Sensory Tetanization to Induce LTP-Like Plasticity:

A Review and Reassessment of the Approach

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Abstract

Background

Great interest has been given to developing non-invasive approaches for studying cortical plasticity in humans. High frequency presentation of auditory and visual stimuli, or *sensory tetanization*, can induce LTP-*like* changes in cortical activity. However, contrasting effects across studies suggest that sensory tetanization may be unreliable.

Method

We used sensory tetanization to try to induce auditory and visual LTP-like plasticity in younger and older adults. We measured auditory-evoked amplitude changes following tetanization to 1 kHz and 4 kHz tone bursts and following a slow-presentation control. We also measured visual-evoked amplitude changes following tetanization to horizontal and vertical sign gradients.

Results

Auditory and visual response amplitudes decreased following tetanization, consistent with some studies but contrasting with others finding amplitude increases (i.e. LTP-Like). Older adults exhibited more modest auditory-evoked amplitude decreases, but visual-evoked amplitude decreases like those of younger adults. Changes in response amplitude were not specific to tetanized stimuli. Importantly, slow presentation of auditory tone-bursts produced changes in response amplitude that were like those observed following tetanization.

Comparison with Existing Methods

A meta-analysis incorporating our results with studies employing similar tetanization techniques to study cortical plasticity revealed that the overall effect size across studies

and labs is not significant, suggesting sensory tetanization does not produce reliable changes in cortical responses.

Conclusions

We discuss our findings with respect to other inconsistent findings across the literature concerning stimulus specificity and age effects and conclude that sensory tetanization is an unreliable method for inducing human cortical plasticity in vivo.

Key Words

auditory; high frequency stimulation; plasticity; sensory tetanization; visual; LTP.

Introduction

Much attention has been given to the development of non-invasive techniques for inducing functional and structural plastic changes in the brain. Such techniques can be valuable for studying neural plasticity in humans and how neural plasticity is affected by environmental, neurochemical, clinical, and genetic factors. High frequency presentation of sensory stimuli, or *sensory tetanization* (Clapp et al., 2005a; Teyler et al., 2005), has emerged as a popular technique for inducing changes in cortical activity that are often attributed to long-term potentiation (LTP) (for reviews, see Kirk et al., 2021; Sanders et al., 2018; Sumner et al., 2020b). While some have heralded sensory tetanization as a valuable non-invasive tool for the study of human cortical plasticity in vivo (Kirk et al., 2021; Sumner et al., 2020b), there are many inconsistent findings across studies that should be considered. Here, we provide background for the development and use of sensory tetanization as a technique for studying plasticity in the human brain. We then report our own study of auditory and visual tetanization in younger and older adults and compare our results to other studies. Finally, we report a meta-analysis to determine the extent to which sensory tetanization effects are consistent across studies and study sites.

Approaches to Study Neural Plasticity

Long-term potentiation (LTP) describes the changes in synaptic structure that follow repeated neural stimulation that can facilitate efficient neural communication. First discovered in invertebrates (Kandel & Tauc, 1964, 1965) and later in vertebrate animals (Bliss & Lømo, 1973; Lømo, 1966; Lømo, 2003), LTP has emerged as a strong candidate neural mechanism for learning and memory (Bliss & Collingridge, 1993;

Cooke & Bliss, 2006). Animal studies of LTP typically employ invasive techniques, including extracellular electrical stimulation of neural populations followed by local field recordings of population responses and post-mortem tissue analyses. Such invasive methods have limited the study of LTP in humans. As such, some of the most direct evidence for LTP in humans comes from studies demonstrating LTP in the resected cortical tissue of epileptic patients (e.g., Beck et al., 2000; Chen et al., 1996). Repetitive transcranial magnetic stimulation (rTMS) can non-invasively induce LTP-like changes in cortical activity in vivo, eliciting changes in cortical activity that reflect those observed in animal studies (e.g., Esser et al., 2006; Wischnewski & Schutter, 2015; for reviews, see Chung et al., 2016; Suppa et al., 2016). These changes in cortical activity are described as LTP-*like* because changes in cortical activity after rTMS reflect those which accompany LTP changes in synaptic structure that are observed in animal studies, but synaptic structure is not (cannot be) directly measured in vivo.

Clapp et al. (2005a) and Teyler et al. (2005) introduced another non-invasive method for inducing LTP-like plasticity by eliciting changes in cortical electrophysiological (EEG) activity after high frequency presentation of auditory and visual stimuli. This *sensory tetanization* produced amplitude increases in the N1 and N1b components of auditory and visual evoked responses that they attributed to LTP in sensory cortex and described as LTP-like plasticity. Since the publication of these seminal studies, sensory tetanization has been used extensively to study plasticity in the human brain (for reviews, see Kirk et al., 2021; Sanders et al., 2018; Sumner et al., 2020b). Functional magnetic resonance imaging (fMRI) studies have reported changes in the BOLD response after tetanization that are localized in the sensory cortex

(auditory or visual) coinciding with the modality of the test stimuli (Clapp et al., 2005b; Lahr et al., 2014; Wijtenburg et al., 2017; Zaehle et al., 2007). Magnetic resonance spectroscopy (MRS) studies have found that higher concentrations of excitatory neurotransmitters (glutamate) and lower concentrations of inhibitory neurotransmitters (GABA) are associated with larger ERP amplitude increases following tetanization (Abuleil et al., 2019; Wijtenburg et al., 2017). Pharmaceuticals that can regulate these neurotransmitters can also modulate the effects of tetanization on ERP amplitudes (Forsyth et al., 2015; Sumner et al., 2020a). Studies of aging find that older adults exhibit more modest changes in ERP amplitude after tetanization than younger adults (Abuleil et al., 2019; de Gobbi Porto et al., 2015; Spriggs et al., 2017). Studies of patients diagnosed with schizophrenia (Çavuş et al., 2012; D'Souza et al., 2018; Forsyth et al., 2017; Hamilton et al., 2020; Jahshan et al., 2017; Mears & Spencer, 2012; Valstad et al., 2021; but see Wynn et al., 2019), bipolar disorder (Elvsåshagen et al., 2012; Valstad et al., 2021; Zak et al., 2018), and depression (Normann et al., 2007; Sumner et al., 2020a) have also found that these patient populations exhibit more modest changes in response amplitudes after tetanization compared to healthy controls, while adults with autism spectrum disorder (ASD) can exhibit more pronounced response amplitude increases (Wilson et al., 2017). The broad interdisciplinary use of sensory tetanization to study plasticity and how plasticity changes across different experimental groups demonstrates the potential value of this in vivo approach. However, across these studies, a disturbing degree of variability in the type and degree of changes in neural activity elicited by sensory tetanization are evident, raising

concerns regarding the reliability and validity of the approach to induce and study plasticity in the human brain.

Inconsistent Changes in Response Amplitudes

The seminal studies introducing sensory tetanization as an in vivo approach to studying plasticity reported an *increased* N1 and N1b amplitude in the sensory-evoked ERP after tetanization to auditory (Clapp et al., 2005a) and visual (Teyler et al., 2005) stimuli. Subsequent studies have since replicated these results in young healthy adults, reporting increases in the N1/N1b (and the C1, P1, P2) amplitude of sensory-evoked ERPs after tetanization (Kleeva et al., 2022; Lei et al., 2017; Lengali et al., 2021; McNair et al., 2006; Moore et al., 2020; Moore & Loprinzi, 2021; Normann et al., 2007; Ross et al., 2008; Rygvold et al., 2020; Smallwood et al., 2015; Spriggs et al., 2017; Spriggs et al., 2018; Spriggs et al., 2019; Sumner et al., 2018; Wilson et al., 2017; Zak et al., 2018). However, despite the number of studies finding sensory ERP amplitude increases after tetanization, several others have found no effect of tetanization on response amplitudes (D'Souza et al., 2018; Rygvold et al., 2020; Sumner et al., 2018) and several more have even found that response amplitudes *decrease* after tetanization (Kleeva et al., 2022; Klöppel et al., 2015; Rebreikina et al., 2021; Spriggs et al., 2018; Wynn et al., 2019). These contrasting effects of tetanization are also evident in fMRI studies, with three studies finding an increased BOLD response following tetanization (Clapp et al., 2005b; Wijtenburg et al., 2017; Zaehle et al., 2007) and one finding a decrease in BOLD response (Lahr et al., 2014). These variable findings are all reported in groups of younger healthy adults across the various studies. For this review, we are not considering the variability reported in treatment groups or clinical samples.

These contrasting effects across studies raise concerns regarding the principal value of sensory tetanization as an in vivo method for studying neural plasticity. The initial finding that sensory tetanization increased ERP response amplitudes reflected the observations from animal studies that directly measured LTP, and so changes in ERP amplitudes after sensory tetanization were attributed to LTP in the human brain (Clapp et al., 2005a; Teyler et al., 2005). However, findings across subsequent studies that employed methods similar to those initially reported by Clapp et al. (2005a) and Teyler et al. (2005) suggest that sensory tetanization can result in response amplitude increases, decreases, or no change at all.

Current Investigation

Though a large corpus of published studies has used sensory tetanization to study LTP-like plasticity in the human brain, contrasting findings across these studies suggest the approach may lack reliability and validity. Here we report a study of our own to determine whether sensory tetanization can elicit changes in the sensory-evoked potentials of younger and older adults. To provide a rigorous test of the specificity of changes in sensory-evoked potentials to tetanization, we incorporated a control condition absent of high-frequency stimulus presentation, instead exposing participants to a slow presentation of our test stimuli. We also incorporated different tetanizing and test stimuli to examine the degree to which changes in sensory-evoked potentials after tetanization were specific to the tetanized stimulus.

Following our study, our results and those reported in past studies were examined in a meta-analysis to determine whether the average effect of sensory tetanization on sensory-evoked ERPs was significant across studies. The studies

included in our meta-analysis (Table 1) all used sensory tetanization to study LTP-like plasticity in the style of Clapp et al. (2005a) and Teyler et al. (2005) and reported amplitude changes in the N1/N1b component of sensory-evoked ERPs in groups of younger healthy adults (e.g., Clapp et al., 2005a; Teyler et al., 2005). The degree to which studies not included in the meta-analysis support sensory tetanization as a reliable method for studying LTP-like plasticity in the human brain is considered in the Discussion.

Sensory Tetanization Study

Methods

Participants. Our study sample consisted of 29 younger adults (18-29 years of age, M=22.52 years of age, SE=0.536, 20 women) and 33 older adults (55-83 years of age, M=67.61 years of age, SE=1.138, 22 women). Younger participants were graduate and undergraduate student volunteers from the Medical University of South Carolina and the College of Charleston. Older participants consisted of volunteers from an ongoing longitudinal study on presbycusis and volunteers from the greater Charleston, SC area. Several participants in both age groups had previous experience with hearing tasks, but all were unfamiliar with the auditory and visual tetanization tasks in the current study. All participants were native English speakers and had normal cognitive ability, having completed the Mini-Mental State Examination (Folstein et al., 1983) with no more than 3 errors. This study was approved by the Institutional Review Board of the Medical University of South Carolina and all participants provided written informed consent prior to participation.

Participants were limited to those with normal hearing or mild-to-moderate sensorineural hearing loss. Audiometric thresholds for conventional test frequencies are reported in Figure 1. The hearing thresholds of younger adults were within normal clinical limits (≤25 dB HL). The hearing thresholds of older adults were more variable, ranging from within normal clinical limits to mild-to-moderate high frequency hearing loss. Audiometric thresholds averaged across 500 to 4000 Hz were higher for older participants ($M = 21.057$ dB HL, $SE = 2.186$) than for younger participants ($M = 1.807$ dB HL, $SE = 0.483$), $t(60) = -8.095$, $d = 9.343$, $p < 0.001$. To identify any variance in the effects of auditory tetanization that may be accounted for by differences in audiometric thresholds, average thresholds were included in our statistical analyses.

Participants had a visual acuity ≤ 20/50 on the Snellen Eye Chart and a visual log contrast sensitivity ≥ 1.00 on the Pelli-Robson Contrast Sensitivity Chart. Younger adults had visual acuity between 20/10 and 20/25 ($N = 27$, $M = 14.960$, $SE = 0.628$) and visual log contrast sensitivity between 1.50 and 1.95 ($N = 26$, $M = 1.685$, $SE = 0.017$). Older adults had visual acuity between 20/13 and 20/50 ($N = 29$, $M = 23.340$, $SE = 1.805$) and visual log contrast sensitivity between 1.35 and 1.80 ($N = 29$, $M = 1.557$, $SE = 0.023$). There were significant age-group differences in visual acuity ($t[54] = -4.260$, $d = 7.358$, $p < 0.001$) and contrast sensitivity ($t[53] = -4.381$, $d = 0.108$, $p < 0.001$). Visual acuity and contrast sensitivity were included in our statistical analyses to determine whether these age-group differences in vision could account for variability in the effects of visual tetanization.

Auditory Tetanization. The auditory tetanization task was similar to procedures previously reported to elicit LTP-like changes in auditory ERP amplitudes (e.g., Clapp et

al., 2005a; Kleeva et al., 2022). The stimuli used to elicit auditory ERPs were 1 kHz and 4 kHz tone-bursts with a duration of 50 ms (including a 5 ms ramp on and a 5 ms ramp off) presented at 90 dB SPL. Baseline auditory ERPs were measured from two sessions of 220 presentations of 1 kHz and 4 kHz tone bursts. Each stimulus was randomly presented 110 times at a presentation frequency of ~0.41-0.54 Hz – stimulus duration 50 ms and random ISI between 1800 and 2400 ms. Following baseline recording, participants were tetanized to either 1 kHz or 4 kHz tone bursts or repeated the baseline trial (non-tetanized slow presentation of both 1 kHz and 4 kHz tone bursts). For the tetanization conditions, the tetanizing stimulus was presented for 4 minutes at a presentation frequency of 13.3 Hz – stimulus duration 50 ms and an ISI of 25 ms. Following tetanization or slow presentation, participants were given 5 minutes to rest. Post-tetanization and post-slow-presentation auditory ERPs were then measured following the same procedure used to record baseline auditory ERPs. Of our 29 younger participants, 20 completed 1 kHz tone-burst tetanization, 20 completed 4 kHz tone-burst tetanization, and 22 completed the slow presentation control. Of our 33 older participants, 28 completed 1 kHz tone-burst tetanization, 28 completed 4 kHz tone-burst tetanization, and 26 completed the slow presentation control. Tone-burst stimuli were delivered through ER-3C Etymotic insert earphones inserted into the left and right ears. Stimulus delivery and timing was controlled with TDT RPvds and a Tucker-Davis Technologies RZ6 auditory processing (Tucker-Davis Technologies, Alachua, FL).

Visual Tetanization. The visual tetanization task was similar to procedures previously reported to elicit LTP-like changes in visual ERP amplitudes (e.g., Smallwood et al., 2015; Spriggs et al., 2017). The stimuli used to elicit visual ERPs were two

circular disks, each containing a black and white sine gradient with a size of 1000 x 1000 pixels and a spatial frequency of approximately 1.4 cycles per degree. These disks were oriented either horizontally or vertically, as illustrated in Figure 2. Baseline visual ERPs were measured from two sessions of 220 presentations of the horizontal and vertical stimuli. Each stimulus was randomly presented 110 times at a presentation frequency of ~0.67-1 Hz – stimulus duration of 33 ms and a random ISI between 1000 and 1500 ms, accounting for the 60 Hz refresh rate of the computer screen. Following baseline recording, participants were tetanized to one of the two visual stimuli, either horizontal or vertical. The tetanizing stimulus was presented 2000 times at a presentation frequency of ~8.6 Hz – stimulus duration of 33 ms and a random ISI between 67 and 100 ms, accounting for the 60 Hz refresh rate of the computer screen. Following tetanization, participants were given 5 minutes to rest and allow any afterimages of the tetanizing stimulus to dissipate. Post-tetanization visual ERPs were then measured following the same procedure used to record baseline visual ERPs. Visual tetanization was completed by 18 younger and 30 older participants. Visual stimuli were presented on a 27” Asus VN279 LCD computer monitor at a visual angle of approximately 14□. Stimulus delivery and timing was controlled with a combination of PsychoPy software (Peirce et al., 2019) and a Cedrus StimTracker Quad (Cedrus Corp., San Pedro, CA, United States) equipped with photodiodes for accurate timing of stimulus delivery.

EEG Recording and ERP Analysis. Electroencephalography (EEG) was recorded from a 64-channel Neuroscan QuickCap (international 10-20 system) connected to a SynAmpsRT 64-Channel Amplifier. Bipolar electrodes placed above and

below the left eye recorded vertical electro-oculogram activity and bipolar electrodes placed on the outer canthi of both eyes recorded horizontal electro-oculogram activity. Curry 8 software was used to record the EEG signal at a 10,000 Hz sampling rate while participants passively completed the auditory and visual tetanization tasks.

EEG data were then processed offline using a combination of EEGLab (Delorme & Makeig, 2004) and ERPLab (Lopez-Calderon & Luck, 2014). The recorded EEG data were down-sampled to 1000 Hz, bandpass filtered from 1-30 Hz, and re-referenced to the average of all electrodes. Auditory tetanization data were corrected for ocular artifacts by removing ocular source components following independent components analysis. Individual trials were then segmented into epochs around the stimulus onset (-100 ms – +500 ms) and then baseline corrected (-100 ms – 0 ms). Any epochs contaminated by peak-to-peak deflections in excess of 100 µV were rejected using an automatic artifact rejection algorithm. Visual tetanization data were also visually inspected to reject any epochs with amplitude deflections in the vertical and horizontal eye channels that could indicate blinks or eye-movements during the visual task.

For each participant, epoched data were averaged across trials to compute the average waveform (event-related potential, ERP). ERPs were analyzed in a cluster of frontal-central electrodes for auditory data: F1, FZ, F2, FC1, FCZ, FC2, C1, CZ, C2 (e.g., Dias et al., 2018; Dias et al., 2021; Harris et al., 2012; Narne & Vanaja, 2008; Tremblay et al., 2001), and in a cluster of posterior-central electrodes for visual data: P7, TP7, CP5, P5, PO7, P8, TP8, CP6, P6, PO8 (McNair et al., 2006; Smallwood et al., 2015). First, ERPs were averaged across the channels. Then, post stimulus onset, the latencies of the first prominent negative peak (C1/N50), first prominent positive peak

(P1), second prominent negative peak (N1), second prominent positive peak (P2), and third prominent negative peak (N2) were recorded. These latencies were used to compute temporal intervals for the automatic detection of the P1, N1, and P2 peak amplitudes and latencies in each of our channels of interest, individually, using custom MATLAB scripts. P1 was defined as the maximum positive peak between C1/N50 (or from stimulus onset if no C1/N50 was detected) and N1. N1 was defined as the maximum negative peak between P1 and P2. P2 was defined as the maximum positive peak between N1 and N2. P1, N1, and P2 peak amplitudes and latencies were then averaged across channels to yield a single metric for the P1 peak amplitude, P1 peak latency, N1 peak amplitude, N1 peak latency, P2 peak amplitude, and P2 peak latency for each participant. If a P1, N1, or P2 peak was not found in a channel between their respective latency windows defined from the average waveform across all of our channels of interest, then that channel was omitted from the computed average of each component characteristic (peak amplitude and peak latency). As with previous studies, this approach allowed for automatic peak peaking across channels, reducing the risk of human error, while more accurately measuring components by not considering those channels that failed to exhibit an identifiable component, likely as a result of noise from poor impedance (e.g., Anderer et al., 1996; Dias et al., 2018; Dias et al., 2021).

Auditory ERPs are represented in Figure 3 and visual ERPs are represented in Figure 4. These figures illustrate the average ERP prior to tetanization (blue) and after tetanization (red) with the shaded area representing the standard error. Included in these figures are the pre-post tetanization waveforms for individual participants, represented as red/blue ribbons. Light blue shading of these ribbons highlights where a

participant's pre-tetanization waveform was larger than their post-tetanization waveform and light red (pink) shading highlights where a participant's post-tetanization waveform was larger than their pre-tetanization waveform. Evident from these figures is a high degree of individual variability, with most participants exhibiting larger pre-tetanization amplitudes, but many others exhibiting larger post-tetanization amplitudes.

Analytical Approach. Linear mixed effects regression (LMER) models were used to test for N1 amplitude changes in stimulus responses following 1 kHz tone-burst tetanization, 4 kHz tone-burst tetanization, and slow presentation of 1 kHz and 4 kHz tone bursts. N1 peak amplitude was selected as the outcome variable for all models because previous ERP studies largely report tetanization effects for this component (Clapp et al., 2005a; see also Mears & Spencer, 2012). Trial (pre-tetanization and post-tetanization), stimulus (1 kHz and 4kHz), and age group (younger and older) were included as fixed factors, including the interaction terms for trial and stimulus with age-group. Participant served as a random factor. LMER is a valuable non-parametric statistical approach that can test hypothesis-driven relationships while accounting for the variability of multi-level factors nested within participants (i.e., trial and stimulus). Significant interaction terms were further evaluated in post-hoc LMER models.

Similarly, an LMER model was used to test for response differences following visual tetanization. The fixed factors of trial and age group were included in the model, along with their interaction term, and participant served as a random factor. Tetanization condition (horizontal or vertical tetanization) and stimulus type (horizontal or vertical stimulus), along with their interactions with trial and age group, were then added to this model to determine whether model fit was improved.

Results

Slow Presentation of 1 kHz and 4 kHz Tone Bursts. For participants who completed the slow-presentation control condition, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.462 μV, SE = 0.242) was larger than to 4 kHz tone bursts (M = -1.606 μV, SE = 0.157) both before and after slow presentation, B = 0.926, SE_B = 0.091, β = 0.631, SE_β = 0.062, t = 10.145, p < 0.001. N1 peak amplitude was also larger prior to the slow presentation (M = -2.199 μV, SE = 0.228) than after (M = -1.866 μV, SE = 0.192), B = 0.703, SE_B = 0.117, β = 0.479, SE_β = 0.080, t = 5.997, p < 0.001. N1 peak amplitude did not significantly differ between younger (M = -2.314, SE = 0.239) and older adults (M = -1.805, SE = 0.184), B = 0.723, SE_B = 0.370, β = 0.493, SE_β = 0.252, t = 1.954, p = 0.056. Pre-post changes in N1 peak amplitude did not significantly interact with stimulus, suggesting that decreases in N1 peak amplitude following slow presentation were similar for both 1 kHz and 4 kHz stimuli, B = -0.139, SE_B = 0.129, β = -0.095, SE_β = 0.088, t = -1.078, p = 0.282. However, pre-post changes in N1 peak amplitude did interact with age group, suggesting that decreases in N1 peak amplitude following slow presentation were smaller for older adults, B = -0.515, SE_B = 0.131, β = -0.351, SE_β = 0.089, t = -3.932, p < 0.001. Adding audiometric thresholds to the model did not change the pattern of significant relationships or improve model fit, $\chi^2(1)$ = 0.751, p = 0.386. To examine the significant interaction between trial and age group, separate LMER models were fit to the data from younger and older adults. For younger adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.716 μV, SE = 0.398) was larger than to 4 kHz tone bursts (M = -1.912 μV, SE = 0.251) both before and after slow presentation, B = 0.905, SE_B = 0.162, β = 0.572, SE_β = 0.102, t =

5.601, $p < 0.001$. The N1 peak amplitudes of younger adults were also larger prior to slow presentation (M = -2.605 μV, SE = 0.359) than after (M = -2.016 μV, SE = 0.302), B = 0.735, SE_B = 0.164, β = 0.464, SE_β = 0.103, t = 4.489, $p < 0.001$. Trial did not interact with stimulus, B = -0.204, SE_B = 0.230, β = -0.129, SE_β = 0.145, t = -0.888, p = 0.376. For older adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.254 μV, SE = 0.292) was larger than to 4 kHz tone bursts (M = -1.355 μV, SE = 0.187) both before and after slow presentation, B = 0.942, SE_B = 0.101, β = 0.711, SE_β = 0.076, t = 9.360, $p < 0.001$. However, the N1 peak amplitudes of older adults did not significantly change after slow presentation (M = -1.864 μV, SE = 0.275) to after (M = -1.746 μV, SE = 0.245), B = 0.162, SE_B = 0.101, β = 0.122, SE_β = 0.076, t = 1.607, p = 0.110. Trial did not interact with stimulus, B = -0.087, SE_B = 0.142, β = -0.066, SE_β = 0.107, t = -0.614, p = 0.540. Results from the slow-presentation control condition suggest that even a slow presentation of 1 kHz and 4 kHz tone bursts can produce a significant decrease in the N1 peak amplitudes of responses to both stimuli, but this affect is limited to younger adults.

1 kHz Tone-Burst Tetanization. For participants who completed the 1 kHz tone burst tetanization condition, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.491 μV, SE = 0.213) was larger than to 4 kHz tone bursts (M = -1.588 μV, SE = 0.139) both before and after tetanization, B = 0.998, SE_B = 0.076, β = 0.752, SE_β = 0.060, t = 12.541, $p < 0.001$. N1 peak amplitude was also larger prior to 1 kHz tone burst tetanization (M = -2.202 μV, SE = 0.203) than after (M = -1.877 μV, SE = 0.177), B = 0.604, SE_B = 0.104, β = 0.456, SE_β = 0.078, t = 5.825, $p < 0.001$. N1 peak amplitude did not significantly differ between younger (M = -2.257, SE = 0.215) and older adults

(M = -1.884, SE = 0.172), B = 0.531, SE_B = 0.335, β = 0.400, $SE_β$ = 0.253, t = 1.583, p = 0.120. Pre-post changes in N1 peak amplitude did not significantly interact with stimulus, suggesting that decreases in N1 peak amplitude following 1 kHz tone burst tetanization were similar for both the 1 kHz and 4 kHz stimuli, B = -0.190, SE_B = 0.113, β = -0.144, $SE_β$ = 0.085, t = -1.692, p = 0.092. However, pre-post changes in N1 peak amplitude did interact with age group, suggesting that decreases in N1 peak amplitude following 1 kHz tone burst tetanization were smaller for older adults, B = -0.316, SE_B = 0.114, β = -0.238, $SE_β$ = 0.086, t = -2.770, p = 0.006. Adding audiometric thresholds to the model did not change the pattern of significant relationships or improve model fit, $χ^2(1)$ = 0.010, p = 0.920. To examine the significant interaction between trial and age-group, separate LMER models were fit to the data from younger and older adults. For younger adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.648 μV, SE = 0.334) was larger than to 4 kHz tone bursts (M = -1.865 μV, SE = 0.242) both before and after tetanization, B = 0.873, SE_B = 0.120, β = 0.644, $SE_β$ = 0.088, t = 7.299, p < 0.001. The N1 peak amplitudes of younger adults were also larger prior to 1 kHz tone burst tetanization (M = -2.511 μV, SE = 0.327) than after (M = -2.002 μV, SE = 0.268), B = 0.600, SE_B = 0.120, β = 0.442, $SE_β$ = 0.088, t = 5.010, p < 0.001. Trial did not interact with stimulus, B = -0.181, SE_B = 0.169, β = -0.133, $SE_β$ = 0.125, t = -1.069, p = 0.287. For older adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.378 μV, SE = 0.277) was larger than to 4 kHz tone bursts (M = -1.390 μV, SE = 0.156) both before and after tetanization, B = 1.086, SE_B = 0.106, β = 0.846, $SE_β$ = 0.082, t = 10.256, p < 0.001. N1 peak amplitudes of older adults were also larger prior to 1 kHz tone burst tetanization (M = -1.981 μV, SE = 0.251) than after (M = -1.788 μV,

SE = 0.234), B = 0.291, SE_B = 0.106, β = 0.223, $SE_β$ = 0.082, t = 2.751, p = 0.007. Trial did not interact with stimulus, B = -0.197, SE_B = 0.150, β = -0.153, $SE_β$ = 0.117, t = -1.315, p = 0.190. The results suggest that 1 kHz tone-burst tetanization can decrease the N1 peak amplitudes of responses to both 1 kHz and 4 kHz stimuli in both younger and older adults, though the effect is somewhat lessened in older adults.

4 kHz Tone-Burst Tetanization. For participants who completed the 4 kHz tone burst tetanization condition, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.422 μV, SE = 0.212) was larger than to 4 kHz tone bursts (M = -1.561 μV, SE = 0.139) both before and after tetanization, B = 0.964, SE_B = 0.077, β = 0.737, $SE_β$ = 0.059, t = 12.548, p < 0.001. N1 peak amplitude was also larger prior to 4 kHz tone burst tetanization (M = -2.146 μV, SE = 0.202) than after (M = -1.837 μV, SE = 0.173), B = 0.590, SE_B = 0.101, β = 0.451, $SE_β$ = 0.077, t = 5.841, p < 0.001. N1 peak amplitude did not significantly differ between younger (M = -2.122, SE = 0.195) and older adults (M = -1.901, SE = 0.181), B = 0.376, SE_B = 0.335, β = 0.288, $SE_β$ = 0.257, t = 1.122, p = 0.267. Pre-post changes in N1 peak amplitude did not significantly interact with stimulus, suggesting that decreases in N1 peak amplitude following 4 kHz tone burst tetanization were similar for both 1 kHz and 4 kHz stimuli, B = -0.206, SE_B = 0.109, β = -0.158, $SE_β$ = 0.083, t = -1.901, p = 0.058. However, pre-post changes in N1 peak amplitude did interact with age group, suggesting that decreases in N1 peak amplitude following 4 kHz tone burst tetanization were smaller for older adults, B = -0.320, SE_B = 0.111, β = -0.245, $SE_β$ = 0.085, t = -2.891, p = 0.004. Adding audiometric thresholds to the model did not change the pattern of significant relationships or improve model fit, $χ^2(1)$ = 0.141, p = 0.707. To examine the significant interaction between trial and age-

group, separate LMER models were fit to the data from younger and older adults. For younger adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.443 μV, SE = 0.309) was larger than to 4 kHz tone bursts (M = -1.801 μV, SE = 0.224) both before and after tetanization, B = 0.812, SE_B = 0.122, β = 0.659, SE_β = 0.099, t = 6.660, p < 0.001. The N1 peak amplitudes of younger adults were also larger prior to 4 kHz tone burst tetanization (M = -2.378 μV, SE = 0.303) than after (M = -1.865 μV, SE = 0.232), B = 0.656, SE_B = 0.122, β = 0.533, SE_β = 0.099, t = 5.370, p < 0.001. Trial did not interact with stimulus, B = -0.338, SE = 0.172, β = -0.275, SE_β = 0.140, t = -1.960, p = 0.052. For older adults, the N1 peak amplitude of the response to 1 kHz tone bursts (M = -2.407 μV, SE = 0.290) was larger than to 4 kHz tone bursts (M = -1.395 μV, SE = 0.169) both before and after tetanization, B = 1.069, SE_B = 0.096, β = 0.790, SE_β = 0.071, t = 11.123, p < 0.001. The N1 peak amplitudes of older adults were also larger prior to 4 kHz tone burst tetanization (M = -1.984 μV, SE = 0.266) than after (M = -1.817 μV, SE = 0.245), B = 0.224, SE_B = 0.096, β = 0.165, SE_β = 0.071, t = 2.329, p = 0.021. Trial did not interact with stimulus, B = -0.115, SE_B = 0.136, β = -0.085, SE_β = 0.100, t = -0.845, p = 0.399. As with 1 kHz tone-burst tetanization, the results suggest that 4 kHz tone-burst tetanization can decrease the N1 peak amplitudes of responses to both 1 kHz and 4 kHz stimuli in both younger and older adults, though the effect is somewhat lessened in older adults.

Comparing Results Across Auditory Conditions. Across the independent LMER models, one for each auditory condition (slow presentation, 1 kHz tone-burst tetanization, and 4 kHz tone-burst tetanization), we found that response amplitudes decreased following every experimental manipulation for younger adults and only

following tetanization for older adults. To determine whether the effects of trial differed across our models, we performed Z-tests of the trial-coefficient differences between the auditory conditions for each age-group. Z scores for the coefficient differences were calculated as:

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{{SE_{\beta_1}}^2 + {SE_{\beta_2}}^2}}$$

where β_1 and β_2 are the standardized coefficients from two different models that were compared and SE_{β_1} and SE_{β_2} are the standard errors for the respective standardized coefficients (Clogg et al., 1995; Cohen et al., 2003; Dias et al., 2021; McClaskey et al., 2018; Paternoster et al., 1998).

For younger adults, slow presentation of the 1 kHz and 4 kHz stimuli produced a decrease in N1 peak amplitude that was not significantly different from the decreases in N1 peak amplitude following 1 kHz tone-burst tetanization (Z = 0.162, p = 0.436) and 4 kHz tone-burst tetanization (Z = -0.483, p = 0.315). There was also no difference in the decrease in N1 peak amplitude following 1 kHz tone-burst tetanization and 4 kHz tone-burst tetanization (Z = -0.687, p = 0.246).

Interestingly, even though the LMER models reported above suggest that tetanization is needed to elicit decreases in N1 peak amplitude in older adults, slow presentation of the 1 kHz and 4 kHz stimuli produced a decrease in N1 peak amplitude that was not significantly different from the decreases in N1 peak amplitude following 1 kHz tone-burst tetanization (Z = -0.903, p = 0.183) and 4 kHz tone-burst tetanization (Z = -0.413, p = 0.340). This suggests that for older adults though the decrease in N1 peak amplitude following slow presentation was not significant, this decrease was also not

significantly different from the significant decreases in N1 peak amplitude following 1 kHz and 4 kHz tetanization. Additionally, there was no difference in the decrease in N1 peak amplitude following 1 kHz tone-burst tetanization and 4 kHz tone-burst tetanization ($Z = 0.535$, $p = 0.296$).

The results suggest, overall, that slowly presenting tone-burst stimuli produced similar changes in N1 peak amplitude to those produced by tetanization for both younger and older adults.

Visual Tetanization. For participants who completed the visual tetanization condition, N1 peak amplitude was larger prior to tetanization ($M = -1.170$ μV, $SE = 0.181$) than after ($M = -1.006$ μV, $SE = 0.166$), $B = 0.212$, $SE_B = 0.073$, $\beta = 0.176$, $SE_\beta = 0.061$, $t = 2.891$, $p = 0.004$. N1 peak amplitude did not significantly differ between younger ($M = -0.888$, $SE = 0.192$) and older adults ($M = -1.209$, $SE = 0.158$), $B = -0.279$, $SE_B = 0.342$, $\beta = -0.232$, $SE = 0.284$, $t = -0.817$, $p = 0.418$. Pre-post changes in N1 peak amplitude did not significantly interact with age group, $B = -0.074$, $SE_B = 0.093$, $\beta = -0.061$, $SE_\beta = 0.077$, $t = -0.794$, $p = 0.428$. Adding visual acuity (Snellen) and contrast sensitivity (Pelli-Robson) scores to the model did not change the pattern of significant results or improve model fit, $\chi^2(2) = 1.813$, $p = 0.404$. Similarly, adding tetanization condition (horizontal or vertical tetanization) and stimulus type (horizontal or vertical gradient), along with their interaction terms with trial and age group, did not significantly improve model fit, $\chi^2(6) = 10.403$, $p = 0.110$. The results suggest that visual tetanization can decrease the N1 peak amplitudes of responses to visible sine gradients similarly in younger and older adults. Variability in N1 amplitude was not accounted for by tetanizing condition or stimulus gradient.

Summary. The results of our tetanization study find that the N1 amplitude of auditory and visual evoked potentials decrease after auditory and visual tetanization, respectively. The decreases in N1 amplitude that we observe are not stimulus specific within either sensory modality. Tetanization to either 1 kHz tone bursts or 4 kHz tone bursts resulted in a decrease in the N1 amplitude of potentials evoked by either tone stimulus. Similarly, tetanization to either the horizontal or vertical sine gradient resulted in a decrease in the N1 amplitude of potentials evoked by either sine gradient. We also found that decreases in the N1 amplitudes of auditory evoked potentials were smaller for older adults than for younger adults, the first such report of an age-group differences in modulation of auditory evoked potentials after tetanization. We did not find an age-group difference in the degree to which the N1 amplitude of visual evoked potentials decreased after visual tetanization. Importantly, the decrease in N1 amplitude after auditory tetanization was not significantly different from the decrease in N1 amplitude following slow presentation of 1 kHz and 4 kHz tone bursts, suggesting that high-frequency stimulus presentation is not needed to modulate the N1 amplitude of auditory evoked potentials. Our results join a growing corpus of studies reporting contrasting effects of sensory tetanization on sensory-evoked potentials. To determine the extent to which sensory tetanization effects are significant across studies, we conducted a meta-analysis.

Meta-Analysis

Finding a decrease in N1 amplitude after tetanization is consistent with the findings of some studies, but not others. Our study joins numerous others that have used sensory tetanization to elicit changes in event related potentials. While sensory

tetanization may be a valuable non-invasive approach to induce LTP-like plasticity in humans (Kirk et al., 2021; Sumner et al., 2020b), contrasting effects across studies must be considered. As previously discussed, some studies find that tetanization can increase the amplitude of event related potentials (Kleeva et al., 2022; Lei et al., 2017; Lengali et al., 2021; McNair et al., 2006; Moore et al., 2020; Moore & Loprinzi, 2021; Normann et al., 2007; Ross et al., 2008; Rygvold et al., 2020; Smallwood et al., 2015; Spriggs et al., 2017; Spriggs et al., 2018; Spriggs et al., 2019; Sumner et al., 2018; Wilson et al., 2017; Zak et al., 2018), others find no change in response amplitude following tetanization (D'Souza et al., 2018; Rygvold et al., 2020; Sumner et al., 2018), and still others, including ourselves, find that response amplitudes decrease after tetanization (Kleeva et al., 2022; Klöppel et al., 2015; Rebreikina et al., 2021; Spriggs et al., 2018; Wynn et al., 2019). These conflicting results are troubling, especially when considering that most studies use methods very similar to those initially reported by Clapp et al. (2005a) and Teyler et al. (2005). Recent reviews of the growing number of studies employing tetanization as a method for studying cortical plasticity have not systematically examined the contrasting effects of tetanization reported across studies (Kirk et al., 2021; Sanders et al., 2018; Sumner et al., 2020b). We conducted a meta-analysis to determine whether the average effect of sensory tetanization is significant and, subsequently, whether tetanization is a reliable approach to induce cortical plasticity in the human brain.

Methods

Studies. We first conducted a citation search in Google Scholar to find papers that cite either Clapp et al. (2005a) or Teyler et al. (2005) These two seminal papers

introduced the sensory tetanization paradigm and we reasoned that subsequent papers using the paradigm would site at least one of them. Search results were then screened for empirical studies that used “high frequency stimulation” or “sensory tetanization” to modulate responses to sensory stimuli, resulting in a list of 42 studies. From this list, we excluded 10 studies that did not employ EEG to evaluate changes in sensory-evoked ERPs after tetanization. We then excluded 4 studies that did not parallel the original approach of Clapp et al. (2005a) or Teyler et al. (2005) and conduct ERP analyses that explicitly test for amplitude changes in the N1/N1b component of sensory evoked potentials, the component most widely reported to exhibit change after tetanization. Additionally, we excluded 2 more studies that conducted ERP analyses, but did not explicitly report data for the N1/N1b component. We further excluded 6 studies that lacked a group of younger healthy participants. One other study (Moore & Loprinzi, 2021) was excluded for reporting the same data from a previous study (Moore et al., 2020) to avoid any explicit repetition of study findings. We used the remaining 19 studies, the details for which are reported in Table 1, in our meta-analysis. Studies that did not fit the criteria for our meta-analysis still report findings that are important for understanding the reliability of sensory tetanization effects and are considered in the Discussion.

Analytical Approach. The effect size ($r_{effect\ size}$) for the change in N1/N1b amplitude after tetanization was computed from the descriptive and inferential statistics available from the group of younger healthy adults in each of the 19 studies selected for the meta-analysis. Study effect sizes were transformed into Fisher’s Z scores that were then coded as reflecting an increase (positive value) or decrease (negative value) in

amplitude after tetanization. These Z scores were used as the outcome variable of our meta-analysis (Hansen et al., 2022; Rosenthal, 1991; Rosnow et al., 2000). Many studies included multiple tetanization conditions, where participants were tetanized and tested on different stimuli, like in our own study (e.g., tetanization to 1 kHz and 4 kHz tones and tetanization to horizontal and vertical sine gradients). In such cases, different tetanization conditions were nested within studies. LMER was used to conduct the meta-analysis, allowing us to account for the nested nature of different tetanizing conditions within different studies. The LMER model included the Z scores as the outcome variable and study as a random factor (grouping variable). This intercept-only LMER model was used to determine whether the intercept (the average effect size of N1/N1b amplitude change across all studies) was different from zero. The studies included in this study-level meta-analysis were each conducted at 1 of 9 study sites. As such, many of these studies were conducted at the same study site (by the same research group), yet these studies do not provide enough detail regarding their sample composition to know whether participants' tetanization data overlapped across different studies. To control for this uncertainty, we conducted a follow-up analysis that nested studies within study sites, including both study and study site as random factors (grouping variables). We also tested whether changes in amplitude differed between studies of auditory and visual tetanization.

Results

The intercept of the study-level LMER model was not significant, B = 0.156, SE = 0.086, DF = 19.282, t = 1.811, p = 0.086. Adding sensory modality (visual, auditory) did not improve model fit, $\chi^2(1) = 1.641$, p = 0.200. The study-level analysis found that the

average effect size of N1/N1b amplitude change after sensory tetanization across studies is not significantly different from zero and that effect sizes do not vary significantly between studies of visual and auditory tetanization. The intercept of the site-level LMER model was also not significant, B = 0.096, SE = 0.147, DF = 8.254, t = 0.654, p = 0.531. Adding sensory modality did not improve model fit, $\chi^2(1) = 0.522$, p = 0.470. The results of the site-level LMER model are consistent with the study-level analysis. Both the study-level and site-level analyses suggest that the average effect of sensory tetanization on N1/N1b amplitude is not significant across studies and study sites. To emphasize this point, the average Z score taken from the site-level LMER model intercept translates to a small effect size, $r_{\text{effect size}} = 0.096$. Figure 5 reports the binomial effect size display (BESD) (Rosenthal, 1991) for this $r_{\text{effect size}}$. The BESD illustrates how only 55% of studies using sensory tetanization can be expected to produce a significant change in N1/N1b amplitude after tetanization, and of those studies only 55% of them can be expected to increase response amplitude while the other 45% can be expected to decrease response amplitude. The results of our meta-analysis suggest that sensory tetanization may not be a reliable tool for studying cortical plasticity in young healthy adults.

Discussion

Though there is much interest in developing non-invasive approaches to study cortical plasticity in humans, contrasting results across studies suggest that sensory tetanization (Clapp et al., 2005a; Teyler et al., 2005) may not be a reliable option. Our study of auditory tetanization found that N1 amplitude decreased after tetanization. This decrease in the N1 amplitude of auditory evoked potentials was not specific to the

tetanizing stimulus, such that tetanization to either the 1 kHz or 4 kHz tone decreased the N1 amplitude of responses to both stimuli. We found that older adults exhibited a more modest decrease in N1 amplitude after tetanization, but the effects of tetanization were no different from our slow-presentation control across age-groups. The results of our study of visual tetanization reflected our auditory findings, with participants exhibiting decreases in N1 amplitude after visual tetanization that were not stimulus specific. However, unlike our study of auditory tetanization, these decreases in visual N1 amplitude were similar for younger and older adults. Our auditory and visual tetanization results contribute to the growing number of contrasting effects reported across studies of sensory tetanization. Our meta-analysis of a subset of these studies found that the average effect of sensory tetanization on sensory-evoked ERPs is not significant. Contrasting effects of sensory tetanization on ERP amplitudes, along with other inconsistent and conflicting findings concerning age effects and stimulus specificity, raise important concerns regarding the validity of sensory tetanization as a tool for studying human cortical plasticity in vivo.

Cortical Response Changes Induced by Sensory Tetanization

Contrasting sensory-evoked amplitude changes after tetanization are not limited to the studies included in the meta-analysis. As discussed earlier, fMRI studies report BOLD increases (Clapp et al., 2005b; Wijtenburg et al., 2017; Zaehle et al., 2007) and decreases (Lahr et al., 2014) after sensory tetanization. Similarly, studies concerned primarily with localizing the source of N1/N1b amplitude changes after sensory tetanization report amplitude increases (Spriggs et al., 2019), decreases (Spriggs et al., 2018), and even no change in amplitude (Sumner et al., 2018). Such variability in

amplitude change after sensory tetanization is not limited to the N1/N1b component. C1 amplitude can increase (Rygvold et al., 2020), decrease (Forsyth et al., 2015; Lengali et al., 2021; Zak et al., 2018), or not change (Elvsåshagen et al., 2012) after tetanization. Similarly, P1 amplitude can increase (Elvsåshagen et al., 2012; Normann et al., 2007; Rygvold et al., 2020; Zak et al., 2018) or remain unchanged (Lengali et al., 2021; Teyler et al., 2005) after tetanization. P2 amplitude can also increase (Kleeva et al., 2022; Rygvold et al., 2020; Spriggs et al., 2017; Spriggs et al., 2018), decrease (Forsyth et al., 2015), or not change (Teyler et al., 2005) after tetanization. In fact, even though slightly more studies report ERP component amplitude increases after sensory tetanization, two EEG studies not included in our meta-analysis for reporting global metrics of response amplitude find that overall ERP amplitudes decrease after sensory tetanization (Abuleil et al., 2019; Mears & Spencer, 2012).

The contrasting changes in sensory-evoked response amplitudes after sensory tetanization observed across studies suggests that sensory tetanization may not be a reliable tool for studying LTP-like plasticity. The same study design should not produce amplitude increases attributed to LTP in some studies (e.g., Kirk et al., 2021; Sanders et al., 2018; Sumner et al., 2020b) and amplitude decreases sometimes attributed to long-term depression (LTD, the opposite of LTP) in others (e.g., Abuleil et al., 2019; Kleeva et al., 2022). Any meaningful inference of the mechanisms that underlie changes in sensory-evoked response amplitudes after sensory tetanization are difficult given the contrasting effects reported across studies. Additionally, our finding that changes in N1 amplitude after tetanization do not differ from changes in N1 amplitude after slow stimulus presentation further complicates interpretation of current and past results.

Importantly, the contrasting effects of tetanization on ERP amplitude changes are only one example of conflicting results found across studies.

Age Effects on Sensory Tetanization

We found that older adults exhibited a significant decrease in the N1 amplitudes of auditory-evoked and visual-evoked potentials after auditory and visual tetanization, respectively. Finding that older adults can exhibit a change in sensory-evoked response amplitudes after sensory tetanization is inconsistent with studies finding that older adults do not demonstrate *visual*-evoked response amplitude changes after *visual* tetanization (Abuleil et al., 2019; Spriggs et al., 2017). There is one study that reported a change in visual-evoked response amplitudes in older adults, but the response amplitudes *increased* after visual tetanization, contrasting with our results (de Gobbi Porto et al., 2015). Our finding that older adults demonstrated a smaller decrease in *auditory*-evoked response amplitudes than younger adults after auditory tetanization is consistent with one study finding similar age-group differences in the decrease in *visual*-evoked amplitudes after visual tetanization (Abuleil et al., 2019), but it is inconsistent with another study finding that age is unrelated to changes in *visual*-evoked response amplitudes after visual tetanization (Valstad et al., 2020). In contrast, our finding that decreases in *visual*-evoked response amplitudes after visual tetanization are similar for younger and older adults is inconsistent with the one study finding older adults exhibit a smaller decrease in *visual*-evoked response amplitudes after visual tetanization (Abuleil et al., 2019), but it is consistent with the study finding no relationship between age and visual tetanization (Valstad et al., 2020). Finding that the effects of auditory tetanization are weaker for older adults has not been reported previously. It is tempting to infer a

relationship between age and the mechanisms that underly auditory plasticity from these results, as others have done when studying age-group differences in visual tetanization (Abuleil et al., 2019; Spriggs et al., 2017), but the inconsistencies across our results and others' described above raise concerns regarding the reliability and validity of such age effects when using sensory tetanization to study age-related differences in neural plasticity.

Stimulus Specificity of Sensory Tetanization

We found no evidence of stimulus-specific changes in sensory-evoked response amplitudes after sensory tetanization. Tetanization to either the 1 kHz or 4 kHz tone similarly decreased the auditory-evoked response amplitudes of both the 1 kHz and 4 kHz tones. Similarly, tetanization to either the horizontal or vertical sine gradient similarly decreased the visual-evoked response amplitudes of both the horizontal and vertical sign gradients. Other studies have failed to find consistent stimulus-specific changes in sensory evoked responses after similar auditory tone-burst tetanization (Kleeva et al., 2022; Rebreikina et al., 2021) and visual sine-gradient tetanization (Cooke & Bear, 2010; Sumner et al., 2018). However, several other studies have found changes in sensory-evoked responses that are specific to the tetanized auditory tone-burst (Kompus & Westerhausen, 2018; Mears & Spencer, 2012) and visual sine-gradient (McNair et al., 2006; Ross et al., 2008; Spriggs et al., 2017; Wynn et al., 2019). The results across studies suggest that tetanization effects may sometimes affect mechanisms that generalize across stimulus types. What determines when sensory tetanization effects are sometimes stimulus-specific is unclear.

Conclusion

Our study of auditory and visual tetanization joins a large body of work with highly variable findings and contrasting results. Changes in N1/N1b amplitude after sensory tetanization contrast across different studies. Studies testing the extent to which tetanization effects are modulated by age or whether tetanization effects are specific to the tetanizing stimulus have also yielded inconsistent results. Variability is also found in how long tetanizing effects last and whether tetanization effects relate to behavior (for reviews, see Kirk et al., 2021; Sanders et al., 2018; Sumner et al., 2020b). Though we did not discuss these last two topics in detail, they contribute to the overall lack of reliable results evident across sensory tetanization studies.

Variability in the effect of an experimental paradigm across studies is inevitable. Aside from the variability attributed to different researchers, equipment, and samples of participants (just to name a few), methods are often manipulated to test new hypotheses and advance understanding of a mechanism. However, a valid paradigm will reliably produce an expected effect across studies. Our meta-analysis attempted to reduce as much variability across studies as possible by selecting only those studies that reported an effect of sensory tetanization (auditory or visual) on the amplitude of the N1/N1b component of sensory-evoked potentials recorded from groups of younger healthy adults. Yet despite these controls, we still found that the average effect of sensory tetanization across studies was not significant.

Overall, we must conclude from our meta-analysis and our critical review of the extant literature that sensory tetanization may not be a reliable method for studying cortical plasticity in the human brain.

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Table 1
Summary of studies included in the meta-analysis

Study Site	Study	Sense	Tetanic Stimulus	Tetanization Rate	t	df	p	$r_{effect\ size}$	Fisher's Z
General Hospital of the PLA	Lei et al., 2017	Auditory	1000Hz	40Hz	10.384	9	0.000	0.961	0.849
		Auditory	6000hz	40Hz	12.953	9	0.000	0.974	0.942
		Auditory	1000HzNBN	40Hz	21.262	9	0.000	0.990	1.154
		Auditory	6000HzNBN	40Hz	12.084	9	0.000	0.971	0.913
		Auditory	WhiteNoise	40Hz	25.568	9	0.000	0.993	1.233
Medical University of South Carolina	Dias et al., 2022	Auditory	1000Hz	13Hz	-5.477	19	0.000	0.782	-0.457
		Auditory	4000Hz	13Hz	-4.719	19	0.000	0.735	-0.408
		Visual	Sine Gradient	8.6Hz	-3.469	17	0.003	0.644	-0.332
Russian Academy of Sciences	Rebreikina et al., 2021	Auditory	1020Hz	26Hz	-2.897	21	0.009	0.534	-0.259
	Kleeva et al., 2022	Auditory	1020Hz	13.3Hz	-3.974	28	0.000	0.601	-0.301
University of Auckland	Clapp et al., 2005	Auditory	1000Hz	13Hz	3.571	10	0.005	0.749	0.421
	Teyler et al., 2005	Visual	Checkerboard	9Hz	2.950	5	0.032	0.797	0.473
	McNair et al., 2006	Visual	Sine Gradient	8.6Hz	4.785	7	0.002	0.875	0.588
	Ross et al., 2008	Visual	Sine Gradient	8.6Hz	2.131	17	0.048	0.459	0.216
	Smallwood et al., 2015	Visual	Sine Gradient	8.6Hz	4.118	20	0.001	0.677	0.358
	Srpiggs et al., 2017	Visual	Sine Gradient	8.6Hz	1.953	28	0.061	0.346	0.157
	Wilson et al., 2017	Visual	Checkerboard	9Hz	2.420	11	0.034	0.589	0.294
University of California, Los Angeles	Wynn et al., 2019	Visual	Sine Gradient	10Hz	-1.840	64	0.070	0.224	-0.099
University of Freiburg	Normann et al., 2007	Visual	Checkerboard	2Hz	1.515	73	0.134	0.175	0.077
	Klöppel et al., 2015	Visual	Checkerboard	2Hz	-6.824	36	0.000	0.751	-0.424
University of Mississippi	Moore et al., 2020	Visual	Checkerboard	8.6Hz	2.761	18	0.013	0.545	0.266
University of Oslo	Elvsåshagen et al., 2012	Visual	Checkerboard	2Hz	2.450	39	0.019	0.365	0.166
	Rygvold et al., 2020	Visual	Checkerboard	9Hz	7.001	92	0.000	0.590	0.294
		Auditory	1000Hz	9Hz	0.009	92	0.993	0.001	0.000
	Lengali et al., 2021	Visual	Checkerboard	8.55Hz	3.986	39	0.000	0.538	0.261
Yale University	D'Souza et al., 2018	Visual	Checkerboard	8.87Hz	-0.680	27	0.251	0.130	-0.057

NOTE: t-test values represent the inferential test for pre-post tetanization differences. All data comes from groups younger healthy participants (controls).

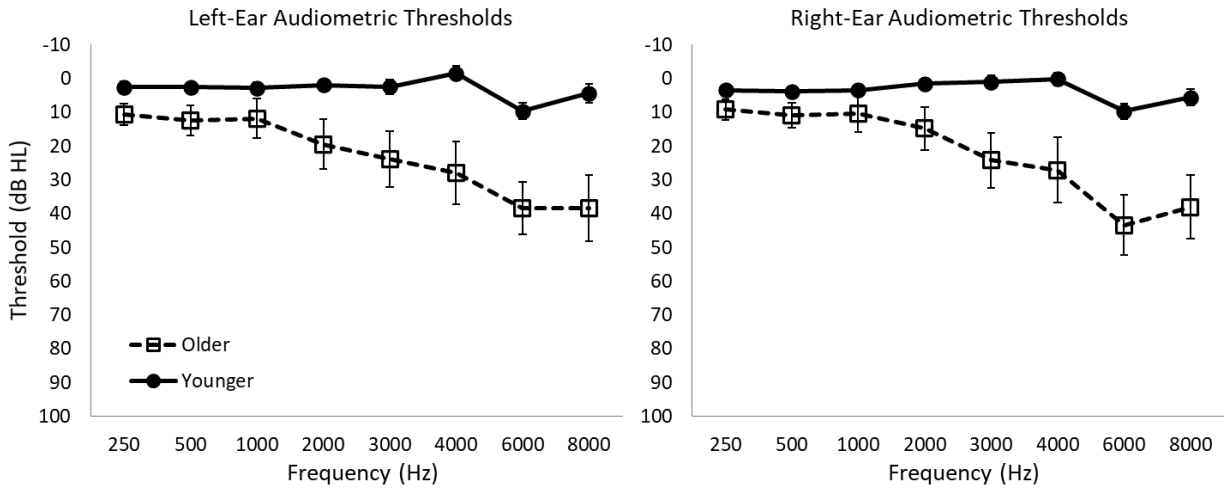

Figure 1. Audiometric thresholds for the left and right ears of younger and older adults. Error bars represent standard error (SE) of the mean.

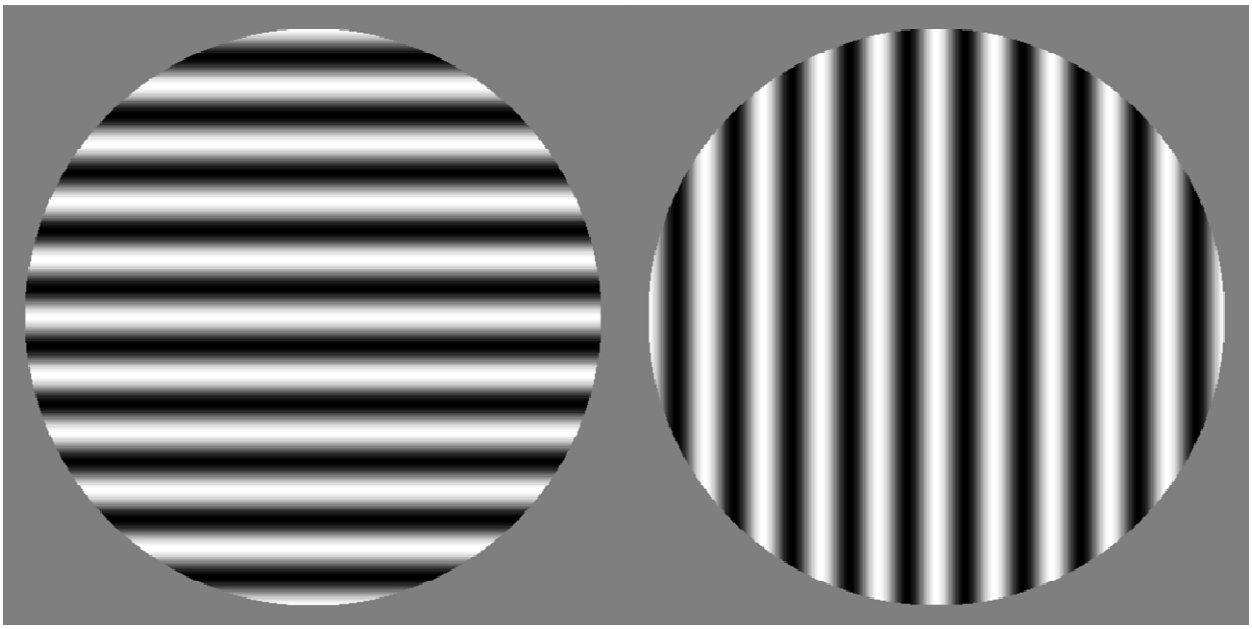

Figure 2. The horizontal (left) and vertical (right) sine gradients used in the visual tetanization task.

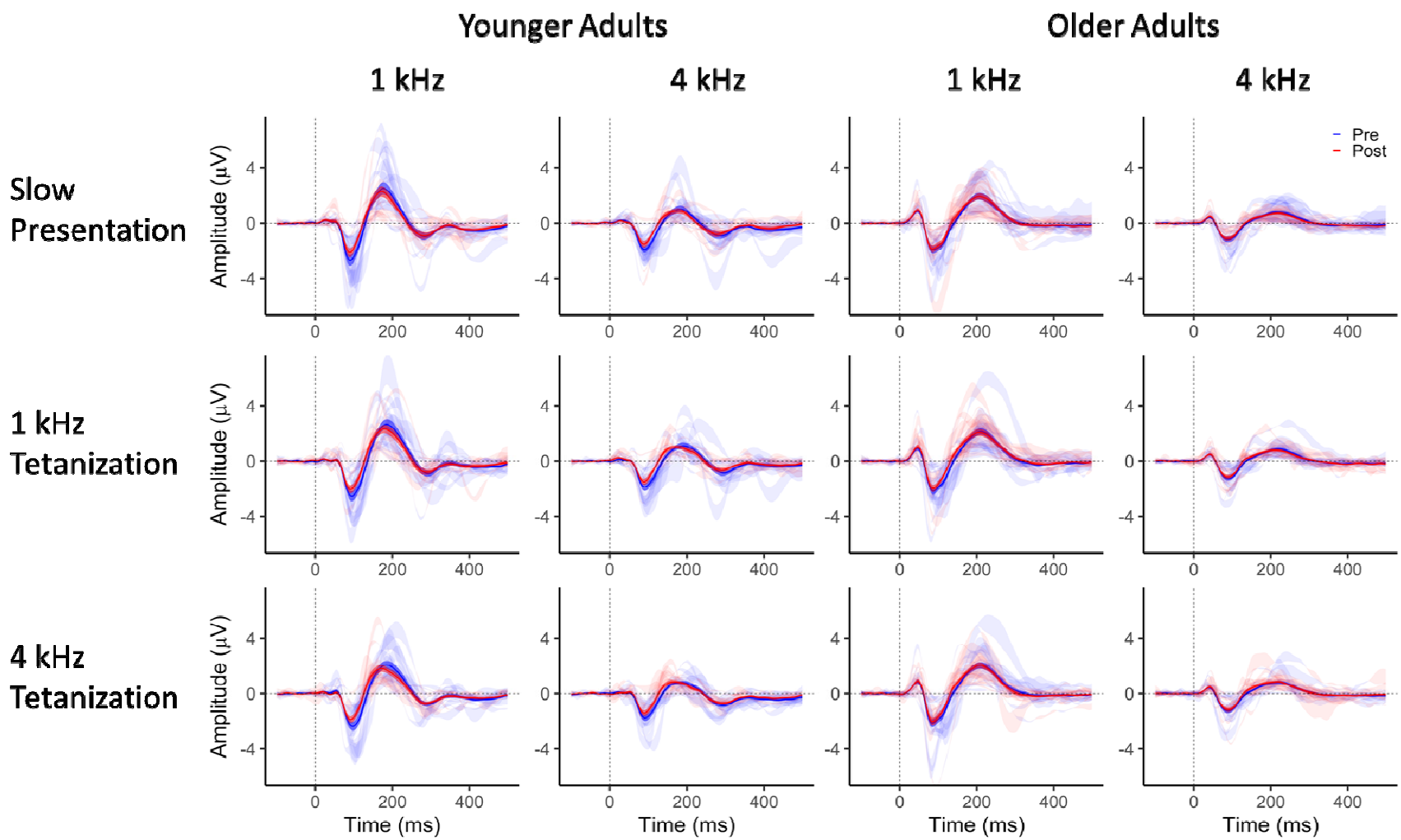

Figure 3. Average ERP waveforms for the different auditory tetanization conditions. Solid blue = before tetanization, solid red = post tetanization. Shading around each solid line represents the standard error (SE) of the average waveform. The

pre-post waveforms for individual participants are plotted as ribbons in the background of the average waveforms. Light blue shading of these ribbons highlights where a participant's pre-tetanization waveform was larger than their post-tetanization waveform and light red (pink) shading highlights where a participant's post-tetanization waveform was larger than their pre-tetanization waveform.

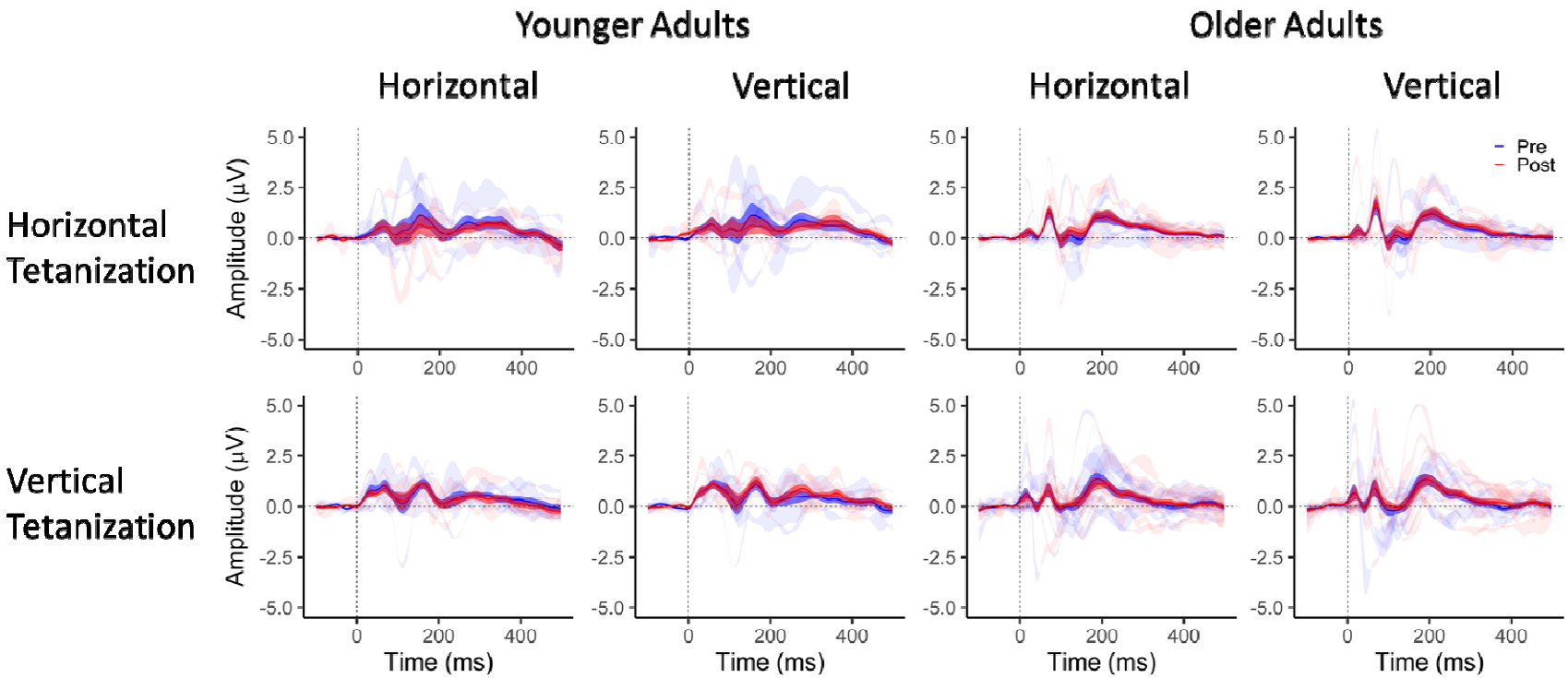

Figure 4. Average ERP waveforms for the different visual tetanization conditions. Solid blue = before tetanization, solid red = post tetanization. Shading around each solid line represents the standard error (SE) of the average waveform. The pre-post waveforms for individual participants are plotted as ribbons in the background of the average waveforms. Light blue shading of these ribbons highlights where a participant's pre-tetanization waveform was larger than their post-tetanization waveform and light red (pink) shading highlights where a participant's post-tetanization waveform was larger than their pre-tetanization waveform.

Binomial Effect Size Display	Significant Amplitude Change	Non-Significant Amplitude Change
Amplitude Increases	55%	45%
Amplitude Decreases	45%	55%

Figure 5. Binomial effect size display (BESD) for the average effect size ($r_{effect\ size}$) derived from the site-level LMER meta-analysis.