Effective Deepening of Meditative-States with Focused Ultrasound Stimulation and its Moderation by Prior-Experience

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Dear Editor,

Herein contains first-in-man results with broad appeal due to the strong public and scientific interest in both meditation and Focused Ultrasound Stimulation (FUS). We argue that these findings, supported by rigorous methodology, warrant rapid publication in this format. This report, while easily standing alone, presents a subset of a wider, more multimodal, dataset[1]—completion of which awaits additional funding but remains intended for near-term publication.

Empirical studies are increasingly demonstrating the benefits of meditation—both psychological and physical—for health and well-being[2]. Concurrently, cognitive neuroscience is providing an ever clearer, albeit incomplete, understanding of the functional architecture underlying the altered state(s) induced by meditation[3]. These developments **1)** *Compel* superior methods for assisting the attainment of *meditative states* (i.e., "meditative aids"), and **2)** *Enable* methods that promote the *brain states* underlying them. Aspiring practitioners experience considerable difficulty maintaining the consistent, years-long practice (i.e., "meditative development")[4] required to fully realize meditation's benefits, even while using extant aids (e.g., mobile applications, neurofeedback[5])—a greater struggle yet, ironically, for those possessing the disabilities (in e.g., motivation, concentration) meditation may most remedy. Accordingly, we present here supporting evidence for a first-in-kind FUS-based meditative aid. Among methods for non-invasive neuromodulation, FUS *alone* can target *any* chosen brain region[6] with unrivaled spatial precision. Critically, prominent neural correlates of meditation (NCM) disproportionately reside below superficial cortex, precluding non-invasive direct targeting by *any* other method[7] (e.g., TMS). Thus, FUS offers an unprecedented translation of predominantly *correlational data* supporting NCMs into the *causal induction* of (deep) meditation—simultaneously interrogating NCM validity while possibly uncovering a superior means of reducing the barriers to meditation's clear value.

FUS—using parameters with consistent empirical support[1,6,7] for "net-inhibitory" effects—was applied to three NCM-targets (separate days), *during* Vipassana meditation in subjects comprising: **1) expert** (**E_{med}**; n=12; practice>20min,>5days/week,>5*years*) and **2) novice** (**N_{med}**; n=12; spiritual/contemplative-practice<2hrs *prior-to training*) cohorts. The specific NCMs targeted were selected for their robust, yet distinct, supporting evidence: **1)** ***posterior cingulate cortex (PCC)***-selection was justified by this structure's consistent activity-reduction during (deep) meditation—*notably, an experience-dependent-effect*, with experienced practitioners achieving greater PCC-inhibition[3,8]. Purportedly, this reflects PCC-mediation of self-referential-thinking—itself, thought (therapeutically) reduced by meditation. **2)** ***Caudate nucleus (CN; head; bilateral)***-selection, despite neuroimaging correlates[3] as well, was relatively-more theory-driven; CN-damage (esp. bilateral) can induce a condition (sometimes, "Athymhormia") with symptoms (e.g., passivity/apathy/equanimity, heightened pain-tolerance, reduced/fully-absent inner-monologue) previously-likened to an exaggerated or "pathological" meditative-state (Shinzen Young). Thus, we hypothesized CN-FUS to produce similar effects—though temporary/attenuated—that deepen meditation by promoting the "non-judgmental awareness" that these effects closely-resemble and which Vipassana training instills. Finally, **3)** ***Ventral anterior insula (I_{av}; bilateral)*** is another consistent NCM[3]—though one apparently driven by Vipassana practitioners[3]—perhaps reflecting I_{av}-mediation of awareness of bodily sensation—a core tenet of Vipassana (e.g., via "body-scans").

N_{med} underwent pre-training (four sessions, total-meditation: 3-hours) with all subjects experiencing: ***Session 1)*** MRI-data collection and ***Sessions 2-5)*** near-identical meditation/FUS sessions—FUS-condition cycling through PCC, CN, I_{av}, and Sham-FUS (within-subject, no repeats, target counterbalanced). Each included meditation (uninterrupted; 1-hour) with FUS/Sham (12-minutes-long; bilateral targets 6-minutes/hemisphere sequentially, left/right-order-counterbalanced) beginning at ~minute-12 (Figure 1a). Every ~4min±30s throughout, subjects reported **1)** meditative "depth" and **2)** subjective "intensity" (degree of phenomenology altered—along any dimension—from normal, waking-consciousness) via 1:5 (5=high) button-presses. Just-prior FUS-onset, FUS-trajectories were captured in Brainsight© neuronavigation-software (error<3_{mm}) for use in (144-total) post-hoc simulations of FUS-propagation through subject-specific skull-models. FUS's utility and safety has arguably been most-limited by skull-introduced focal variability (location, pressure). Among the earliest adopters of the technique, we estimate voxel-wise FUS-pressure, study-wide—with the unprecedented validity provided by neural-network skull-segmentation[9] and precise, real-world trajectories (Figure 1b). Critically, no significant difference in skull-induced attenuation or refraction was found between cohorts for any condition with highly similar focal-patterns observed for each (overlaid in Figure 1b-right). When combining cohorts, we estimate a mean-refraction/attenuation of 5.5mm/72.5%(I_{sppa}) for the PCC condition, 6.7mm/77.0% for CN, and 4.0mm/87.8% for I_{av}—values in-line with expectations, prior findings[7], and our more-traditional, pre-experiment simulations (supplement) that justified these target-regions. In contrast, skull-refractory effects *were* target-region-specific—e.g., greater refraction in CN(right) vs. PCC, p <0.001; these were fully-expected, but do emphasize **1)** the importance of the Sham-normalization performed here and **2)** the value of per-session simulations in revealing and/or controlling for the confounds introduced by skull.

Critically, Sham-detection-rate probed post-session was unaffected by condition, overall (E_{med}, p=0.318; N_{med}, p=0.681), or pairwise-comparisons (e.g., Sham-PCC; uncorrected). Within each four-minute-period (15-total, 12 plotted—those following FUS-onset), we assessed effects (depth/intensity) of FUS-condition within-cohorts before assessing experience-driven (i.e., between-group) effects. Figure 1c shows all results, plotting values normalized by Sham-FUS (stats performed pre-normalization). Marginal p-values remain shown and p-values, uncorrected-throughout—given the 36-subject-cohort needed[1] to offset multiple-comparisons alongside this short-report's more exploratory nature. However, several effects already surpass the rigorous thresholding/correction intended[1] for this wider cohort (e.g., several timepoints demonstrating increased depth following CN-FUS [E_{med}, E_{med}–N_{med}]).

Broadly, E_{med} results **1a)** firmly support FUS's potential for increasing meditative depth, *especially through CN-modulation*. E_{med} results further suggest both **1b)** CN-FUS *and* PCC-FUS induced felt-sensations above expectation-effects (Sham-FUS), joining the few prior-examples[10] of FUS-induced phenomenological-changes. In contrast, N_{med} (supplement) demonstrated **2a)** no altered depth of significance despite, interestingly, **2b)** reporting less-novel-phenomenology ("intensity") *generally* (active-FUS-conditions vs. Sham-FUS). Speculatively, the latter may reflect minimal-experience with altered-states and the corresponding induction of distraction, confusion, and/or reducing response-confidence—though this awaits planned parsing of phenomenological-dimensions. A more-expected finding, I_{av}-FUS, contrasting other active-FUS conditions, failed to alter phenomenology in E_{med} while particularly-decreasing "intensity" in N_{med}; indeed, we hypothesized a-priori that I_{av}-FUS may blunt interoception—decreasing the detection/report of (even spontaneous) fluctuations in phenomenology. Relatedly, we expected I_{av}-FUS-disruption of body-scan techniques and, consequently, reduced-depth; however, a few periods of *increased* depth were observed. **3)** Consistent with FUS *causing* the effects we've identified, they universally-appear only after FUS-onset (no baseline-normalization, figures with-baseline in supplement). Fascinatingly, nearly-all significant effects study-wide appear *after* FUS-*offset*, especially between 5-to-25-minutes post-FUS-offset. For example, effects on depth in E_{med} even form a generally parabolic pattern that peaks ~15-minutes post-FUS-offset, descending-thereafter. While "offline"-effects persisting after-FUS are commonplace[6,7]—these uniquely-frequent repeated-measures over 36-min post-FUS particularly-informs ongoing debate surrounding their time course. Furthermore, it's notable that many spurious effects—from e.g., expectation, auditory/tactile-confounds—are more likely *during*-FUS, since subjects readily-detect FUS-onset/offset.

Collectively, these data generally support FUS's potential as an emergent meditative aid while preliminarily suggesting its "therapeutic window" may not open until, at least, after the very start of contemplative practice. However, this should not discourage future study in novice-subjects. Novices in this study possess <6-hours of lifelong meditation-experience (or practicing *any* mind-body practice) and may not represent *still-novice* practitioners with considerably more—or somehow, higher-quality—prior-experience. Another potential caveat: relative to E_{med}, N_{med}'s likely inability to rapidly categorize micro-phenomenology, a crucial skill in this situation, may allow for any benefit provided N_{med} to go undetected here—again, something our future analyses may address (e.g., of phenomenological-probes/self-report post-meditation). All-considering, the first formal publication of this technique makes for an exciting overture for our imminent future work—one that also hopefully inspires that of others.

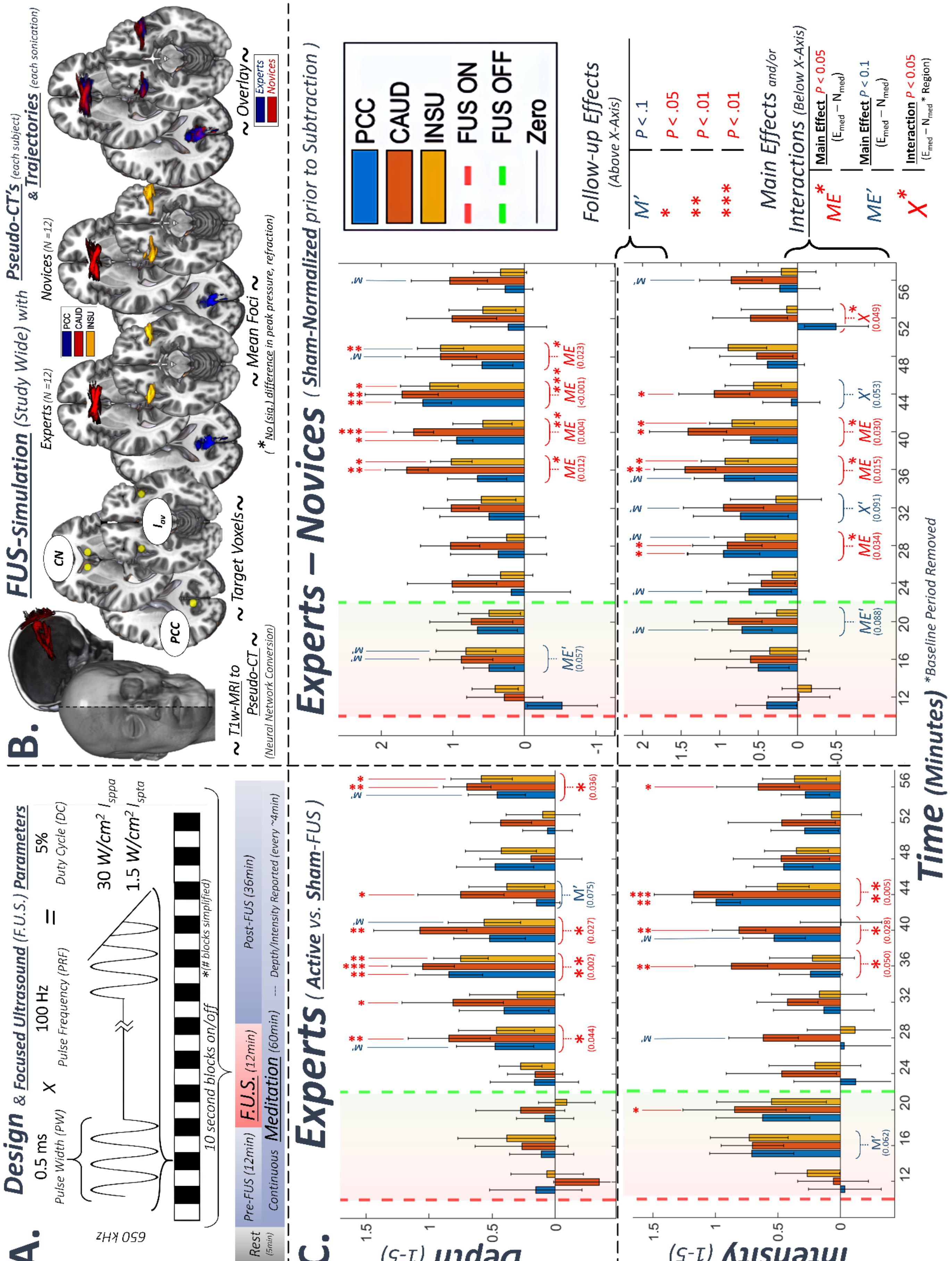
A.
Design & Focused Ultrasound (F.U.S.) Parameters
0.5 ms
Pulse Width (PW)
X
100 Hz
Pulse Frequency (PRF)
=
5%
Duty Cycle (DC)
650 kHz
30 W/cm² Isppa
1.5 W/cm² Ispta
10 second blocks on/off
*(# blocks simplified)
Rest (5min)
Pre-FUS (12min)
F.U.S. (12min)
Post-FUS (36min)
Continuous Meditation (60min) --- Depth/Intensity Reported (every ~4min)
B.
FUS-Simulation (Study Wide) with Pseudo-CT's (each subject) & Trajectories (each sonication)
~ T1w-MRI to Pseudo-CT ~
(Neural Network Conversion)
PCC
CN
Iov
~ Target Voxels ~
Experts (N =12)
Novices (N =12)
PCC
CAUD
INSU
~ Mean Foci ~
(*No (sig.) difference in peak pressure, refraction)
~ Overlay ~
Experts
Novices
C.
Experts (Active vs. Sham-FUS)
Experts – Novices (Sham-Normalized prior to Subtraction)
Depth (1-5)
Intensity (1-5)
Time (Minutes)
*Baseline Period Removed
PCC
CAUD
INSU
FUS ON
FUS OFF
Zero
Follow-up Effects (Above X-Axis)
M′ P < .1
* P < .05
** P < .01
*** P < .01
Main Effects and/or Interactions (Below X-Axis)
ME* Main Effect P < 0.05 (Emed – Nmed)
ME′ Main Effect P < 0.1 (Emed – Nmed)
X* Interaction P < 0.05 (Emed – Nmed * Region)

Figure 1. A) Design and FUS parameters. White/black blocks represent 10-second on/off periods throughout 12-minutes of FUS (number not accurate). Though also mentioned in-text, note that PCC receives 12-minutes to one location while bilateral regions (CN, I_{av}) receive 6-min to each hemisphere sequentially. **B) Study-wide acoustic modeling of FUS propagation.** ***Left:*** example of the neural-network skull-segmentation used, which converts T1-weighted images into pseudo computerized-tomography images that can be more easily/accurately used in these simulations(note that the simulation shown in the top-left is just for demonstration/is set at an arbitrary-threshold). ***Right:*** Depiction of spatial variation in target-specific-precision for each cohort, and study-wide, within standard (MNI)-space (non-linear co-registration with 1mm^3 template performed and visually validated). These are generated from real-world trajectories captured during data collection (relative to subject heads/skulls). In these, a threshold is applied at: maximum in-brain pressure -3dB (~50%) such that all values above 50%-less-than the peak-pressure in-brain are included—a common method[7]. Among regions, maximal-variability in focal location occurred while targeting CN, perhaps a result of the highly variable skull shape and/or density in the temporo-frontal-junction nearby the entry-point for our FUS-targeting of CN. Despite the small size of this region, significant pressure does not appear to have been deposited in unintended gray-matter-tissue—given our trajectory and the elongated-nature of single-element FUS-foci for deep targets, with most pressure outside the CN landing in white-matter. Importantly, the peak mean pressure remains on our caudate target while no foci for any subject appear to deviate fully-outside our target, and no severe, consistent, bias towards an unintended-portion of CN is suggested(or in any target), in line with expected/desired-precision. **C) Online depth and intensity**. ***Left:*** Within-group (E_{med}) values normalized to Sham (non-zero values indicate possible effect of active-FUS, positive values indicate higher-depth). ***Right:*** Between-group values of E_{med}-cohort – (*order-matched)* N_{med}-cohort (sham-normalized pre-subtraction). The 1-hour meditation-period is shown discretized into 4-minute sections alongside the results of appropriate statistical tests for effects within each section (*note that the pre-FUS section is removed* to save space and can be seen in the supplement). For within-group effects of target, below-x-axis *p*-values indicate main effects of target identified by a 1-way repeated-measures ANOVA; red text indicates significance (p<0.05) while blue indicates marginal findings (0.05<p<0.10). For between-group effects of experience, below-x-axis *p*-values below "ME" indicate a significant or marginal (marginal marked with a "prime" symbol) main effect of group (2-way mixed-model ANOVA), and values below "X" indicate a significant or marginal interaction between target region and experience-level—color coded as with within-group results. For all follow-up tests within a given region, a blue "M(prime)" indicates 0.05<p<0.10, while a red *=p<0.05, **=p<0.01, ***=p<0.001. All *p*-values are uncorrected for these early results so please note the relative-significance of the various findings.

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Author contributions

JC and NR conceived of the study design. JC led NS, and JM in conducting data collection. JC conducted data analysis. JC and NR wrote the first draft of the manuscript with other authors contributing to minimal writing/editing thereafter. All novel code used in analysis, including that required for K-wave-based computational simulations, were designed and written by JC.

Competing interests

Alexander Bystritsky is the Chairman and Founder of Brainsonix, who manufactures the transducers used in this study. Other authors declare no competing interests.

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