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RESEARCH ARTICLE

Ultrasound neuromodulation as a novel dementia therapy—Investigation of possible long-term confounds

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Abstract

INTRODUCTION: Ultrasound neuromodulation has emerged as a promising adjunctive therapy in Alzheimer's disease (AD), yet a controversial issue remains: whether its reported long-term therapeutic effects could be attributed to potential confounds rather than genuine neuromodulatory mechanisms. Although auditory confounds via air- or bone-conducted sound have been discussed for immediate effects, their relevance for enduring therapeutic outcomes—essential for clinical application—remains unknown. This exploratory study is the first to examine whether long-term cognitive and neural effects of transcranial pulse stimulation (TPS) in AD are linked to persistent auditory network activation.

METHODS: A comprehensive re-analysis of task-based and resting-state functional magnetic resonance imaging (fMRI) data was conducted using data from the currently largest sham-controlled clinical ultrasound neuromodulation study (Matt et al., 2025). To isolate possible auditory contributions, we applied a contrast-based framework targeting (1) air-conducted sound, (2) combined air- and possibly bone-conducted sound, and (3) bone-conduction–specific effects. Analyses included: (a) task-based auditory cortex co-activation, (b) functional connectivity between auditory and dorsal attention networks (the latter was modulated in the original study), (c) global efficiency within the auditory network, and (d) correlations with neuropsychological test battery scores.

RESULTS: No significant long-term activation of auditory cortices was observed in task-based fMRI. Resting-state analyses showed no altered connectivity between auditory and attention networks, no changes in auditory network global efficiency, and no associations between auditory metrics and cognitive performance. Effect-size estimates were small, and 95% confidence intervals placed conservative upper bounds that argue against sizeable, sustained auditory confounds. These findings were consistent across all contrast conditions.

CONCLUSION: Using data from a rigorously controlled cognitive trial, we found no evidence of long-term auditory network effects following TPS. This makes it unlikely that auditory confounds are a key factor underlying the cognitive network effects

observed with long-term ultrasound neuromodulation in typical verum-sham settings as investigated here.

KEYWORDS
Alzheimer's disease, auditory confounds, functional MRI (fMRI), transcranial pulse stimulation (TPS), ultrasound neuromodulation

Highlights

- Long-term transcranial pulse stimulation effects were evaluated for potential auditory confounds using functional magnetic resonance imaging (fMRI).
- Analyses included task-fMRI, resting-state functional connectivity, and auditory network efficiency.
- No auditory long-term effects were detected.
- Auditory confounds are unlikely to be the key factor for cognitive network effects.

1 | INTRODUCTION

Transcranial-focused ultrasound stimulation (tFUS) is increasingly recognized as a promising neuromodulatory technique. With its unique ability to non-invasively reach deep brain regions at high spatial precision, tFUS offers a compelling alternative to electromagnetic approaches, and has shown the potential to modulate neural activity across a variety of preclinical and clinical contexts.[1–3] Particularly in Alzheimer's disease (AD), transcranial pulse stimulation (TPS) has progressed rapidly, starting with the first clinical neuromodulation study in 2019.[4] Subsequent imaging evidence showed cortical-thickness increases paralleling clinical improvement[5] and target-specific network modulation explaining domain-selective effects.[6] Further findings in AD include short-term cognitive gains in a small retrospective study,[7] marked reductions in neuropsychiatric symptoms,[8] electroencephalography (EEG) evidence of acute modulation of oscillatory networks,[9] and a large real-world cohort reporting cognitive improvement.[10] Most recently, a randomized sham-controlled crossover trial in AD[11] demonstrated long-term, age-dependent cognitive improvements supported by functional magnetic resonance imaging (fMRI). Other ultrasound modalities have likewise shown clinical effects in AD, with a pilot study in a mixed AD/Parkinson's disease (PD) cohort reporting that 62.5% improved on at least one cognitive measure without an opposing decline on other scales (a proportion for the pooled cohort, not AD alone).[12] In addition, a randomized AD trial indicated a slowing of cognitive decline.[13] Ultrasound stimulation in AD has been associated with memory gains and higher functional connectivity,[14] along with corpus callosum and orbitofrontal volume gains, where corpus callosum enlargement correlated with cognitive improvement.[15] With typically small sample sizes in a novel therapeutic field, several studies report only partial improvements concerning secondary endpoints. Evidence of brain worsening, however, is rather limited (see Supporting Information). Furthermore, no serious adverse events were reported (see Supporting Information). Overall, the evidence shows promising clinical signals—albeit largely from small, heterogeneous, short-term studies—in a young field increasingly focused on bias control.

In this context, there is a vivid debate about the extent to which auditory confounds—acoustic by-products of the procedure—may contribute to observed effects of ultrasound neuromodulation. Discussed mechanisms include air conduction,[16] bone conduction,[17] or shear wave propagation in the human skull.[18] In practical terms, such by-products could directly drive auditory pathways that project into attention, salience, and motor networks. This sound-driven activity could modulate blood oxygen level–dependent (BOLD)/EEG signals and behavior independently of any spatially targeted ultrasound action, thereby mimicking neuromodulatory effects or masking true treatment-related changes. Clinically, resolving this question ensures that any perceived gains reflect true ultrasound treatment effects.

Overall, the preclinical literature presents a mixed picture. In rodents, silencing the ear largely abolishes ultrasound-induced brain and motor responses, consistent with an auditory confound.[19,20] Yet when the ear is out of play and stimulation waveforms are adjusted appropriately, motor effects remain, indicating that ultrasound can also drive motor circuits independently of the peripheral auditory pathway.[21] In humans, a recent comprehensive study concluded that audible sound was the principal driver of reduced motor-evoked potentials *during* motor-cortex ultrasound, pointing to an auditory confound.[16] There is also evidence that sound ramping or masking may reduce such short-term sound-associated effects.[17,22]

However, whether significant auditory activation exists in long-term ultrasound neuromodulation settings has not yet been tested. If so, audible sound might be a relevant effector for long-term improvements seen in cognitive networks in AD. Several findings argue against this: basic studies show that ultrasound pulses induce neuroplastic changes mainly in the stimulated cells,[23] and a human fMRI study

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature on ultrasound neuromodulation, with emphasis on auditory artifacts in humans and preclinical models, sham/control design, and network specificity. We found no prior study directly testing persistent auditory confounds within ultrasound neuromodulation. To examine such long-term auditory involvement, we drew on findings from our previous randomized controlled trial in Alzheimer's disease (AD), which reported cognitive and neural improvements with transcranial pulse stimulation (TPS) (search via traditional sources, e.g., PubMed; details in the article).
2. **Interpretation**: Applying a contrast framework to task and resting-state functional magnetic resonance imaging (fMRI), region of interest (ROI)-to-ROI connectivity, graph-theoretical metrics, and behavior in a randomized AD cohort, we found no evidence for long-term auditory network involvement. Together with prior network-constrained findings, persistent auditory confounds are unlikely to explain TPS-related changes; acute effects were outside scope.
3. **Future directions**: Future studies could track the transition from online to offline auditory confound effects using longitudinal fMRI with repeated assessments.

found no evidence of auditory cortex involvement during tFUS of deep brain structures.[24] Clinical neuromodulation data likewise suggest functional specificity that is difficult to explain by auditory confounds alone.[1,6]

In light of the ongoing controversy, we present the first study exploring whether the long-term cognitive improvement and the modulation of functional brain activation and connectivity observed in patients with AD after TPS[11] also involve long-term auditory network effects. Even in well-controlled ultrasound studies, both sham and verum typically produce some audible sound, and unequal bone-conduction components (more likely with verum) may be included. In the present study, both verum and sham involved audible clicking sounds, raising the question of whether these acoustic components may have produced a relevant and differential activation of the auditory network.

To investigate this question, we conducted a re-analysis of task-based and resting-state fMRI data from the aforementioned largest sham-controlled clinical ultrasound neuromodulation study to date.[11] The imaging data were acquired on average 6.55 days after the final session of a two-week ultrasound neuromodulation regimen, providing the opportunity to examine whether any measurable traces of auditory co-stimulation persisted beyond the acute phase. To assess auditory system long-term involvement from multiple perspectives, we conducted four analyses:

1. Task-based fMRI to detect cross-modal co-activation of auditory regions during cognitive engagement;
2. resting-state functional connectivity (FC) to examine spontaneous coupling between auditory regions of interest (ROIs) and attention-related networks, with the latter having been shown to be modulated in the original study;
3. resting-state global efficiency (GE, assessed via graph-theoretical metrics) within the auditory network to detect potential increases in information transfer efficiency that may result from sustained auditory co-stimulation; and
4. correlations between auditory network efficiency changes and cognitive performance (as measured by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) corrected total score (CTS)) to assess potential behavioral relevance.

These analyses were selected to probe distinct pathways through which auditory stimulation might exert lasting effects, ranging from task-specific co-activation to intrinsic connectivity, network-level integration, and functional-behavioral links. To disentangle the contributions of different types of auditory stimulation, we employed a contrast-based framework that was uniformly applied across all fMRI modalities to isolate (1) air-conducted sound (sham TPS), (2) combined air- and bone-conducted sound (verum TPS), and (3) bone-conducted sound controlled for air-conducted sound (verum vs sham TPS). This approach was made possible by the original study's rigorous design, featuring a matched sham condition and verified blinding, which enabled a meaningful retrospective examination of the research question.

2 | MATERIALS AND METHODS

2.1 | Participants and original study

2.1.1 | Original randomized controlled trial (RCT; source dataset)

In a published randomized controlled trial (RCT)[11] (ClinicalTrials.gov ID: NCT03770182), 60 patients diagnosed with AD underwent two treatment cycles of either verum or sham TPS, with six stimulation sessions targeting frontoparietal areas (for stimulation details see the original study[11] and its Supporting Information) over 2 weeks in each cycle. Sham treatment used the same ultrasound transducer as verum treatment, with a stand-off device mimicking the appearance, tactile feel, and sound of verum ultrasound without emitting ultrasound pulses. Patient questionnaires confirmed that participants could not distinguish between verum and sham stimulation, supporting the effectiveness of blinding. Participants underwent fMRI scans and neuropsychological assessments in the week before and after each stimulation period, including the widely used CERAD test battery,[25,26] which covers multiple cognitive domains typically affected in AD. Written informed consent was obtained from all participants, and

ethical approval was granted by the Ethics Committee of the Medical University of Vienna.

2.1.2 | Present analysis

From this trial, the current analysis includes data from 54 patients who completed both baseline and post-intervention MRI sessions. For details regarding MRI acquisition see the original study.[11] Here, we used MATLAB with statistical parametric mapping (SPM) for task-fMRI data and the CONN toolbox for connectivity analyses. Behavioral analyses and confidence interval (CI) estimation were carried out in R via RStudio.

2.2 | Task-based fMRI

In the published study, fMRI data were collected during a visual face–name association task for both stimulation cycles. Using SPM12 (Version 7771), preprocessed data entered first-level analysis, which employed a general linear model (GLM) with task blocks convolved with the hemodynamic response function. Individual and session-specific task contrasts for novel versus repeated face–name associations were subsequently entered into the group analysis. A second-level flexible factorial design (factors Condition (verum/sham), Session (baseline/post stimulation), Subject) was applied (for preprocessing and statistical modeling details see the original study[11]; see Section 2.5 for contrast rationale). In the present study, a very low activation threshold ($p_{uncorrected} = 0.01$, cluster extent $k = 10$) was used to check for any possible auditory cortex involvement.

2.3 | Resting-state fMRI: ROI-to-ROI connectivity

To address auditory confounds in attention network modulation (see the original study[11] for the latter), FC changes between auditory and the dorsal attention network (DAN) were investigated. This included bilateral core auditory areas (Heschl's gyrus [HG], posterior superior temporal gyrus [pSTG], and planum temporale [PT]) for the auditory network, and bilateral key nodes of the dorsal attention network (frontal eye fields [FEF] and intraparietal sulcus [IPS]). All ROIs were derived from the Harvard–Oxford atlas. Auditory ROIs were selected for their relevance to non-linguistic acoustic features such as audible clicks (see Supporting Information).[27,28] The DAN was included as the target based on increased GE following verum TPS in the original study.

Resting-state fMRI data were analyzed using the CONN toolbox v22a. Preprocessed and denoised data were entered into first-level analysis, where ROI-to-ROI connectivity matrices for 132 Harvard–Oxford atlas regions were computed using Fisher-z-transformed bivariate correlations of the corrected BOLD time series (for preprocessing details see the original study[11]). In the present study, main effects for sham post > baseline, verum post > baseline, and the interaction ((verum post > baseline) > (sham post > baseline)) were computed at the group level (see Section 2.5 for contrast rationale), controlling for age as a relevant baseline characteristic. For connectivity inferences we used CONN's multivariate F-test with the between-targets contrast set to "any effects (F)": the bilateral DAN ROIs (FEF, IPS; four nodes) were treated as targets, and the bilateral auditory ROIs (HG, pSTG, PT; six nodes) as seeds/sources (see Figure S1–S3). This yields one target-level F-test per DAN ROI, jointly assessing its six auditory connections ($df_1 = 6$). All second-level inferences used two-sided tests. Multiple comparisons were controlled using Benjamini–Hochberg false discovery rate (FDR) correction at $p < 0.05$ across the four DAN targets per contrast.

2.4 | Resting-state fMRI: Graph-theoretical analysis

The present analysis focused on the previously defined subset of ROIs, specifically bilateral core auditory areas (HG, pSTG, and PT). For graph-theoretical analysis, GE—a measure of network integration reflecting the capacity for parallel information processing—was computed from binary, undirected graphs based on ROI-to-ROI connectivity matrices derived from the resting-state fMRI data. As described in Section 2.3, these matrices were constructed using Fisher-z-transformed bivariate correlations between 132 regions defined by the Harvard–Oxford atlas (for preprocessing details see the original study[11]). Group-level analyses examined the main effects of sham post > baseline, verum post > baseline, and the interaction ((verum post > baseline) > (sham post > baseline)) (see Section 2.5 for contrast rationale). Each analysis was adjusted for age. Graph-theoretical analyses employed the same adjacency threshold as the original study ($r = 0.35$, one-sided positive), and GE was computed on the induced six-node auditory subgraph (bilateral HG, pSTG, PT). At the network level, results were considered significant at an uncorrected threshold of $p < 0.05$. For node-wise comparisons within this network, Benjamini–Hochberg FDR across the six auditory nodes was applied.

2.5 | Statistical contrasts of interest

To determine whether sustained effects could plausibly arise from auditory confounds rather than from neuromodulation per se, we prespecified three contrasts that isolate distinct auditory components—air conduction, combined air plus bone conduction, and a bone-specific component. Although the verum contrasts could, in principle, capture genuine off-target effects (e.g., auditory cortex activations induced by the targeted networks) rather than auditory confounds, prior work indicates that such influences are network constrained and do not propagate to unrelated systems[4,6,29–32] (see Supporting Information). Moreover, the auditory network was neither targeted nor functionally engaged in our protocol. Thus, this framework attributes any observed effects to auditory confounds rather than to direct ultrasound neuromodulation. As we describe, all analyses were focused on the core auditory cortex. Accordingly, the framework is intended specifically to

TABLE 1 Statistical contrasts for fMRI analyses.

Contrast	Task-based fMRI (co-activation)	Resting-state fMRI (functional connectivity)	Resting-state fMRI (global efficiency)
Sham post > baseline	Isolates air-conducted sound		
Verum post > baseline	Isolates air-conducted sound combined with possible bone-conducted sound		
Interaction (verum post > baseline) > (sham post > baseline)	Isolates possible bone-conducted sound		

Abbreviation: fMRI, functional magnetic resonance imaging.

test for auditory cortex–based confounds. We evaluated the following contrasts (Table 1):

1. **Sham post > baseline**: This contrast tested the effects of air-conducted sound alone, as the sham condition reproduced the acoustic characteristics of TPS without delivering ultrasound energy. A significant result may point to a possible contribution of airborne auditory co-stimulation.
2. **Verum post > baseline**: This contrast captures the combined effects of air-conducted sound (present in both conditions) and possible bone-conducted sound, which may occur in the verum condition only. A significant result could be consistent with the notion that combined air- and potentially bone-conducted auditory input, may generate relevant auditory long-term activation.
3. **Interaction (verum post > baseline) > (sham post > baseline)**: This contrast was designed to isolate possible bone-conduction–specific effects by removing variance attributable to shared air-conducted acoustic stimulation. A significant interaction might suggest that bone conduction contributed uniquely to a possible auditory network effect.

2.6 | Correlational analysis of auditory regions with CERAD

Furthermore, to determine whether possible auditory network changes had behavioral relevance, we analyzed the correlation between changes in GE (post–pre) and changes in CERAD CTS (post–pre), calculated separately for the verum and sham conditions. With regard to statistical assumptions, no relevant outliers were detected in either the verum or sham condition. Given the sufficiently large sample size ($N = 54$), we applied Pearson correlations for both conditions.

2.7 | Confidence intervals

In the present context, the decision-relevant question is not merely whether a test attains conventional significance, but how large any putative auditory confound could still plausibly be. Accordingly, we report effect sizes with 95% CIs, which summarize both the point estimate and the range of values most compatible with the data. The upper bound offers a conservative cap on the largest confound still consistent with our observations. For transparency we present partial eta squared (ηp^2), but we base interpretation on partial omega squared (ωp^2) because it reduces the upward bias of eta squared (η^2) in finite samples, provides a closer approximation to the population proportion of explained variance, and is less sensitive to model complexity and sample size.[33,34] This framing helps to evaluate whether any residual effect would be large enough to be biologically or clinically meaningful.

3 | RESULTS

3.1 | Task-based fMRI

The results of task-based fMRI analysis (Figure 1) show that TPS primarily induced frontoparietal cognitive network activation and less pronounced visual network activity related to the visual task. Despite the low activation threshold ($p_{uncorrected} = 0.01$, cluster extent $k = 10$), no auditory network co-involvement was found in any of the contrasts (sham post > baseline, verum post > baseline, interaction contrast). Effect-size estimates were small and all 95% CIs for ωp^2 included zero. The 95% upper bounds ($\omega p^2 \leq 0.100$) are sufficiently tight to make long-term auditory co-activation of practical relevance unlikely (see Table S1). This suggests that the auditory network was not engaged to a relevant level during activity of the stimulated network.

3.2 | Resting-state fMRI: ROI-to-ROI connectivity

ROI-to-ROI analyses revealed no significant long-term FC changes between auditory ROIs and the DAN after 2 weeks of verum or sham stimulation. Specifically, no effects were observed for the contrast testing air-conducted auditory stimulation alone (sham post > baseline; all $p_{FDR\text{-}corrected}$-values = 0.8021; partial $\omega p^2 = 0.000$–0.050, 95% CI [0.000, up to 0.174]; see Figure S1 and Table S2), for the combined air- and bone-conduction contrast (verum post > baseline; all $p_{FDR\text{-}corrected}$-values = 0.7548; partial $\omega p^2 = 0.000$, 95% CI [0.000, up to 0.053]; see Figure S2 and Table S3), or for the interaction isolating bone-conduction–specific effects ((verum post > baseline) > (sham post > baseline); all $p_{FDR\text{-}corrected}$-values > 0.5626; partial $\omega p^2 = 0.000$–0.009, 95% CI [0.000, up to 0.119]; see Figure S3 and Table S4). Point estimates for ωp^2 were at or near zero across conditions (sham: 0.000–0.050; verum: all 0.000; interaction: 0.000–0.009), and every 95% CI included zero. Sham showed no consistent signal (three targets $\omega p^2 = 0.000$ with upper bounds ≤ 0.051; one target, the left IPS, had a wider bound to 0.174 despite a small estimate of 0.050). Verum effects were tightly bounded (largest upper CI limit 0.053; others ≤ 0.033)

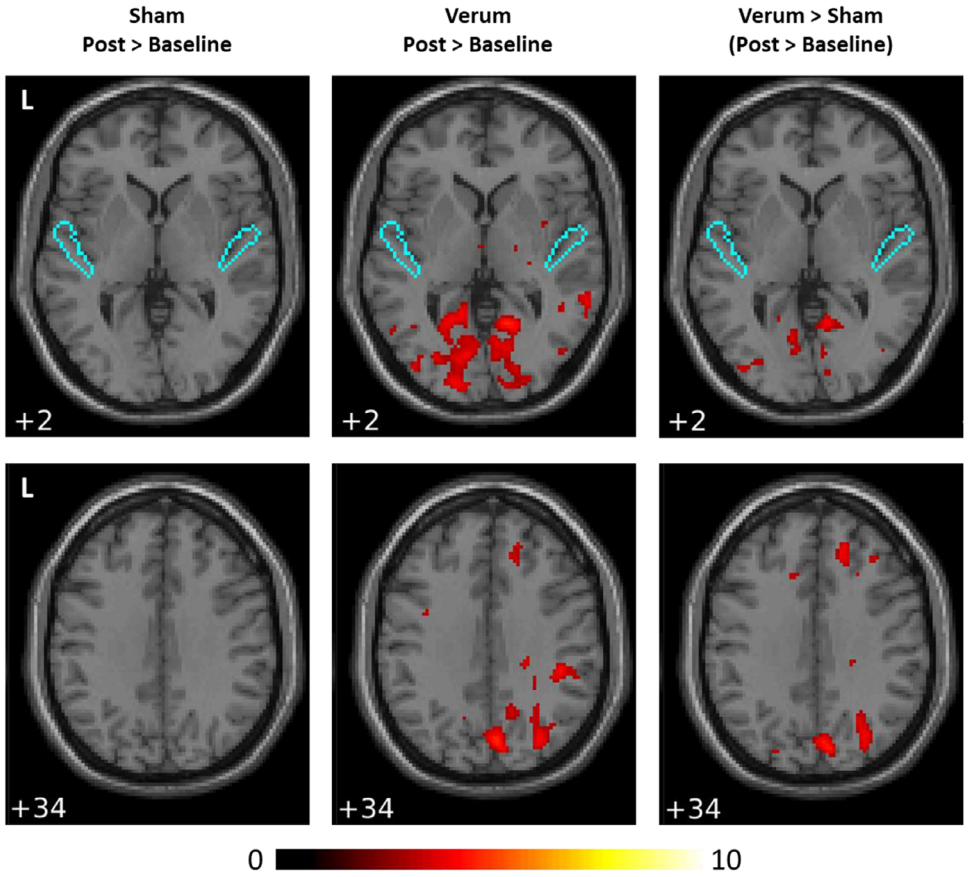

FIGURE 1 Activation contrasts (post > baseline) during the face–name association task. Sham post > baseline (Column 1), verum post > baseline (Column 2), and differential activation for verum compared to sham ((verum post > baseline) > (sham post > baseline)) (Column 3) are presented at a very low threshold ($p_{uncorrected} = 0.01$, cluster extent k = 10). At z = +34, verum > sham shows frontoparietal cognitive-network increases. At z = +2, occipital visual network increases are evident. Across all contrasts, no significant activation increases were observed within the primary auditory cortex (upper row, blue delineations).

and below the conventional moderate threshold. Interaction contrasts showed near-zero point estimates with upper bounds ≤ 0.119, implying that any verum–sham differential, if present at all, is unlikely to be of practical relevance. Taken together, the data provide no practical evidence that 2 weeks of inherent acoustic co-stimulation measurably alters long-term coupling between auditory network and DAN.

3.3 | Resting-state fMRI: Graph-theoretical analysis

Graph-theoretical analyses revealed no significant long-term changes in GE within bilateral auditory areas (HG, pSTG, PT) across any of the examined contrasts. Specifically, no significant effects emerged for the contrast isolating air-conducted auditory stimulation (sham post > baseline; $p_{uncorrected} = 0.1095$; partial $\omega p^2 = 0.010$, 95% CI [0.000, 0.145]), for the contrast capturing the combined impact of air- and potential bone-conducted stimulation (verum post > baseline; $p_{uncorrected} = 0.9589$; partial $\omega p^2 = 0.038$, 95% CI [0.000, 0.192]), or for the interaction designed to isolate bone-conduction–specific contributions ((verum post > baseline) > (sham post > baseline); $p_{uncorrected} = 0.9863$; partial $\omega p^2 = 0.071$, 95% CI [0.000, 0.238]) (for details see Figure S4–S6 and Table S5). Point estimates for ωp^2 were small and all 95% CIs included zero (upper bounds 0.145–0.238). The sham contrast shows a point estimate of 0.010 (lowest possible "small" value) and a wide CI (0.000–0.145). This pattern is more compatible with no effect than with any sizeable one. Of note, both the verum and interaction contrasts yielded negative T-values, indicating a trend toward reduced auditory network GE rather than an increase. Together, these results suggest that exposure to audible sound alone did not enhance long-term information transfer efficiency within the auditory network at a relevant level.

3.4 | Correlational analysis of auditory regions with CERAD

No significant associations were found between individual pre–post changes in GE within auditory regions and changes in CERAD CTS scores. This was true for both verum ($p = 0.998$, 95% CI [−0.267, 0.268]) and sham ($p = 0.212$, 95% CI [−0.421, 0.100]) stimulation. Positive, clinically meaningful associations (e.g., $r \geq 0.30$) are ruled out for

verum and–given the upper CI bound of 0.10–also for sham. These results indicate that auditory network changes do not appear to drive cognitive AD improvements.

4 | DISCUSSION

This exploratory study examined whether long-term cognitive improvements and functional brain changes observed following TPS in patients with AD might be associated with relevant auditory network activations. Building on the currently largest sham-controlled clinical ultrasound neuromodulation study,[11] we conducted a re-analysis of task-based and resting-state fMRI data. Specifically, we tested whether inherent auditory co-stimulation via air- or possibly bone-conducted sound could be associated with cognitive network improvements reported in the original study. To this end, we systematically assessed task-related co-activation, functional connectivity, network-level integration, and relation to cognitive improvement using a contrast framework designed to isolate distinct auditory components. This is the first study to explore whether such auditory elements leave detectable and relevant auditory long-term traces in the human brain following ultrasound neuromodulation.

Across all analytic approaches, we found no compelling evidence supporting a lasting influence of auditory co-stimulation. (1) Task-based fMRI showed no cross-modal involvement of auditory cortices during cognitive engagement. Verum-related activations were located in fronto-parietal control regions and visual cortex, consistent with the results of the original study[11] (see Supporting Information). (2) Resting-state analyses revealed no significant coupling between auditory and attention networks (the latter modulated in the original study). (3) There was no auditory network reconfiguration in terms of GE. (4) There was no behavioral relevance as assessed by correlations with CERAD CTS scores. Our analytic approach allowed for a structured dissection of distinct auditory contributions by applying carefully defined contrasts across all imaging modalities. These contrasts were designed to isolate specific auditory components: (1) air-conducted stimulation common to both groups, (2) combined air- and potential bone-conducted stimulation, and (3) bone-conduction–specific effects. None showed evidence of persistent auditory involvement at a relevant level. This renders auditory confounds unlikely as a key explanation for the cognitive-network effects. We report effect sizes with 95% CIs and interpret the upper bounds as conservative caps on any plausible auditory-confound magnitude. Across task fMRI, auditory–DAN connectivity, intra-auditory GE, and cognition, the consistently small estimates, and constrained upper bounds render a sizeable, sustained confound implausible. Questionnaire data likewise argue against indirect confounds (e.g., placebo), as patients could not distinguish verum from sham.[11]

Concerning statistical power to detect auditory network effects, the only tFUS–fMRI study probing auditory cortex engagement (N = 16) reported that no participant experienced any auditory percept during sonication.[24] Because our protocol involved audible clicking in both verum and sham, the more suitable literature comprises (transcranial magnetic stimulation TMS) trials, where the coil "click" robustly elicits bilateral auditory-cortex BOLD responses even in small cohorts.[35,36] These TMS findings capture acute, in-scanner responses, whereas our MRI assessed sustained effects ≈6 days after stimulation. We therefore reference them not to imply identical time-scales, but as a positive-control benchmark for detectability of audibility-driven responses. Given that such click-evoked responses emerge reliably in small single-center samples (e.g., $N = 8$[35], $N = 12$[36]), our substantially larger sample (N = 54, ≈4.5 times greater) would be expected to have ample sensitivity to detect sustained effects of comparable magnitude.

Taken together, our findings align with emerging evidence that, although audible sound—via air conduction[16] or bone conduction[17]—can modulate immediate brain responses *during* ultrasound neuromodulation, it is unlikely to drive long-term neuroplastic change of non-auditory networks. There is neurophysiological,[23,29] imaging,[24] and clinical[1,6] evidence indicating that long-term ultrasound stimulation effects are driven primarily by direct neuromodulatory mechanisms. Functional specificity of the neuromodulation effects provides further support.[4,6,23,29] A recent fMRI study found that stimulation of anterior and posterior cingulate cortices resulted in target-specific changes in FC that cannot be attributed to sound-related effects.[32] The later work echoes an fMRI seed-based connectivity analysis in nonhuman primates reporting the absence of change in the coupling between any of the stimulation sites and the auditory cortex.[29]

There are limitations to this study. First, this study represents an initial exploration of potential long-term auditory effects, rather than acute auditory responses. Of course, auditory confound effects may have occurred acutely—during or immediately after the stimulation sessions—but dissipated by the time of scanning. Although this temporal delay was instrumental in assessing sustained changes, it may have reduced the likelihood of detecting short-lived auditory responses. Still, if acute auditory artifacts had causally driven the previously reported cognitive and neural benefits, one would expect residual signatures (in auditory ROIs or auditory network coupling); none were observed across task-fMRI, resting-state connectivity, graph measures, or behavior. Second, we focused on early-stage auditory cortices, foregoing multisensory-integration and downstream-plasticity regions. Nevertheless, this deliberate restriction maximized a priori sensitivity and specificity for detecting persistent auditory involvement: if such a mechanism were consequential, a trace should first emerge in core auditory cortex and its canonical couplings. Broadening the analysis to numerous polymodal areas would substantially increase interpretational ambiguity—any signal could reflect generic multisensory integration or downstream plasticity rather than an auditory confound—and would not readily account for selective links to predefined outcomes (e.g., DAN modulation or CERAD CTS) reported in the original trial. Third, although convergent evidence indicates that ultrasound-induced off-target effects are network specific rather than diffuse, our contrast-based analysis cannot definitively exclude some admixture of genuine TPS-related changes with putative auditory confounds within the verum-specific contrasts. It is important to note that such potential conflation would matter only in the presence of positive findings; in the current dataset, no contrast showed a

significant effect. Consequently, our conclusions are not affected and remain consistent with the absence of auditory involvement. Fourth, an active control (e.g., off-target stimulation reproducing skull vibration) would have aided identification of acute auditory confounds.[37] Adding such an arm in the original study would have reduced allocation to verum and thereby statistical power, undermining the trial's primary goal of providing a large-scale RCT demonstration of ultrasound effects in AD. Finally, fMRI may not be sufficiently sensitive to capture subtle or diffuse changes in auditory-network function, particularly in the absence of an auditory task. However, it seems unlikely that such subtle auditory-network activity can be a key factor for the clear cognitive network effects observed. Future experimental studies could employ auditory paradigms to increase sensitivity and to bridge the gap between acute and long-term auditory confound effects.

Overall, within the largest randomized ultrasound neuromodulation trial to date, this pioneering investigation finds no traces of long-term auditory confound effects, strengthening the inference that TPS-related cognitive and neural gains are not artifactual consequences of sound.

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CONFLICT OF INTEREST STATEMENT

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests. Roland Beisteiner reports financial support was provided by Herzfelder Stiftung Austria. Roland Beisteiner reports a relationship with Storz Medical AG that includes funding grants. The other authors declare, that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Any author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Written informed consent was obtained from all study participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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