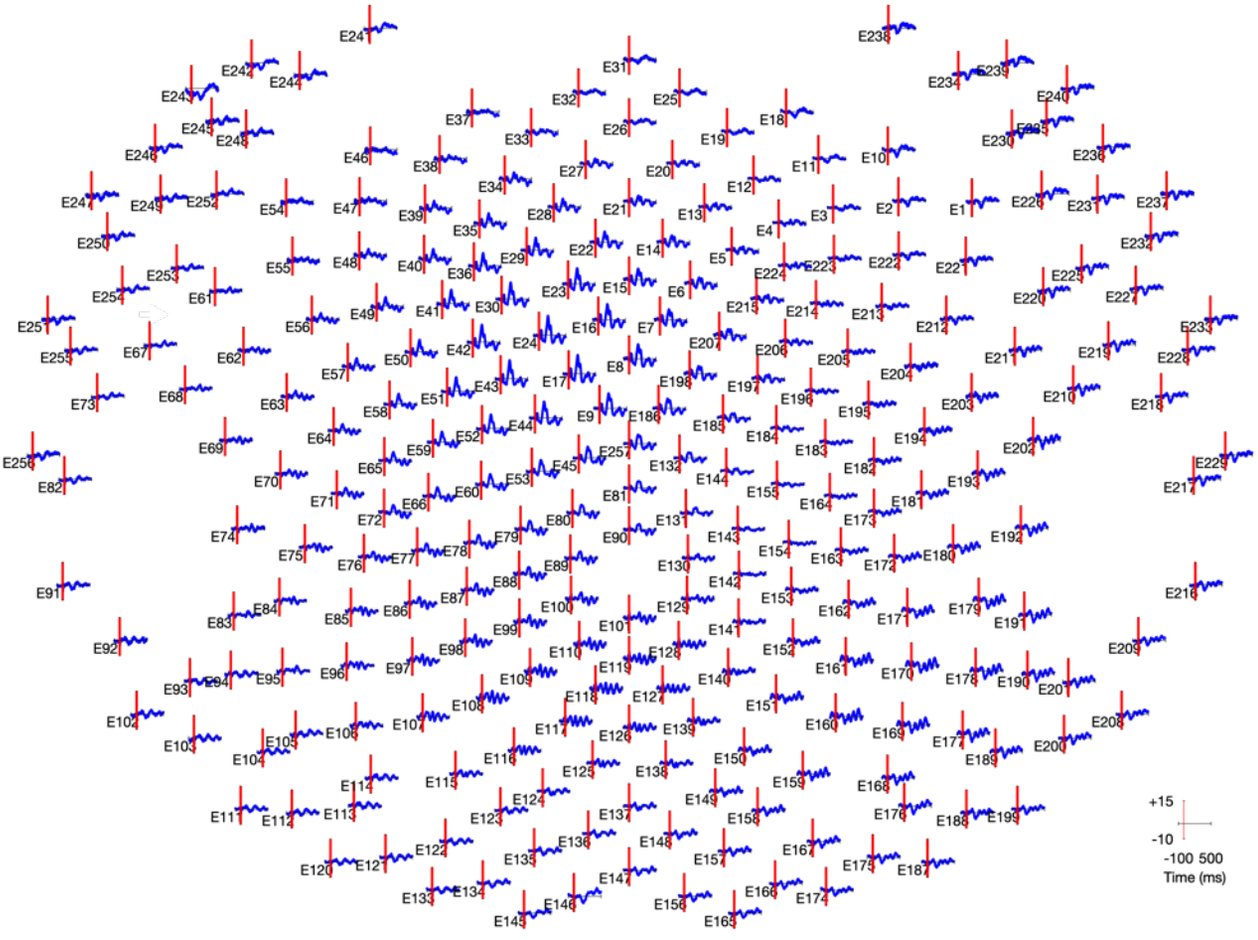
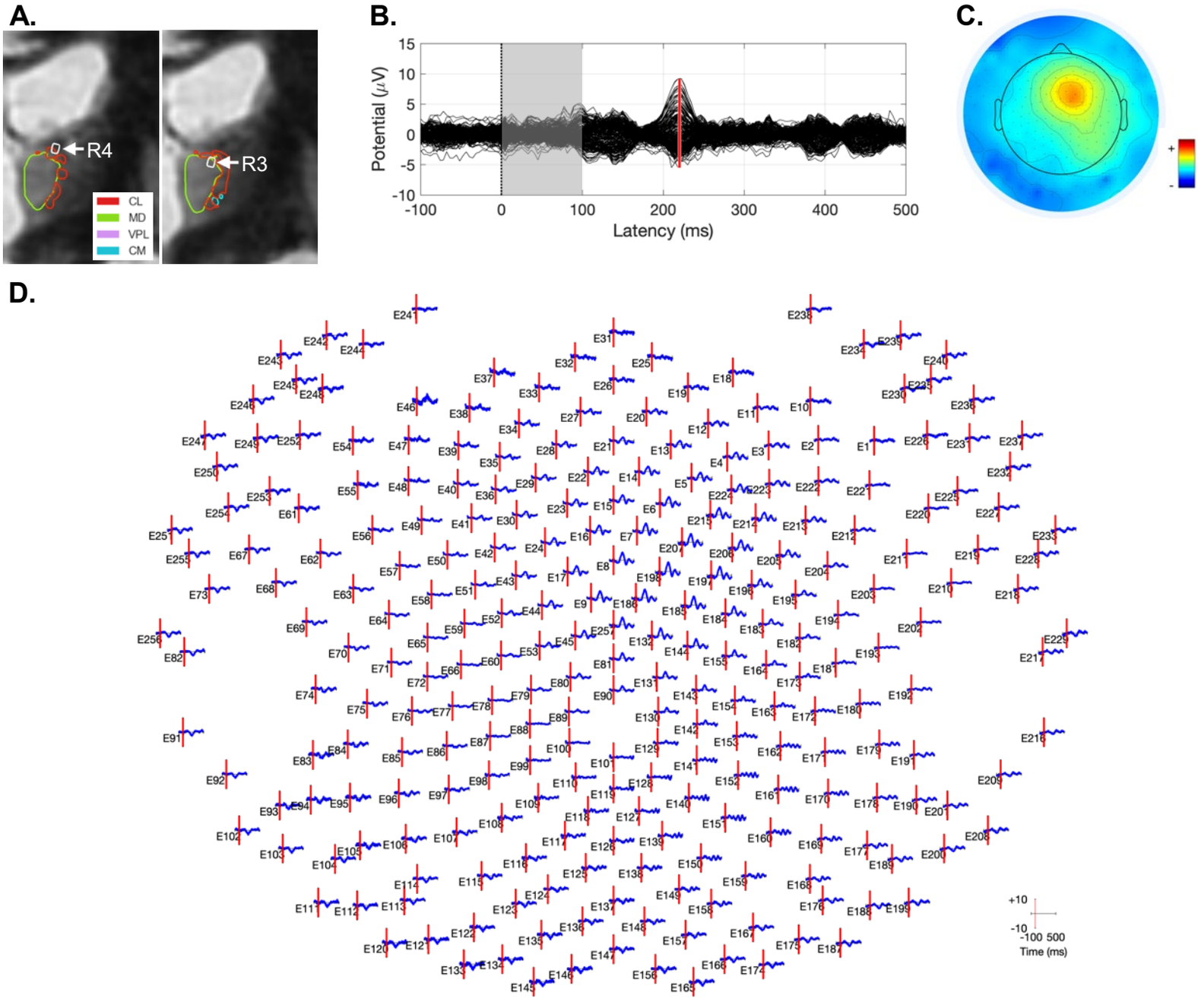


Supplementary Figure 6. Cortical evoked response patterns elicited by active contacts left hemisphere P4.

A. Placement of active contacts (L4, L3) for P4 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). Response pattern demonstrates a dominantly ipsilateral response over frontal and midline channels with modest activation of contralateral frontal midline changes. **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (15 μV to -10 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 7.

Participant 4 (P4). Right Hemisphere

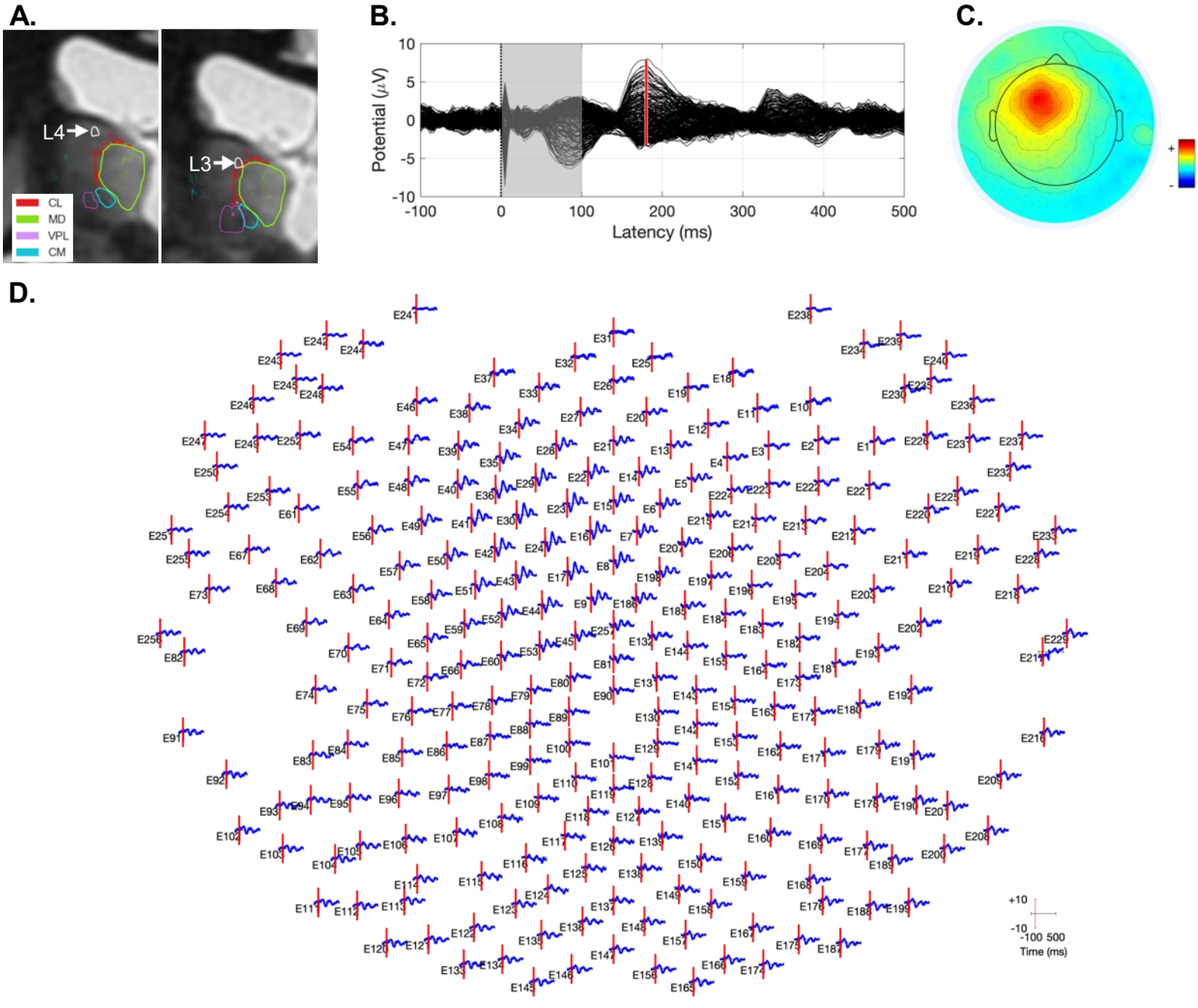


Supplementary Figure 7. Cortical evoked response patterns elicited by active contacts right hemisphere P4.

A. Placement of active contacts (R4, R3) for P4 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (15 μV to -10 μV). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 8.

Participant 5 (P5). Left Hemisphere



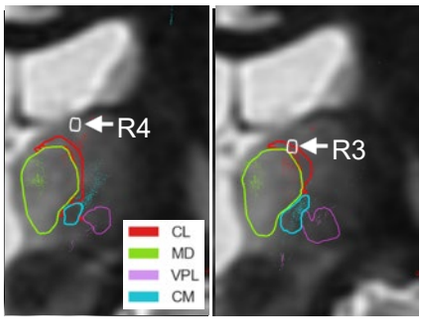
Supplementary Figure 8. Cortical evoked response patterns elicited by active contacts left hemisphere P5.

A. Placement of active contacts (L4, L3) for P5 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (10 μV to -10 μV). **D.** Time average cortical evoked response all 256 channels plotted. See Supplementary Methods for experimental details.

Supplementary Figure 9.

Participant 5 (P5). Right Hemisphere

A.



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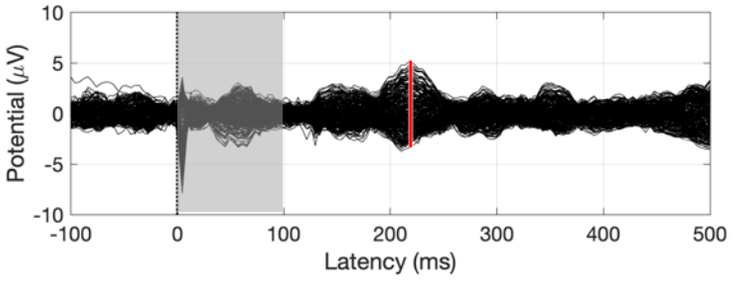

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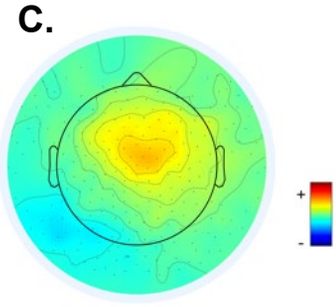

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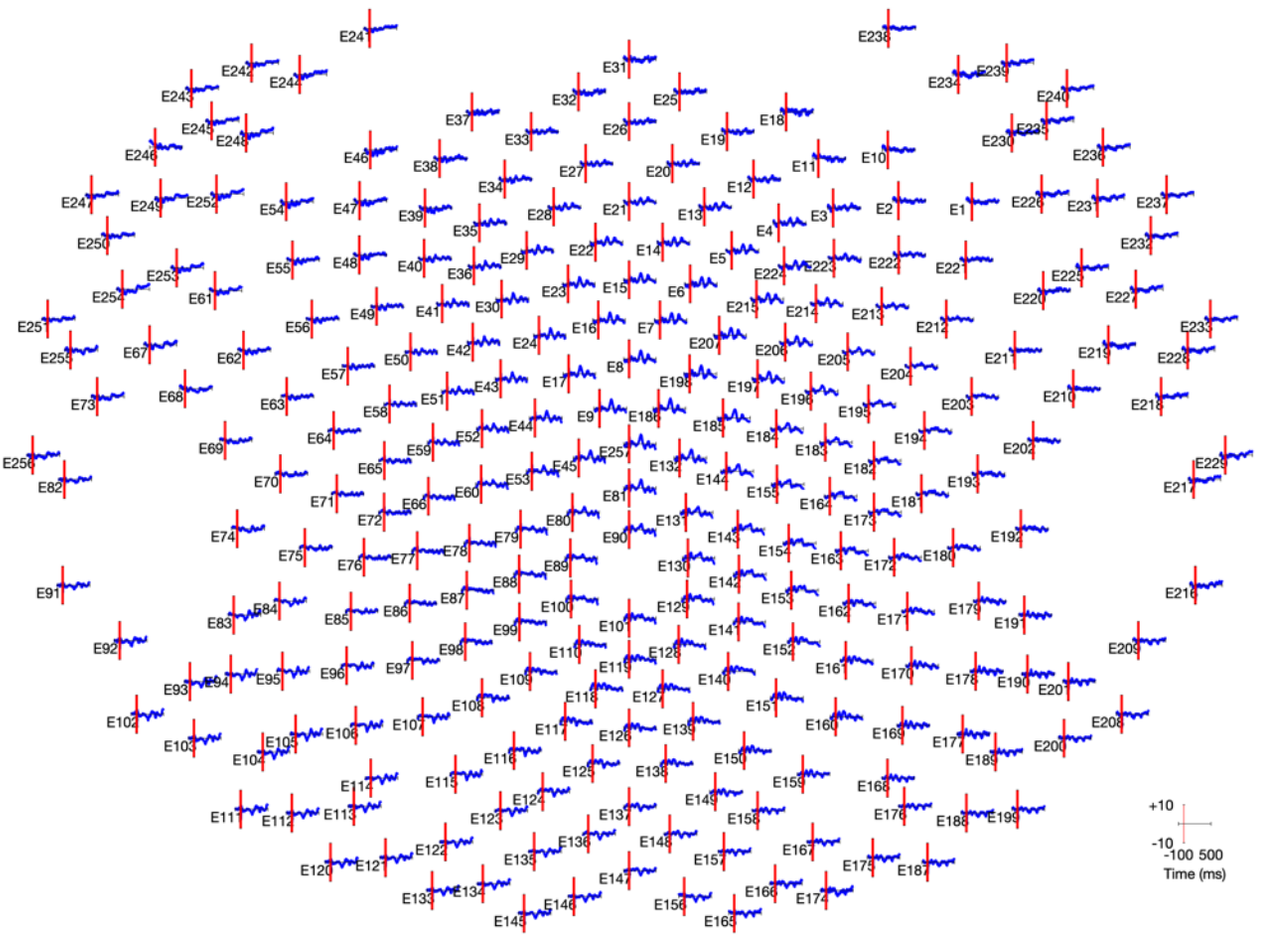
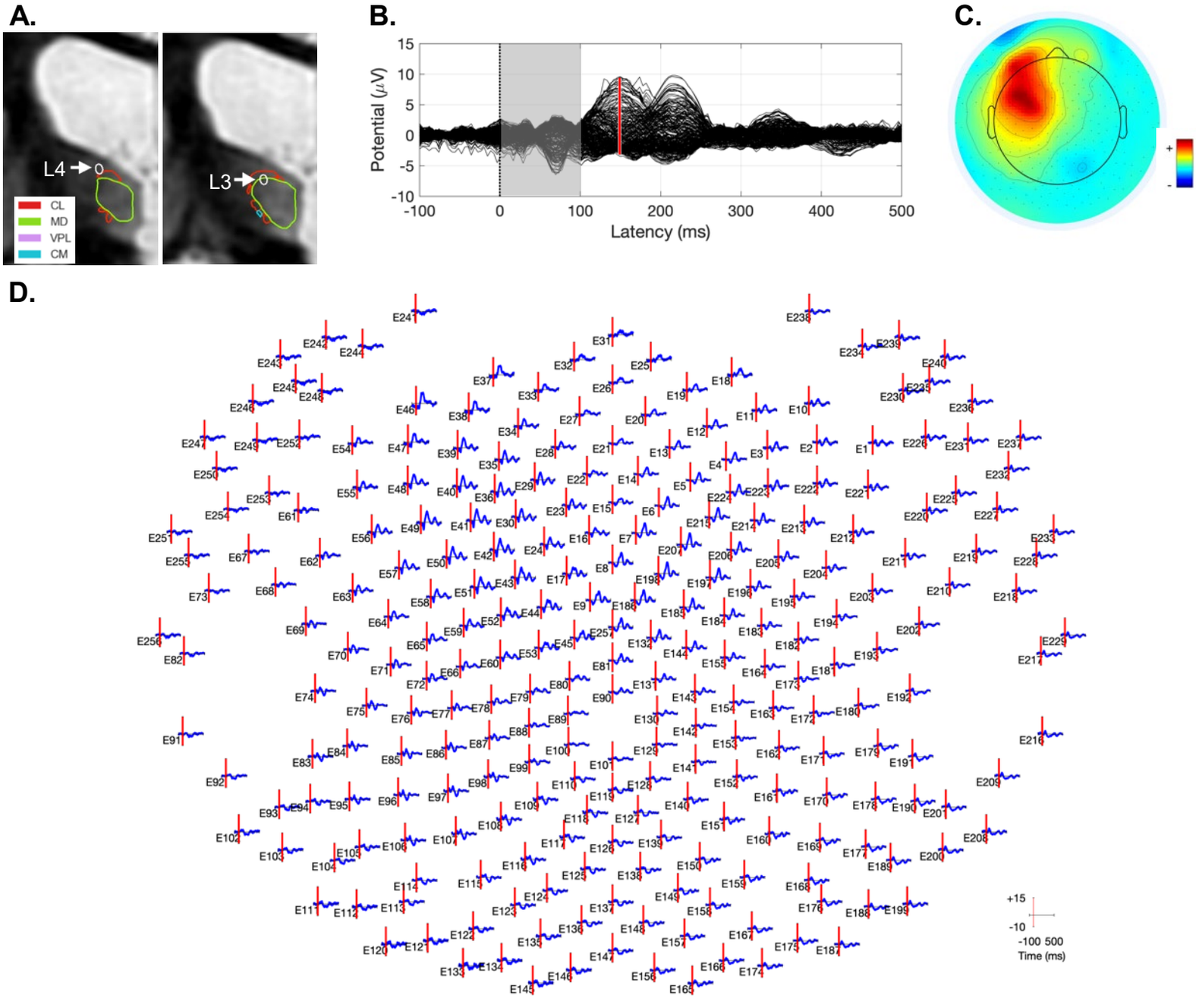


Supplementary Figure 9. Cortical evoked response patterns elicited by active contacts right hemisphere P5.

A. Placement of active contacts (R4, R3) for P5 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (10 μV to -10 μV). **D.** Time average cortical evoked response all 256 channels plotted. Peak response is smaller than identified in the left hemisphere (Supplementary Fig 8); see Supplementary Methods for experimental details.

Supplementary Figure 10.

Participant 6 (P6). Left Hemisphere

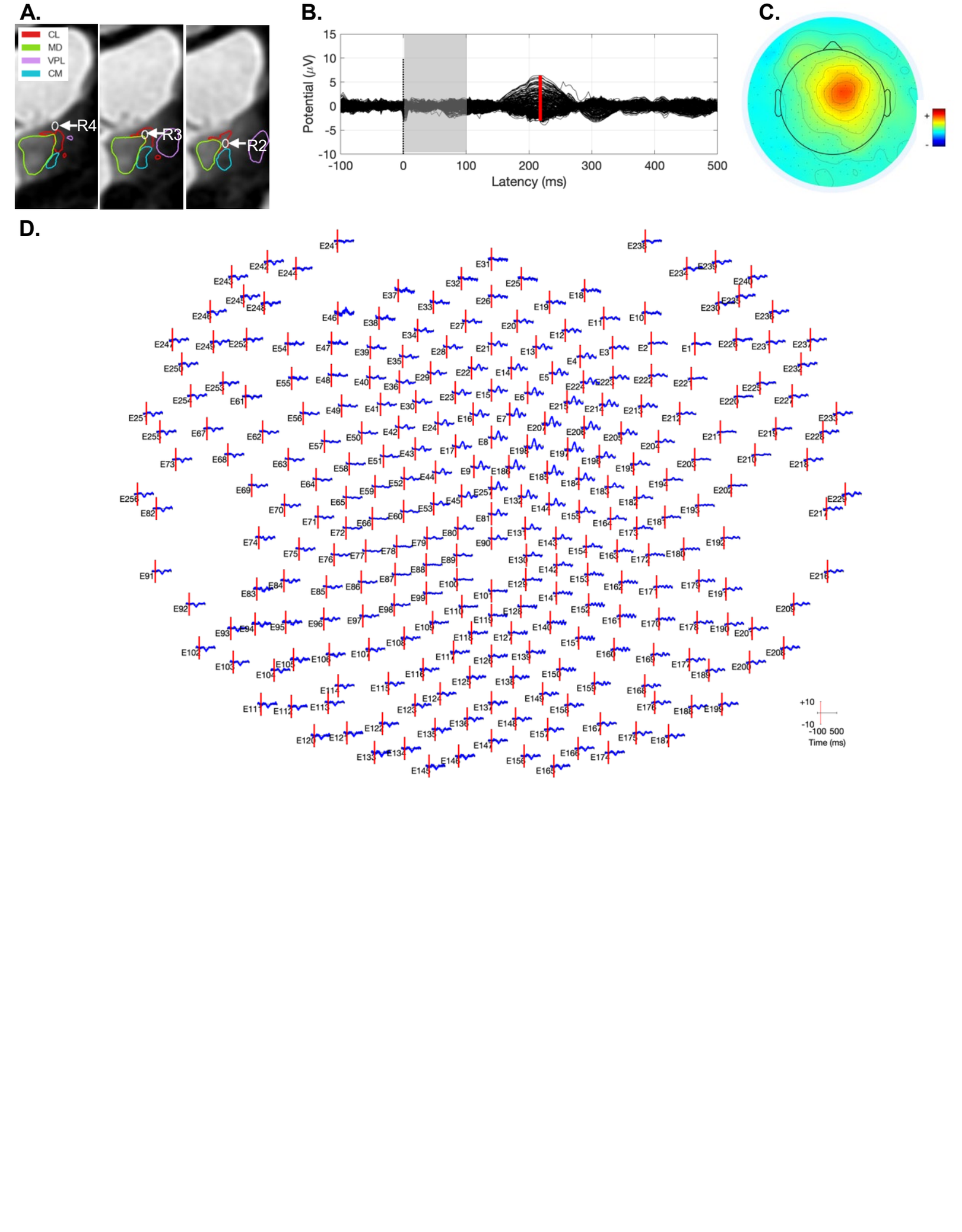


Supplementary Figure 10. Cortical evoked response patterns elicited by active contacts left hemisphere P6.

A. Placement of active contacts (L4, L3) for P6 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (15 μV to -10 μV). Of note, a broader bilateral spread of activation into the contralateral hemisphere is seen compared with the right sided electrode (Supplementary Figure 11) possibly reflecting effects of deafferentation due to the ipsilateral (left) lesion with anterior cingulate cortex (see Supplementary Figures 16,17). **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 11.

Participant 6 (P6). Right Hemisphere

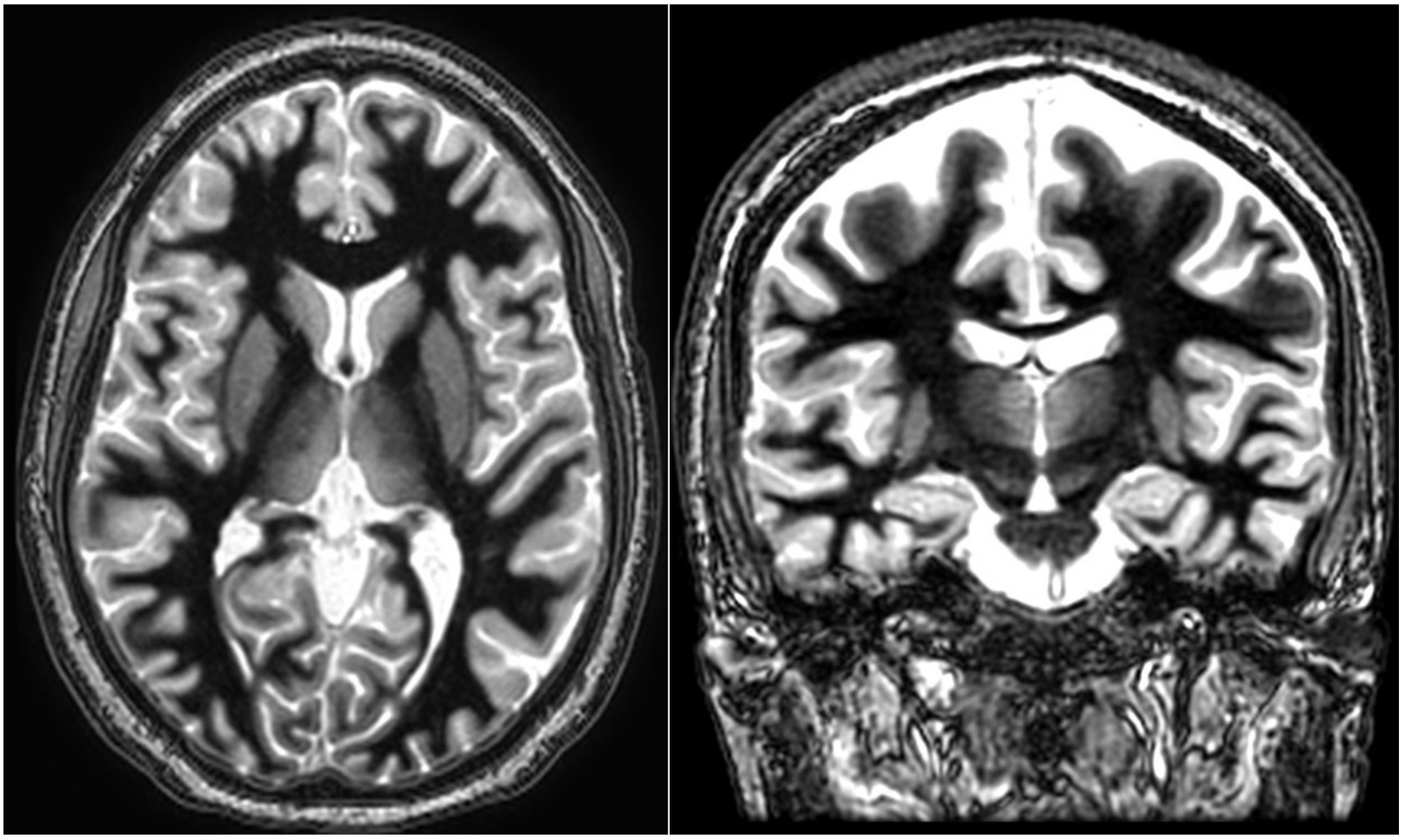


Supplementary Figure 11. Cortical evoked response patterns elicited by active contacts right hemisphere P6.

A. Placement of active contacts (R4, R3) for P6 in relation to CL (red) and MD (green) nuclei. **B.** Array of evoked responses obtained from high resolution EEG recordings (trials, 256 channels, NetStation Review; Electrical Geodesics, Inc.). **C.** EEG topoplot illustrating maximum depth of modulation of evoked potential. Color bar in microvolts (15 μV to -10 μV. **D.** Time average cortical evoked response all 256 channels plotted see Supplementary Methods for experimental details.

Supplementary Figure 12.

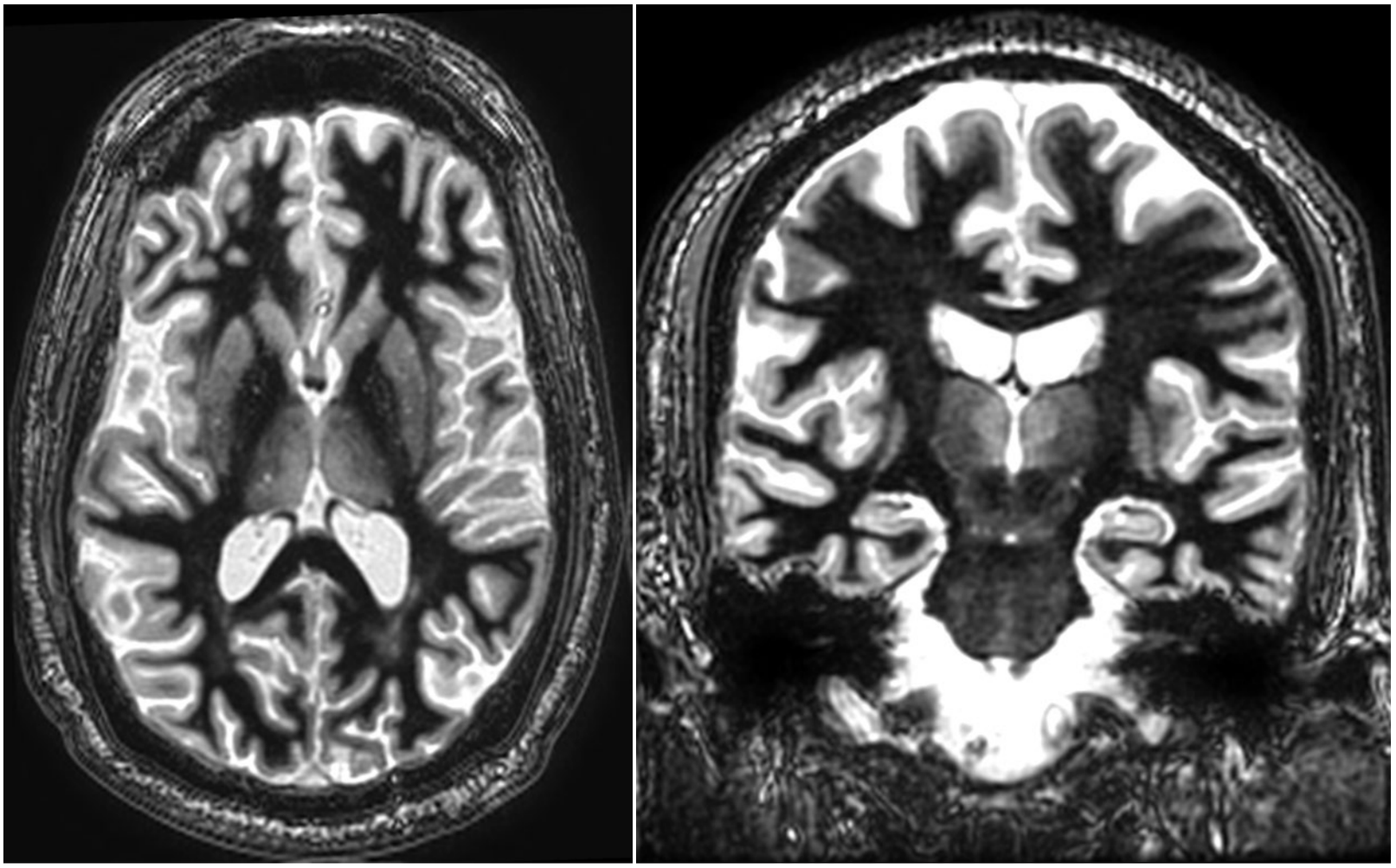
P1 - 3T WMn



Supplementary Figure 12. Structural MRI imaging P1.

Supplementary Figure 13.

P3 - 3T WMn

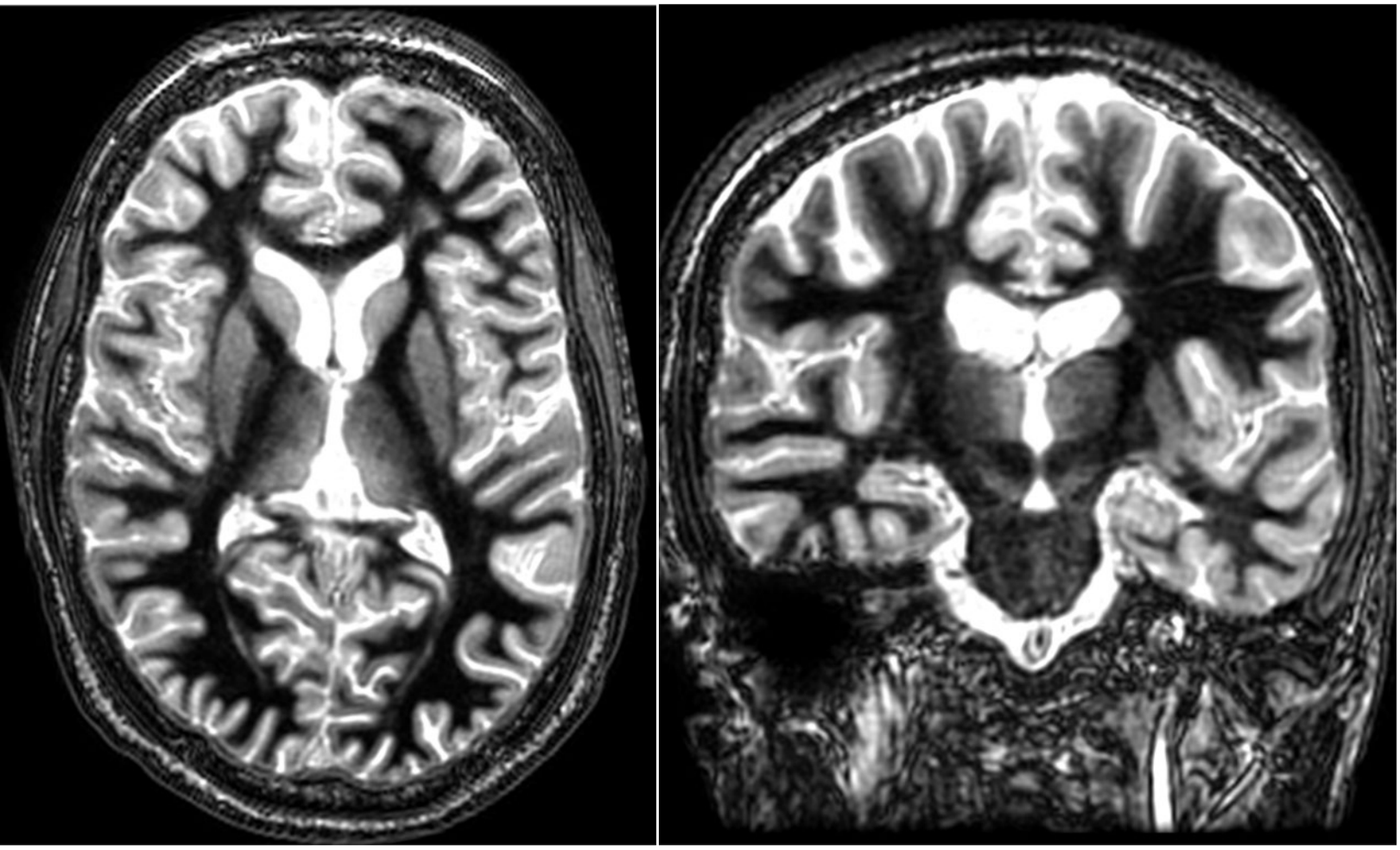


Supplementary Figure 13. Structural MRI imaging P3.

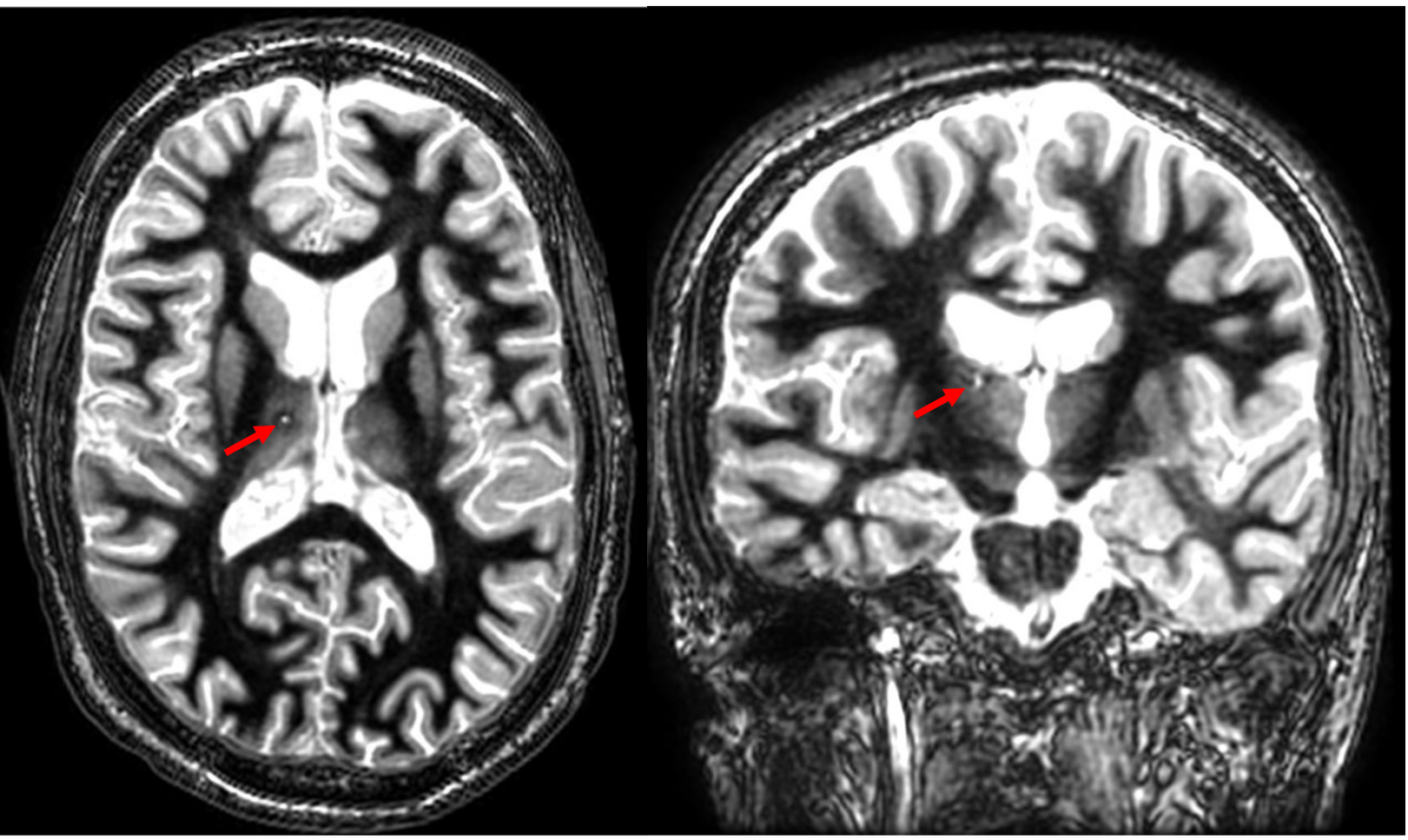
Supplementary Figure 14.

P4 - 3T WMn

A.



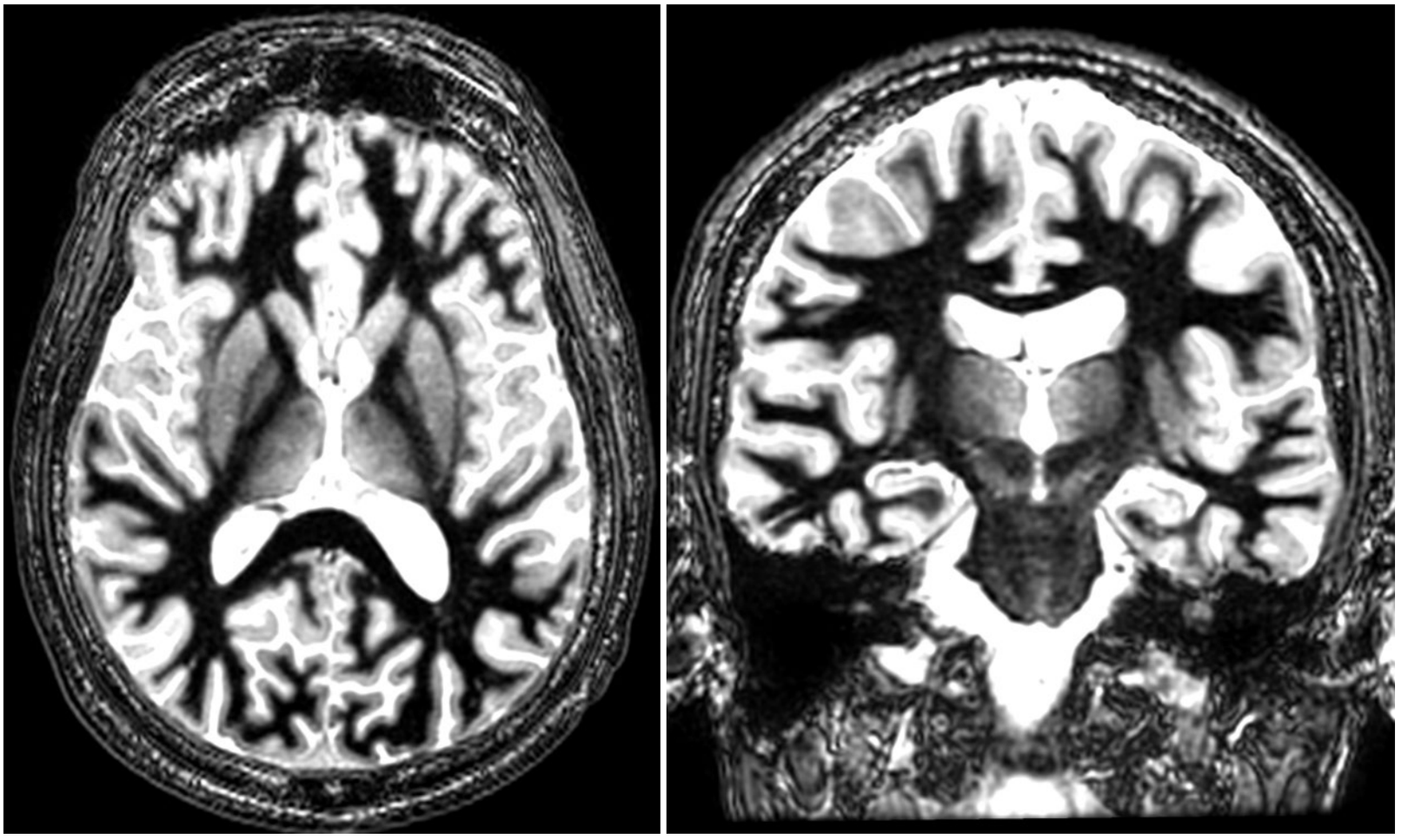
B.



Supplementary Figure 14. Structural MRI imaging P4.

Supplementary Figure 15.

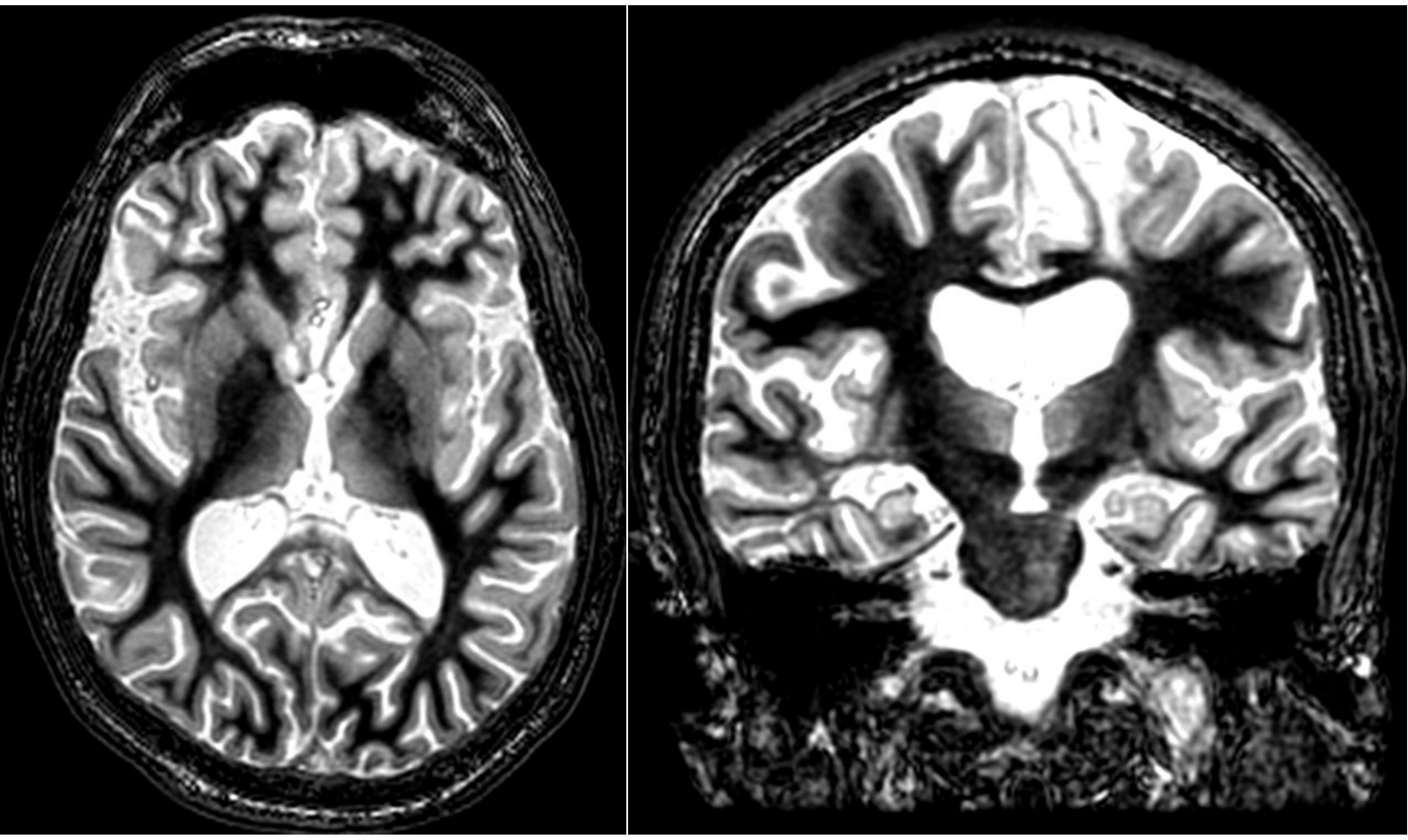
P5 - 3T WMn



Supplementary Figure 15. Structural MRI imaging P5.

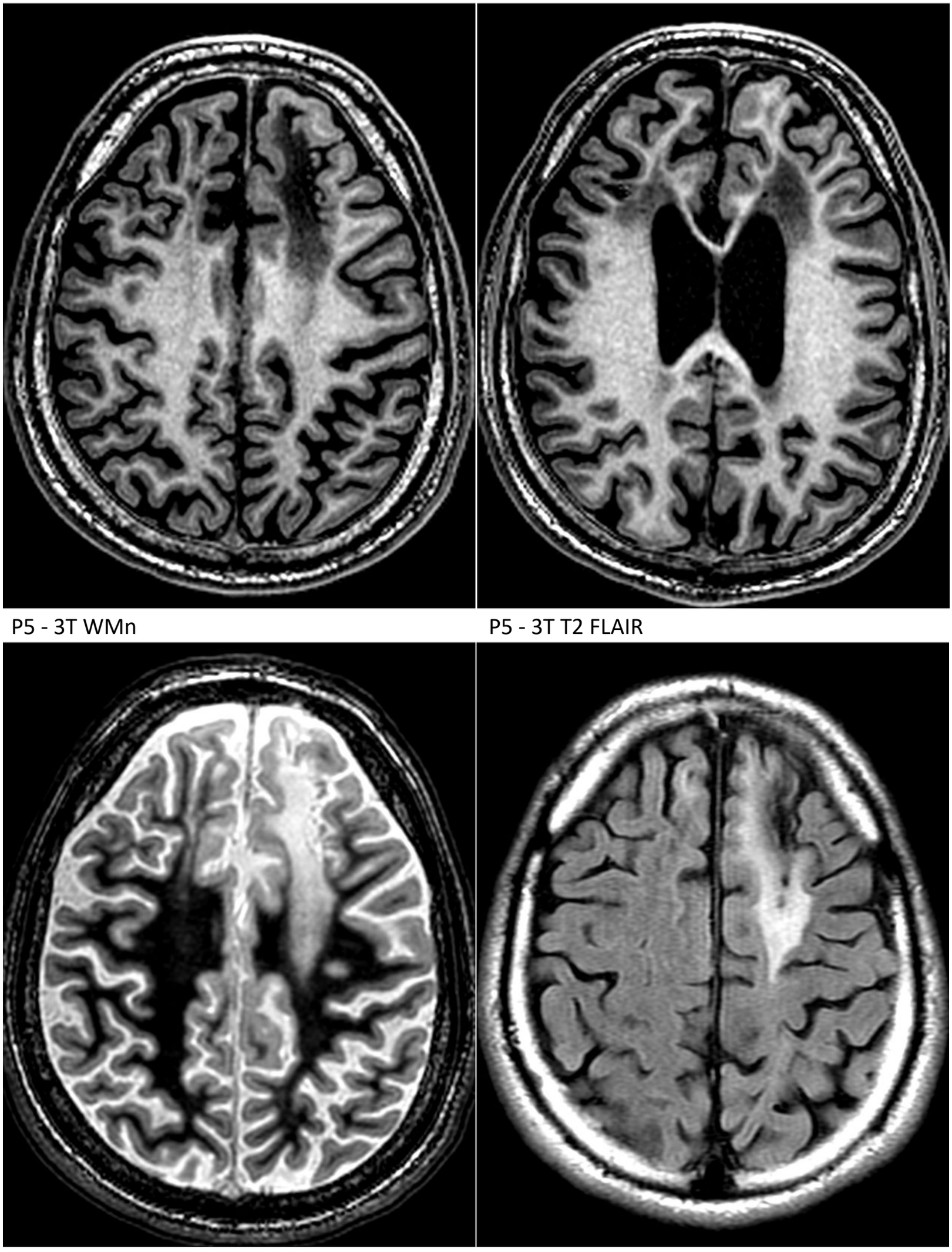
Supplementary Figure 16.

P6 - 3T WMn



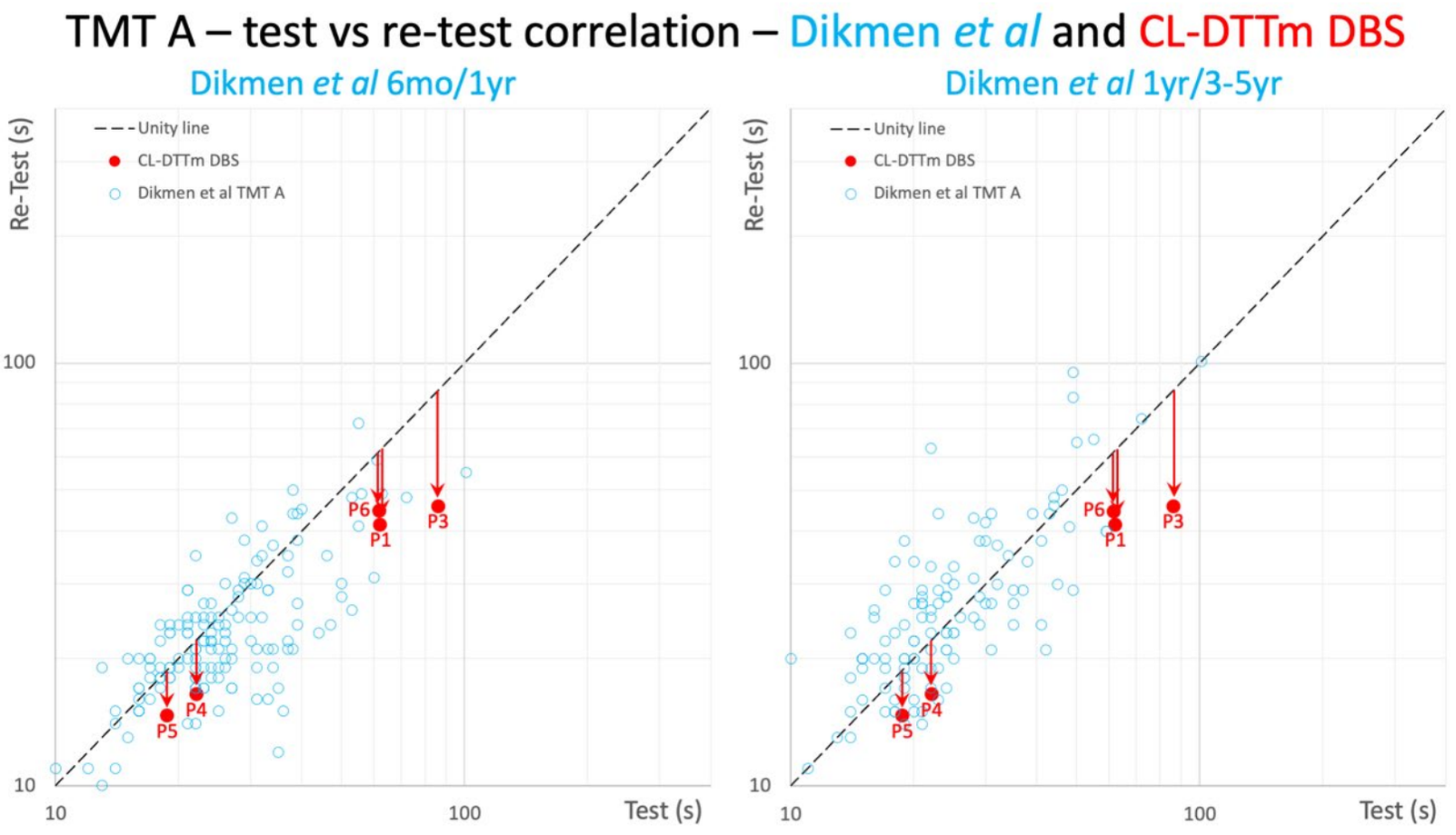
Supplementary Figure 16. Structural MRI imaging P6.

Supplementary Figure 17.



Supplementary Figure 17. Structural MRI imaging, P6, axial images through anterior cingulate cortex lesion left hemisphere.

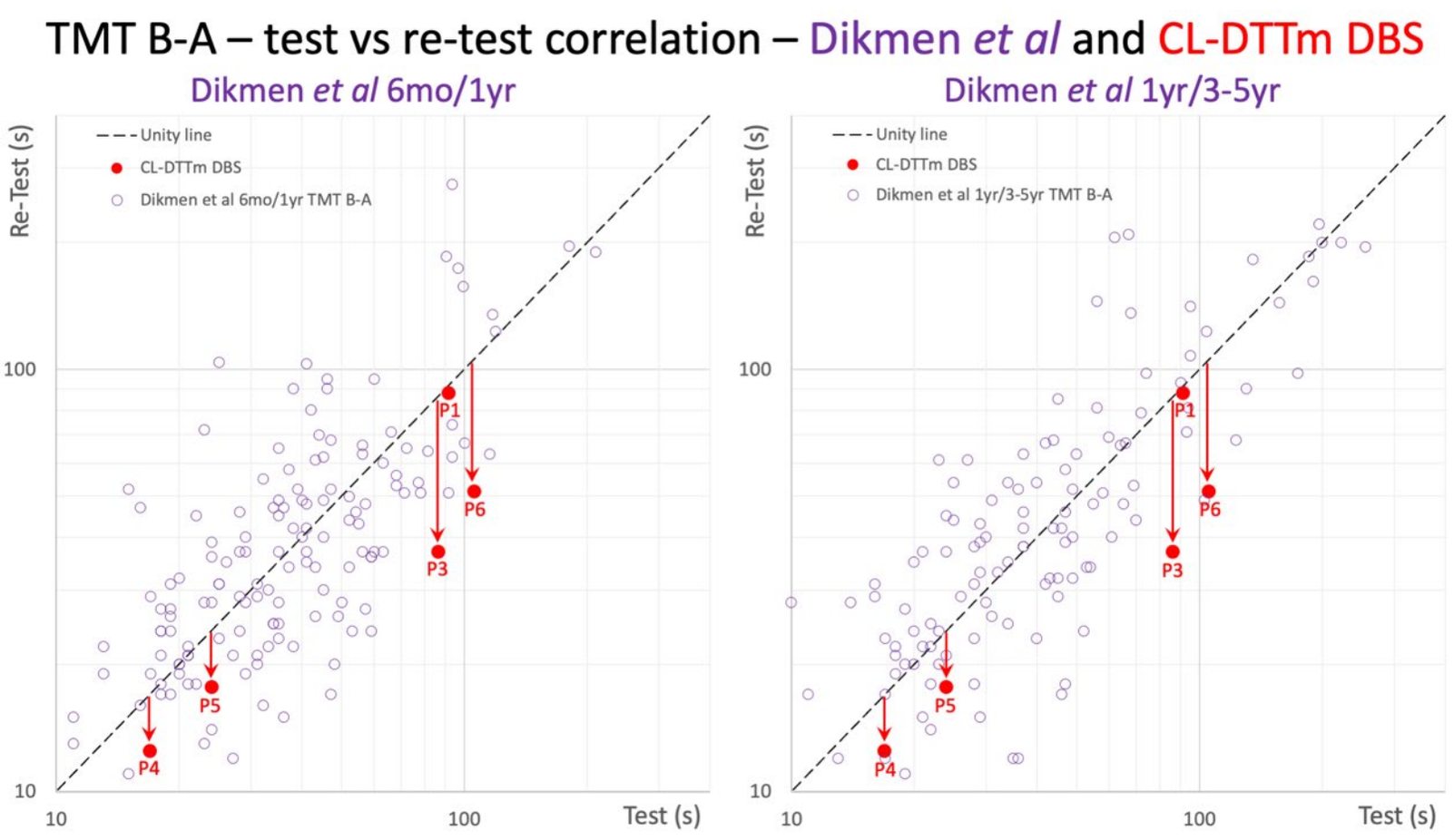
Supplementary Figure 18.



Supplementary Figure 18: TMT-A completion times comparison to Dikmen et al. vs DBS participants.

Figure displays scattergrams of data from 146 (A) and 118 (B) msTBI subjects (light blue dots) followed as part of the Dikmen et al. 2003[5] study (with available TMT-A completion time measurements at time points six months and one year (A) and three to five years (B) after injury (provided by Dr. Dikmen) and the five msTBI participants studied here (red dots). As seen in the scattergrams of the two time points for TMT-A completion time measurements show that the CL/DTTm subjects cluster on the lower edge of both distributions of blue dots. Statistical tests demonstrate that it is unlikely that the CL/DTTm DBS participant values might be drawn at random from the distribution of either sample of the Dikmen et al.[5] data: A) $p<0.02$ Kolmogorov-Smirnov test, one-sided [$p=0.011$], B) $p<0.001$ Kolmogorov-Smirnov, one-sided [0.000570]. Axes scaled logarithmically.

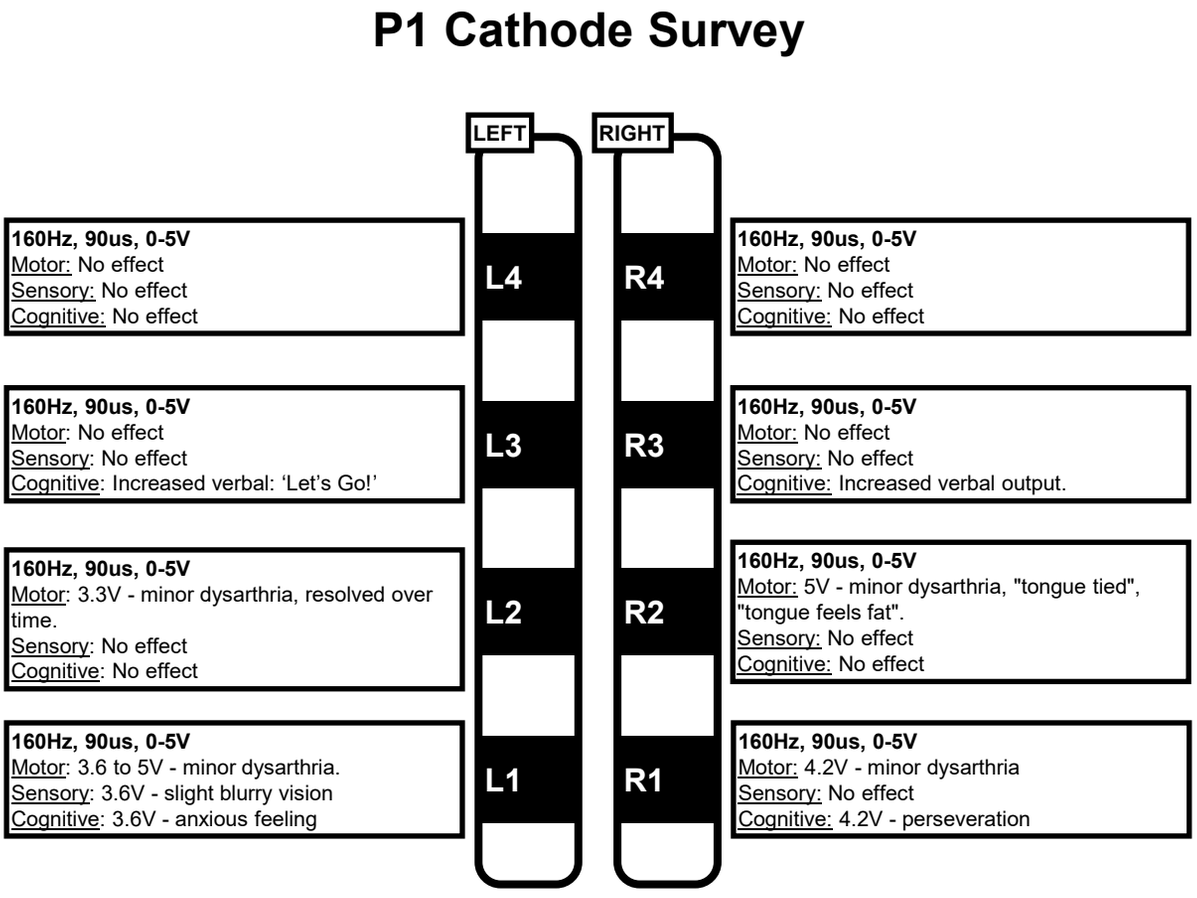
Supplementary Figure 19.



Supplementary Figure 19: TMT (B-A) completion times comparison to Dikmen et al. vs DBS participants.

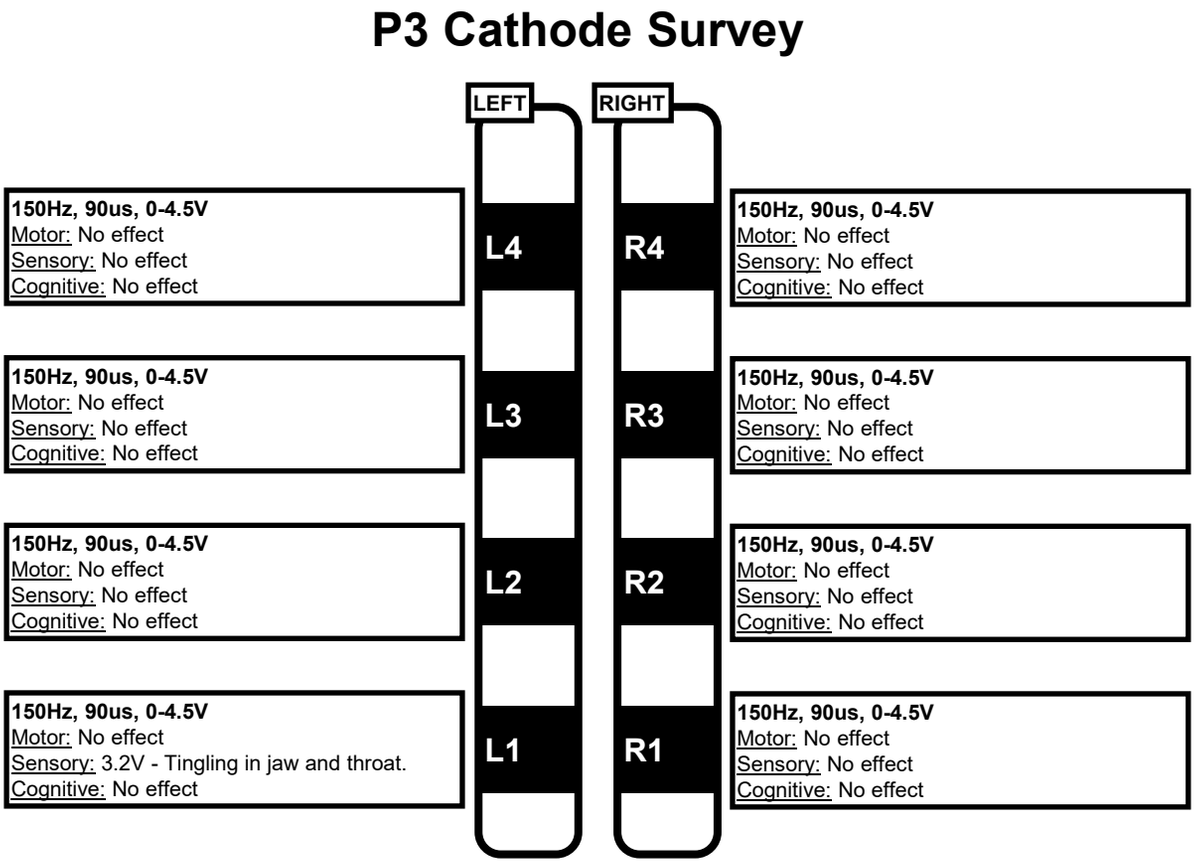
Figure displays scattergrams of data from 146 (A) and 118 (B) msTBI subjects (purple dots) followed as part of the Dikmen et al. 2003 study with available TMT completion time measurements at time points six months and one year (A) and three to five years (B) after injury (provided by Dr. Dikmen) and the five msTBI participants studied here (red dots). As seen in the scattergram of the two time points for TMT B-A completion time measurements show that the CL/DTTm subjects cluster on the lower edge of both distributions of blue dots. Statistical tests demonstrate that it is unlikely that the CL/DTTm DBS participant values might be drawn at random from the distribution of second set (N=118) of Dikmen et al.[5] data: $p<0.05$ Kolmogorov-Smirnov test, one-sided [.0396]. Axes scaled logarithmically. Testing of first set of Dikmen et al.[5] data not significant by K-S test, one-sided [p=0.081275].

Supplementary Figure 20



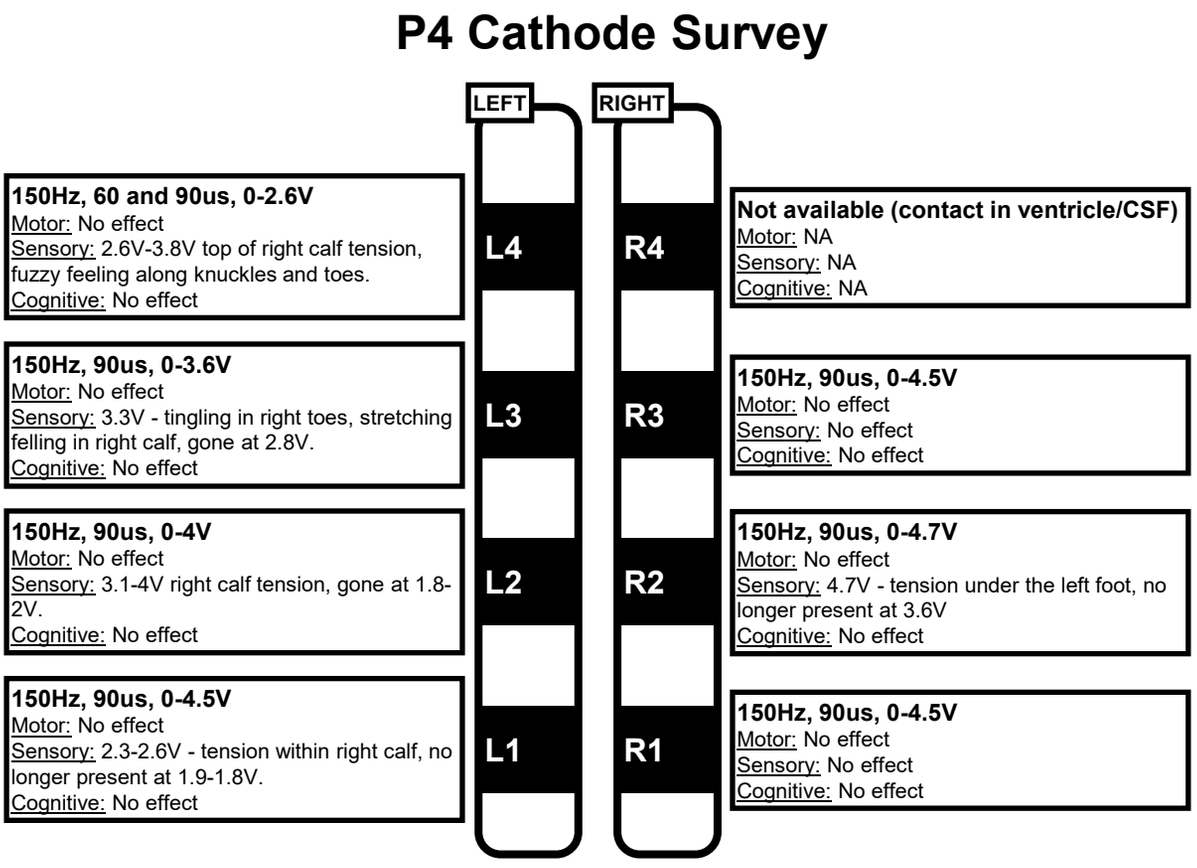
Supplementary Figure 20: Cathode survey overview, P1.

Supplementary Figure 21



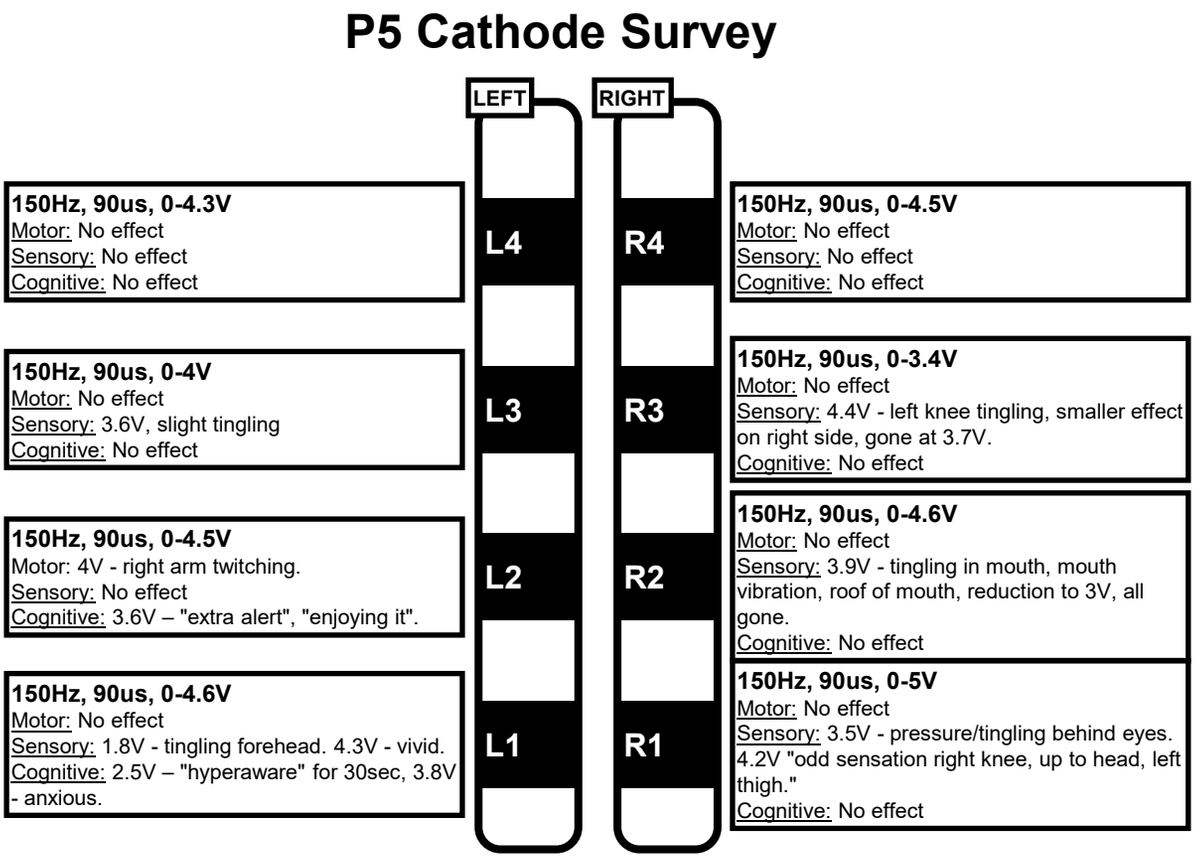
Supplementary Figure 21: Cathode survey overview, P3.

Supplementary Figure 22



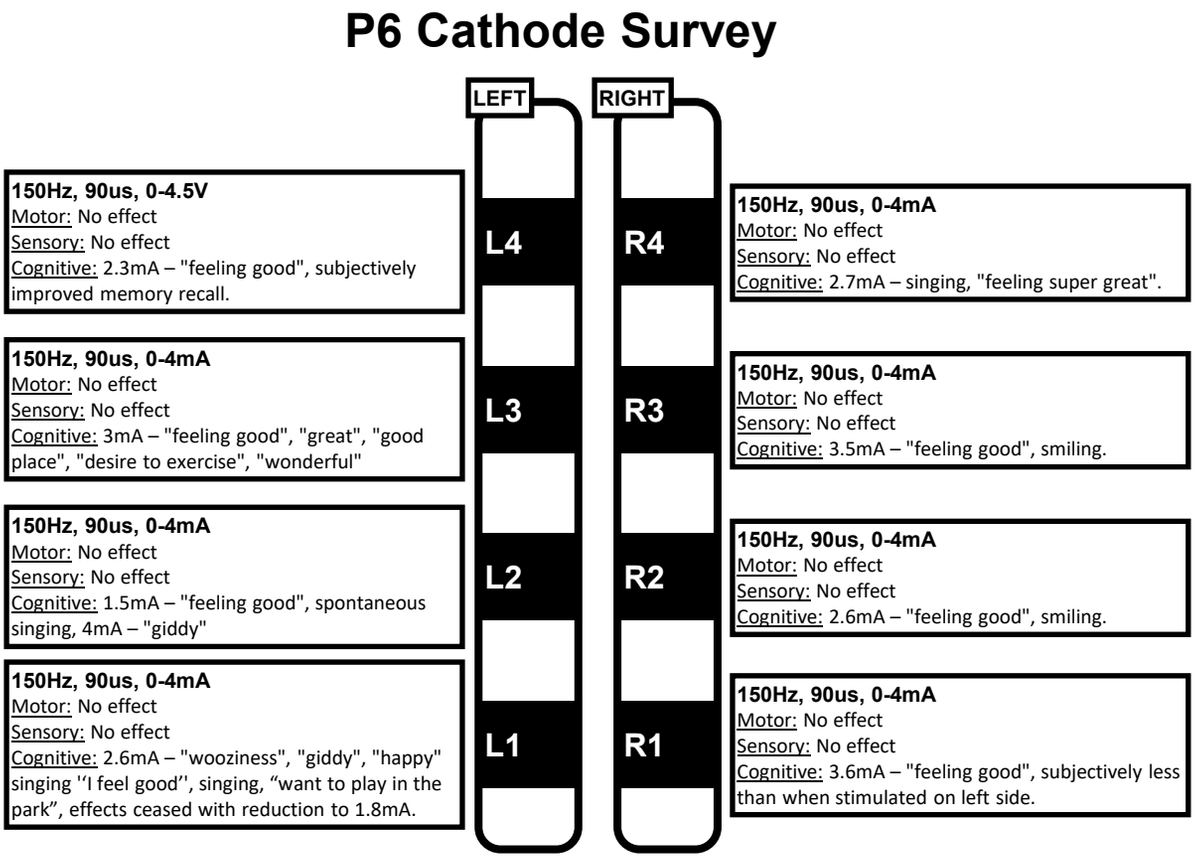
Supplementary Figure 22: Cathode survey overview, P4.

Supplementary Figure 23



Supplementary Figure 23: Cathode survey overview, P5.

Supplementary Figure 24



Supplementary Figure 24: Cathode survey overview, P6.

Supplementary Table 1.

Ruff 2&7 (4 subjects)

Measure by Domain	Performance-based (P) or Self-report (S)	Change in Performance from Pre-surgical Baseline to Treatment End			
		Raw Score		T Score	
		Difference	Percent	Difference	Percent
P1					
		Results invalid: test administration error			
P3					
Auto Detection Accuracy	P	4.63	5.15	11	33.33
Controlled Search Accuracy	P	6.68	7.91	14	45.16
Total Accuracy	P			9	25.71
Auto Detection Speed	P	15	21.13	6	20
Controlled Search Speed	P	12	16.90	5	17.24
Total Speed	P			5	16.13
P4					
Auto Detection Accuracy	P	-1.08	-1.10	-2	-3.92
Controlled Search Accuracy	P	1.06	1.09	2	3.57
Total Accuracy	P			2	3.77
Auto Detection Speed	P	6	3.87	4	8.51
Controlled Search Speed	P	23	17.69	12	27.27
Total Speed	P			8	17.02
P5					
Auto Detection Accuracy	P	1.80	1.83	4	7.55
Controlled Search Accuracy	P	1.31	1.36	3	5.56
Total Accuracy	P			4	7.55
Auto Detection Speed	P	38	23.17	12	21.43
Controlled Search Speed	P	12	7.19	3	4.48
Total Speed	P			8	12.5
P6					
Auto Detection Accuracy	P	13.30	15.67	32	152.38
Controlled Search Accuracy	P	3.27	4.07	7	30.43
Total Accuracy	P			19	86.36
Auto Detection Speed	P	35	47.95	12	54.55
Controlled Search Speed	P	32	48.48	14	70
Total Speed	P			15	68.18

Negative values (-) indicate worsening in performance.

Supplementary Table 1. Ruff 2&7 summary for 4 subjects completing testing.

P1: Change in raw and T-scores from pre-surgery baseline to post-surgery baseline, treatment start and treatment end

Measure by Domain	Pre-Surg Metrics	Pre-Surg to Post-Surg Baseline Score Change				Pre-Surg to Treatment Start Score Change				Pre-Surg to Treatment End Score Change			
		Raw Score		T Score		Raw Score		T Score		Raw Score		T Score	
		Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent
Attentional control													
TMT-B	153	-21.50	14.05%	0	0.00%	0.00	0.00%	0	0.00%	-23.3	15.23%	0	0.00%
TMT-B minus TMT-A	91	0.87	-0.01%			3.38	-3.71%			-2.83	3.10%		
2&7 Auto Detection Accuracy	NA	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
2&7 Auto Detection Errors	NA	Missing	Missing			Missing	Missing			Missing	Missing		
2&7 Controlled Search Accuracy	NA	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
2&7 Controlled Search Errors	NA	Missing	Missing			Missing	Missing			Missing	Missing		
2&7 Total Accuracy Sum of T 2&7 Scores	NA	Missing	Missing			Missing	Missing			Missing	Missing		
2&7 Total Accuracy	NA			Missing	Missing			Missing	Missing			Missing	Missing
2&7 Accuracy Difference	NA	Missing	Missing			Missing	Missing			Missing	Missing		
2&7 Total Speed/Accuracy Difference	NA	Missing	Missing			Missing	Missing			Missing	Missing		
TBI-QoL Exec	36	9	25.00%	7	19.02%	10	27.78%	8.1	22.01%	7	19.44%	5.1	13.86%
TBI-QoL Atten	19	7	36.84%	8.1	22.19%	4	21.05%	4.4	12.05%	11	57.89%	21.7	59.45%
Processing Speed													
TMT-A	62	-22.37	36.08%	9	39.13%	-3.38	5.45%	0	0.00%	-20.47	33.02%	9	39.13%
2&7 Auto Detection Speed	NA	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
2&7 Controlled Search Speed	NA	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
2&7 Total Speed Sum of T Scores	NA	Missing	Missing			Missing	Missing			Missing	Missing		
2&7 Total Speed	NA			Missing	Missing			Missing	Missing			Missing	Missing
2&7 Speed Difference	NA	Missing	Missing			Missing	Missing			Missing	Missing		
Fatigue													
TBI-QoL Fatig	33	-5	15.15%	-3.80	6.22%	-11	33.33%	-8.6	14.08%	-23	69.70%	-28.40	46.48
Psych health													
PHQ-9	10	-1	10.00%			-6	60.00%			-8	80.00%		
Global Function													
GOSE	5	0	0.00%			0	0.00%			1	20.00%		
RPQ	41	-16	39.02%			-21	51.22%			-39	95.12%		

Key for direction of change

TMT: higher=worse

Ruff Speed: higher=better

Ruff Error: higher=worse

Supplementary Table 2. Behavioral testing summary, P1.

P3: Change in raw and T-scores from pre-surgery baseline to post-surgery baseline, treatment start and treatment end

Measure by Domain	Pre-Surg Metrics	Pre-Surg to Post-Surg Baseline Score Change				Pre-Surg to Treatment Start Score Change				Pre-Surg to Treatment End Score Change			
		Raw Score		T Score		Raw Score		T Score		Raw Score		T Score	
		Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent
Attentional control													
TMT-B	171.7	-43.40	25.25%	4	13.33%	-53.70	31.28%	9	30.00%	-88.81	51.72%	18	60.00%
TMT-B minus TMT-A	85.8	-16.73	19.5%			-8.81	10.27%			-48.79	56.86%		
2&7 Auto Detection Accuracy	89.87	1.04	1.15%	2	6.06%	4.10	4.56%	10	30.30%	4.63	5.15%	11	33.33%
2&7 Auto Detection Errors	8	0	0.00%			-3.00	37.50%			-3	37.50%		
2&7 Controlled Search Accuracy	84.52	2.57	3.04%	5	16.13%	7.88	9.32%	16	51.61%	6.68	7.91%	14	45.16%
2&7 Controlled Search Errors	13	-1	7.69%			-7	53.85%			-5	38.46%		
2&7 Total Accuracy Sum of T 2&7 Scores	64	7	10.94%			26	40.63%			25	39.06%		
2&7 Total Accuracy	35			3	9.38%			13	40.63%			12	37.50%
2&7 Accuracy Difference	2	-3	150.00%			-6	300.00%			-3	150.00%		
2&7 Total Speed/Accuracy Difference		0	0.00%			-11	1100.00%			-7	700.00%		
TBI-QoL Exec (S)	20	-5	-25.00%	-4.7	-18.15%	3	15.00%	2.2	8.49%	0	0.00%	0	0.00%
TBI-QoL Atten (S)	6	3	50.00%	6.4	34.41%	8	133.33%	12.4	66.67%	4	66.67%	7.8	41.94%
Processing Speed													
TMT-A	85.9	-26.67	31.05%	13	72.2%	-44.89	53.36%	22	122.22%	-40.02	46.59%	18	100.00%
2&7 Auto Detection Speed	71	9	12.68	3	10%	7	9.86%	3	10.00%	15	21.13%	6	20.00%
2&7 Controlled Search Speed	71	10	14.08%	4	13.79%	2	2.82%	1	3.45	12	16.90%	5	17.24%
2&7 Total Speed Sum of T Scores	59	7	11.86%			4	6.78%			11	18.64%		
2&7 Total Speed	31			3	9.68%			2	6.45%			5	16.13%
2&7 Speed Difference	1	-1	100.00%			2	-200.00%			1	-100.00%		
Fatigue													
TBI-QoL Fatig (S)	40	7	-17.50%	7.2	-10.83%	-3	7.50%	-2.4	3.61%	2	-5.00%	1.7	-2.56%
Psych health													
PHQ-9 (S)	15	3	-20.00%			-5	33.33%			5	-33.33%		
Global Function													
GOSE (S)	5	0	0.00%			0	0.00%			0	0.00%		
RPQ	43	4	-9.30%			9	-20.93%			1	-2.33%		

Key for direction of change

TMT: higher=worse

Ruff Speed: higher=better

Ruff Error: higher=worse

Supplementary Table 3. Behavioral testing summary, P3.

P4: Change in raw and T-scores from pre-surgery baseline to post-surgery baseline, treatment start and treatment end

Measure by Domain	Pre-Surg Metrics	Pre-Surg to Post-Surg Baseline Score Change				Pre-Surg to Treatment Start Score Change				Pre-Surg to Treatment End Score Change			
		Raw Score		T Score		Raw Score		T Score		Raw Score		T Score	
		Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent
Attentional control													
TMT-B	39	-0.98	2.51%	4	6.78%	1.17	-3.00%	0	0.00%	-10.03	25.70%	9	15.25%
TMT-B minus TMT-A	16.9	1.13	-6.69%			4.95	-29.29%			-4.40	26.04%		
2&7 Auto Detection Accuracy	97.48	1.40	1.43%	3	5.88%	1.86	1.91%	4	7.84%	-1.08	-1.10%	-3	-5.88%
2&7 Auto Detection Errors	4	-2	50.00%			-3	75.00%			2	-50%		
2&7 Controlled Search Accuracy	97.01	1.10	1.13%	2	3.50%	-1.94	-2.00%	-4	-7.10%	1.06	1.10%	2	3.50%
2&7 Controlled Search Errors	4	-1	25.00%			3	-75.00%			-1	25.00%		
2&7 Total Accuracy Sum of T 2&7 Scores	107	5	4.67%			0	0.00%			-1	-0.01%		
2&7 Total Accuracy	53			3	5.66%			0	0.00%			0	0.00%
2&7 Accuracy Difference	-5	1	20.00%			8	-160.00%			-5	100.00%		
2&7 Total Speed/Accuracy Difference		8	-160.00%			1	-20.00%			7	-140.00%		
TBI-QoL Exec (S)	25	5	20.00%	3.3	11.19%	10	40.00%	6.6	22.37%	7	28.00%	4.6	15.59%
TBI-QoL Atten (S)	14	2	14.29%	2.2	7.10%	10	71.43%	11.1	35.81%	7	50.00%	7.7	24.84%
Processing Speed													
TMT-A	22.1	-2.11	9.53%	4	8.51%	-3.78	17.08%	8	17.02%	-5.63	25.44%	17	36.17%
2&7 Auto Detection Speed	155	22	14.19%	8	16.67%	-4	-2.58%	-1	-2.08%	6	3.87%	3	6.25%
2&7 Controlled Search Speed	130	26	20.00%	12	26.67%	5	3.85%	3	6.67%	23	17.69%	11	24.44%
2&7 Total Speed Sum of T Scores	91	20	21.51%			2	2.15%			14	15.05%		
2&7 Total Speed	47			11	22.92%			1	2.08%			7	14.58%
2&7 Speed Difference	3	-4	133.33%			-4	133.33%			-8.00	266.67%		
Fatigue													
TBI-QoL Fatig (S)	34	-2	5.88%	-1.5	2.43%	-2	5.88%	-1.5	2.43%	1	-2.94%	0.80	-1.29%
Psych health													
PHQ-9 (S)	13	-3	23.08%			-8	61.54%			-4	30.77%		
Global Function													
GOSE (S)	5	1	20.00%			1	20.00%			1	20.00%		
RPQ (S)	37	1	-2.70%			-35	94.59%			-5	13.51%		

Key for direction of change

TMT: higher=worse

Ruff Speed: higher=better

Ruff Error: higher=worse

Supplementary Table 4. Behavioral testing summary, P4.

P5: Change in raw and T-scores from pre-surgery baseline to post-surgery baseline, treatment start and treatment end

Measure by Domain	Pre-Surg Metrics	Pre-Surg to Post-Surg Baseline Score Change				Pre-Surg to Treatment Start Score Change				Pre-Surg to Treatment End Score Change			
		Raw Score		T Score		Raw Score		T Score		Raw Score		T Score	
		Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent
Attentional control													
TMT-B	42.6	4.48	-10.51%	-5.00	-8.47%	-10.64	24.95%	9.00	15.25%	-10.23	23.99%	9	15.25%
TMT-B minus TMT-A	23.9	3.75	-15.69%			-8.10	33.89%			-6.18	25.86%		
2&7 Auto Detection Accuracy	98.20	-1.50	-1.53%	-4.00	-7.55%	1.23	1.25%	3.00	5.66%	1.80	1.83%	4.00	7.55%
2&7 Auto Detection Errors	3	3.00	-100.00%			-2.00	66.67%			-3	100.00%		
2&7 Controlled Search Accuracy	95.98	1.05	1.09%	2.00	3.70%	0.97	1.02%	2.00	3.70%	1.31	1.36%	3.00	5.56%
2&7 Controlled Search Errors	7	-2.000	28.57%			-2.00	28.57%			-2	28.57%		
2&7 Total Accuracy Sum of T 2&7 Scores	107	-2.00	-1.87%			5.00	4.67%			7.00	6.54%		
2&7 Total Accuracy	53			-1.00	-1.89%			3.00	5.66%			4.00	7.55%
2&7 Accuracy Difference	-1	-6.00	600.00%			1.00	-100.00%			1.00	-100.00%		
2&7 Total Speed/Accuracy Difference		2	-22.22%			-3.00	33.33%			6.00	-66.67%		
TBI-QoL Exec (S)	28	-9.00	-32.14%	-6.40	-20.32%	-2.00	-7.14%	-1.40	-4.44	15	53.57%	10.40	33.02%
TBI-QoL Atten (S)	10	-4.00	-40.00%	-7.80	-29.55%	0	0.00%	0	0.00%	13	92.86%	14.50	54.92%
Processing Speed													
TMT-A	18.7	0.73	-3.90%	0.00	0.00%	-2.54	13.55%	9.00	16.36%	-4.05	21.61%	14	25.45%
2&7 Auto Detection Speed	164	12.00	7.32%	4.00	7.27%	10.00	6.10%	3.00	5.45%	38	23.17%	13.00	23.64%
2&7 Controlled Search Speed	167	-4.00	-2.40%	-2.00	-3.08%	-8.00	-4.79%	-4.00	-6.15%	12	7.19%	5.00	7.69%
2&7 Total Speed Sum of T Scores	123	2.00	1.67%			-1.00	-0.83%			18.00	15.00%		
2&7 Total Speed	64			1.00	1.61%			0	0.00%			10.00	16.13%
2&7 Speed Difference	-11	6	-60.00%			7	-70.00%			8	-80.00%		
Fatigue													
TBI-QoL Fatig (S)	23	18.00	-78.26%	14.10	-26.45%	1.00	-4.35%	0.90	-1.69%	9	-39.13%	7.00	-13.13%
Psych health													
PHQ-9 (S)	12	-1.00	8.33%			-3.00	25.00%			-5	41.67%		
Global Function													
GOSE (S)	6	0	0.00%			0	0.00%			0	0.00%		
RPQ (S)	33	-7	21.21%			-2	6.06%			-27	81.82%		

Key for direction of change

TMT: higher=worse

Ruff Speed: higher=better

Ruff Error: higher=worse

Supplementary Table 5. Behavioral testing summary, P5.

P6: Change in raw and T-scores from pre-surgery baseline to post-surgery baseline, treatment start and treatment end

Measure by Domain	Pre-Surg Metrics	Pre-Surg to Post-Surg Baseline Score Change				Pre-Surg to Treatment Start Score Change				Pre-Surg to Treatment End Score Change			
		Raw Score		T Score		Raw Score		T Score		Raw Score		T Score	
		Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent	Difference	Percent
Attentional control													
TMT-B	166.61	-42.18	25.32%	4	21.05%	-105.61	63.39%	27	142.11%	-70.42	42.27%	13	68.42%
TMT-B minus TMT-A	105.45	-32.09	30.43%			-94.47	89.59%			-53.98	51.19%		
2&7 Auto Detection Accuracy	84.88	10.65	12.55%	25	119.05%	9.40	11.08%	22	104.76%	13.30	15.67%	32	152.38%
2&7 Auto Detection Errors	13	-8	61.54%			-7	53.85%			-11	84.62%		
2&7 Controlled Search Accuracy	80.49	9.78	12.15%	20	86.96%	11.67	14.50%	23	100.00%	3.27	4.07%	7	30.43%
2&7 Controlled Search Errors	16	-5	31.25%			-8	50.00%			3	-18.75%		
2&7 Total Accuracy Sum of T 2&7 Scores	44	45	102.27%			45	102.27%			39.00	88.64%		
2&7 Total Accuracy	22			22	100.00%			22	100.00%			19	86.36%
2&7 Accuracy Difference	-2	5	-250.00%			-1	50.00%			25	-1250.00%		
2&7 Total Speed/Accuracy Difference		-8	--			-11	--			-6	--		
TBI-QoL Exec (S)	24	10	41.67%	6.6	22.92%	12	50.00%	8	27.78%	15	62.50%	10	34.72%
TBI-QoL Atten (S)	14	14	100.00%	17.1	55.16%	10	71.43%	11.1	35.81%	13	92.86%	15.1	48.71%
Processing Speed													
TMT-A	61.16	-10.09	16.50%	4	20.00%	-11.14	18.21%	4	20.00%	-16.44	26.88%	9	45.00%
2&7 Auto Detection Speed	73	34	46.58%	12	54.55%	26	35.62%	9	40.91%	35	47.95%	12	54.55%
2&7 Controlled Search Speed	66	36	54.55%	15	75.00%	28	42.42%	12	60.00%	32	48.48%	14	70.00%
2&7 Total Speed Sum of T Scores	42	27	64.29%			21	50.00%			26	61.90%		
2&7 Total Speed	22			14	63.64%			11	50.00%			13	59.09%
2&7 Speed Difference	2	-3	150.00%			-3	150.00%			-2	100.00%		
Fatigue													
TBI-QoL Fatig (S)	20	-3	15.00%	-3	5.92%	-1	5.00%	-1	1.97%	-4	20.00%	-4.2	8.28%
Psych health													
PHQ-9 (S)	7	-5	71.43%			-6	85.71%			-6	85.71%		
Global Function													
GOSE (S)	6	0	0.00%			0	0.00%			0	0.00%		
RPQ (S)	21	-8	38.10%			-11	52.38%			-13	61.90%		

Key for direction of change

TMT: higher=worse

Ruff Speed: higher=better

Ruff Error: higher=worse

Supplementary Table 6. Behavioral testing summary, P6.

Supplementary Table 7

Behavioral Results Blinded Withdrawal Testing in 3 Participants ON/OFF

Measure by Domain	Peformance Based (P) or Self Report (S)	Treatment End	Rnd DBl End Withdrawal	Raw Score Difference	Raw Score %
P3					
Trails A	P	45.87	54.24	8.37	18.25
Trails B	P	82.89	111.18	28.29	34.13
Auto Detection Accuracy	P	94.51	96.67	2.16	2.29
Controlled Search Accuracy	P	91.21	92.22	1.01	1.11
Total Accuracy	P	44	48		
Auto Detection Speed	P	86	87	1	1.16
Controlled Search Speed	P	83	83	0	0
Total Speed	P	36	39		
P4					
Trails A	P	16.5	17.28	0.78	4.73
Trails B	P	29	32.08	3.08	10.62
Auto Detection Accuracy	P	96.41	98.22	1.81	1.88
Controlled Search Accuracy	P	98.08	94.56	-3.52	-3.59
Total Accuracy	P	55	54		
Auto Detection Speed	P	161	166	5	3.11
Controlled Search Speed	P	153	139	-14	-9.15
Total Speed	P	55	53		
P6					
Trails A	P	44.72	50.35	5.63	12.59
Trails B	P	96.19	82.86	-13.33	-13.86
Auto Detection Accuracy	P	98.18	95.58	-2.6	-2.65
Controlled Search Accuracy	P	83.76	92.73	8.97	10.71
Total Accuracy	P	41	47		
Auto Detection Speed	P	108	108	0	0.00
Controlled Search Speed	P	98	102	4	4.08
Total Speed	P	37	34		

Supplementary Table 7. Behavioral testing results of blinded withdrawal in three participants.

Supplementary Table 8.

Functional changes reported in post-trial narrative interviews of study participants and family members linked to executive function:

Participants	*Families*
P1: "I just –I want to think. I'm bored. Like reading books and stuff –why? I would have thought that was boring, but I am using my mind, and its interesting. I don't know why, it just makes me laugh, but its amazing to me that I enjoy doing these things. Like, I'm a nerd... You guys made me a nerd."	**P1 Family**: "I got my daughter back. I got my daughter back. It's a miracle. It's so profound for us. It's a profound change. Now here comes the tears. If somebody told me in August we would be sitting here having this kind of conversation in January. I never would've believed it. It's beyond my hopes, beyond anticipation. Somebody turned the lights back on."
P3: "…I'm able to watch a TV show, where before I couldn't. I couldn't keep my attention span that long. So, I think in some ways it's gotten better."	**P3 Family**: "He's listening better, he's thinking better... He's making better decisions"
P4: "I've been able to track four regularly and five (activities) … I'm able to kind of switch my attention between things quicker without getting a headache from it and ... keep track of both at the same time, to talk about one topic with one person, switching briefly to, like, say something, like, 'Oh, yeah - no, I wanted to put the groceries over there,' and then [go] back to the first conversation and ... follow where it was and keep track of where we were. That was not possible before the stimulator."	**P4 Family**: "I think the fact that he's able to play League of Legends means the concentration and focus are better. That was just way too overstimulating for him before and I think - I don't know why I associate that with focus and concentration."
P5: "... when the device was first activated I noticed immediate improvements in memory, processing speed, planning, organization. I mean these are pretty basic, functions, mental functions, right? ... Then I started to feel these other effects, which I think was the major functions of planning, organization, attention, focus, memory, that stuff kind of intertwining."	**P5 Family:** "So, he does stay focused on something when he wants to. Now, he also is reading more ... He's got - - stacks and stacks of books that he's reading, these he's read; these he's reading now; and these he wants to get to ... he's been doing that and commenting on how much he can read as opposed to before."

Supplementary Table 8.

P6: “Definitely more organized since the surgery ... everything that’s related to that one, that one homework assignment, that I’m set up to do at my desk, and I essentially complete it, and then, put it away, and (am) onto the next thing. And then I do the same thing with that homework assignment."	**P6 Family:** Subject's parent would ask, "... can you go to the store and get some of this? And he would go to the store and get some of that ... I don't know what that takes (but) it takes follow through, it takes remembering, it also takes where he wouldn't be afraid to do something without asking 100 questions."

Supplementary Table 8. Functional changes reported in post-trial narrative interviews of study participants and family members linked to executive function.

Supplementary Table 9: Adverse Events

Subject	Description	Action taken	Severity	SAE	Resolved	Related to study device
P1	Fatigue	None	Mild	No	Yes	Possibly
P1	Incision scabs fell off with bleeding	Clindamycin to cover early stage/prevention of infection. Monitor wound.	Mild	No	Yes	Definitely
P1	Accidental stimulator deactivation	Reactivation of stimulator	Moderate	No	Yes	Probably
P2	Infection of DBS device	Explant device; treatment with IV antibiotics for 6 weeks post-explant	Severe	Yes	Yes	Definitely
P3	Syncope while standing to urinate	None	Mild	Yes	Yes	Possibly
P3	Headache	Medication	Mild	No	Yes	Possibly
P3	Gait disturbance	None	Mild	No	Yes	Possibly
P5	Back pain	None	Moderate	No	Yes	Not related
P5	Headache	None	Moderate	No	Yes	Not related
P5	Neck pain	None	Moderate	No	Yes	Not related
P5	Lower extremity pain	None	Moderate	No	Yes	Not related
P5	Tinnitus	None	Moderate	No	Yes	Not related
P5	Difficulty with planning, organization and word recall	None	Moderate	No	Yes	Possibly
P5	COVID-like symptoms – headache, fatigue, body aches, chills, diarrhea, poor cognition	None	Mild	No		Not related

1973 **Supplementary Table 9. Adverse Events.**

1974

Supplementary Table 10. Study Events Table

Cohort (n = 6) (2 Subjects per staggered baseline group; random assignment to cohort and treatment withdrawal)	Pre-Screen †	Consent/ Exclude	Screen and Pre-Surgery Baseline (30 Days)	Surgery (Establish baseline field potentials) (4 Days)	Randomize to Multiple Baseline Condition (1 Day)	Post-surgical washout and baseline re-assessment (30, 44, or 58 Days)	DBS Titration/ Optimization (14 Days)	Unblinded Treatment Phase (90 Days)		Randomized Blinded Treatment Withdrawal Phase (21 Days)
1 (n = 2)		Day 0	Days 1-30	Days 31-34	Day 35	Days 36-65	Days 66-79	Days 80-169		Days 170-190
2 (n = 2)		Day 0	Days 1-30	Days 31-34	Day 35	Days 36-79	Days 80-93	Days 94-183		Days 184-204
3 (n = 2)		Day 0	Days 1-30	Days 31-34	Day 35	Days 36-93	Days 94-107	Days 108-197		Days 198-218
Demographics	X									
Medical History	X									
History of Injury	X									
Consent Meeting		X								
Physical Examination			X				X			X
Neurological Examination			X				X			X
Ruff 2 & 7			X			X		X	X	X
Trails B			X			X		X	X	X
Rivermead			X			X			X	X
PHQ-9			X			X			X	X
Neuro-QOL			X			X			X	X
GOSE			X			X			X	X
Patient Interview			X			X		X	X	X

Supplementary Table 10. Study Events Table.

Supplementary Table 11

Patient	Study Protocol Day	Evoked Potential Stimulation Parameters	Therapeutic Contacts
P1	Day 81	4.5V, 185Hz, 90μs pulse width, 100ms ON / 2s OFF	L3/L4; R3/R4
P3	Day 166	4.5V, 185Hz, 90μs pulse width, 100ms ON / 2s OFF	L3/L4; R3/R4
P4	Day 112	3.5V, 150Hz, 60μs pulse width, 100ms ON / 2s OFF	L3/L4; R2/R3
P5	Day 68	2.0V, 185Hz, 90μs pulse width, 100ms ON / 2s OFF	L3/L4; R3/R4
P6	Day 68	3mA, 185Hz, 90μs pulse width, 100ms ON / 2s OFF	L3/L4; R3/R4

Supplementary Table 11. Evoked Potential Testing Summary.

Supplementary Table 12

Participant	LEFT Contacts (+ or -)	LEFT Amplitude (per contact)	LEFT Frequency	LEFT Pulse Width
P1	L3 (+), L4 (+)	3.4V	160Hz	90us
P3	L3 (+), L4 (+)	4.0V	185Hz	60us
P4	L2 (-), L3 (+), L4 (+)	3.5V	150Hz	60us
P5	L3 (+), L4 (+)	3.1, 3.2V	150Hz	60us
P6	L3 (+), L4 (+)	3mA	150Hz	90us
Participant	**RIGHT Contacts (+ or -)**	**RIGHT Amplitude (per contact)**	**RIGHT Frequency**	**RIGHT Pulse Width**
P1	R3 (+), R4 (+)	3.3V	160Hz	60us
P3	R3 (+), R4 (+)	4.0V	185Hz	80us
P4	R2 (-), R3 (+)	3.5V	150Hz	60us
P5	R3 (+), R4 (+)	3.1, 3.2V	150Hz	60us
P6	R2 (-), R3 (+), R4 (+)	3mA	150Hz	90us

Supplementary Table 12. Stimulation settings in treatment phase.

Supplementary Table 13: Evoked potential artifact removal

Participant	Bipolar Evoked Potential Pair	Number of EEG Channels Removed and Interpolated (Total 256 Channels)	Number of Independent Components Rejected (Total 256 Components)
P1	E2-, E3+	4	39
	E2+, E3-	3	37
	E10-, E11+	7	57
	E10+, E11-	4	58
P3	E2-, E3+	53	58
	E2+, E3-	65	50
	E10-, E11+	29	43
	E10+, E11-	43	46
P4	E2-, E3+	14	46
	E2+, E3-	8	40
	E9-, E10+	17	62
	E9+, E10-	9	20
P5	E2-, E3+	20	13
	E2+, E3-	20	15
	E10-, E11+	18	24
	E10+, E11-	28	19
P6	E2-, E3+	12	27
	E2+, E3-	13	24
	E10-, E11+	8	76
	E10+, E11-	4	20

Supplementary Table 13. Evoked potential artifact removal.

Supplementary Video 1. Rocking images of pre-operative left and right hemisphere electrode placements in common template space.

Color code: P1 (yellow), P3 (orange), P4 (green), P5 (blue), P6 (magenta). Movie illustrates clustering of left and right pre-operative electrodes as projected into the common template (synthetic atlas) space (see Methods). Left hemisphere electrodes show a tighter clustering of the contacts for each contact position as compared with the right hemisphere electrode placements.

Supplementary Video 2. Rocking images of post-operative left and right hemisphere electrode placements in common template space.

Color code: P1 (yellow), P3 (orange), P4 (green), P5 (blue), P6 (magenta). Movie illustrates actual post-operative electrode placements after projection into the common template (synthetic atlas) space (see Methods). Left hemisphere electrodes show a tighter clustering of the post-surgical positioning as compared with the right hemisphere electrode placements. Right-sided electrodes demonstrate wider spatial variation at lower contact positions compared with contacts closer to top of thalamus/ventricle.

Supplementary Video 3. Rocking images of pre-operative and post-operative left and right hemisphere electrode placements in common template space.

Color code: P1 (yellow), P3 (orange), P4 (green), P5 (blue), P6 (magenta). Movie illustrates locations of electrodes in common template (synthetic atlas) space, first the pre-operative (planned) followed by the post-operative (actual) placements. Top and bottom active contacts are then identified and rendered as small spheres. Top and bottom active contact centroids are calculated and rendered as larger red spheres whose diameters reflect the spatial spread (standard deviation) across the five participants.

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