Do visual and auditory stimulus-specific response modulation reflect different mechanisms of neocortical plasticity?

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Abstract
Stimulus response modulation (SRM) of sensory evoked potentials represents a promising method as a non-invasive index of long-term potentiation (LTP)-like synaptic plasticity in the human sensory cortices. As of today, however, no consensus exists regarding which experimental parameters elicit the most robust SRM response. The aim of the current study was twofold; firstly, we aimed to replicate former studies demonstrating visual SRM in healthy adults. Second, we integrated visual and auditory stimuli within the same SRM recording session to assay potential cross-modal associations. Such an association between modalities would strengthen the assumption that the SRM effect reflects common mechanisms underlying synaptic plasticity rather than reflecting modality-specific phenomena. A replication of previous findings showing robust potentiation of the visual evoked potential was evident, supporting the majority of previous work using similar paradigms, lending further support to the notion that high-frequency visual stimulation is a viable probe into LTP-like synaptic plasticity in the human visual cortex. The auditory evoked potentials (AEPs) did not, however, fully replicate previous work, though a significant increase of temporally later AEP components was found. In contrast to our hypothesis, there were no significant within-subject cross-modality correlations between the visual and auditory SRM. This lack of significant association might suggest that auditory and visual SRM depend on different mechanisms, and that further SRM studies on non-invasive LTP-like synaptic plasticity should focus on optimizing paradigms within the visual modality.

KEYWORDS
cross-modality, LTP, sensory evoked potentials, synaptic plasticity

Abbreviations: AEPs, Auditory evoked potentials; ANOVA, Analysis of variance; BOLD, Blood-oxygen-level-dependent; EEG, Electroencephalography; ERPs, Event-related potentials; fMRI, functional magnetic resonance imaging; HFS, High-frequency stimulation; LDAEP, Loudness-dependent auditory evoked potential; LTP, Long-term potentiation; NMDA, N-methyl-d-aspartate; SEM, Standard error of the mean; SRM, Stimulus-specific response modulation; VEPs, Visual evoked potentials.

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1 | INTRODUCTION

1.1 | Background

A central tenet of cognitive neuroscience is that memory is encoded as activity-driven changes in the strength of synaptic connections (Bliss, 2016). The Hebbian theory from the mid-20th century postulates that synaptic strength is modifiable and that synaptic efficacy increases in the event of repeated coincidental pre- and post-synaptic stimulation of a synapse, summarized as ‘cells that fire together, wire together’ (Bliss & Collingridge, 1993). Strong empirical support for the Hebbian theory was provided with the discovery of long-term potentiation (LTP). LTP was first demonstrated in vivo by inducing synaptic plasticity in the rodent hippocampal formation through repetitive electrical stimulation of the perforant path to the dentate gyrus (Bliss & Lomo, 1973). Experimentally induced LTP displays certain core properties foreshadowed by Hebb, such as longevity, input-specificity and associativity, that individually and collectively point towards LTP representing a mechanism for neural information storage (Cooke & Bear, 2012). Originally demonstrated in hippocampal slices, LTP expression has since been demonstrated in other parts of the brain such as the primary visual cortex of rodents (Heynen & Bear, 2001).

Due to the inherent invasiveness of inducing LTP directly in the brain, studies on human tissue are few, with the exception of demonstrations ex vivo (Beek, Goussakov, Lie, Helmstaedter, & Elger, 2000). As of now there is no consensus on what constitute definite non-invasive in vivo research paradigms to induce LTP-like plasticity in the human brain. Developing non-invasive techniques to index human LTP-like effects in vivo in order to enable larger-scale studies on the phenomenon is therefore warranted.

1.2 | Stimulus-specific response modulation

It is widely believed that many, if not most, cortical synapses display some sort of activity-dependent synaptic plasticity (Bliss, 2016). As non-invasive assessment of the human neocortex is accessible through electroencephalographic (EEG) methods, studies using sensory event-related potentials (ERPs) have approached the study of human synaptic plasticity through sensory-induced modulation of ERPs originating in the sensory cortices (e.g. Teyler et al., 2005). Several studies suggest that stimulus-specific response modulation (SRM) is a promising candidate indexing synaptic plasticity in humans. High-frequent or prolonged sensory stimulation evoke local field potentials measured as visual or auditory evoked potentials (AEPs), primarily reflecting post-synaptic potentials in sensory cortices. The relative amplitude change in evoked potentials observed following high-frequent or prolonged stimulation could represent a non-invasive probe of synaptic plasticity in the human cortex. Studies using both repetitive visual (e.g. Teyler et al., 2005) and auditory (e.g. Clapp, Kirk, Hamm, Shepherd, & Teyler, 2005) high-frequency stimulation (HFS) have shown modulation of the amplitudes of visual evoked potentials (VEPs) and AEPs, compared to baseline levels. This stimulus-specific response modulation resembles the electrically induced LTP seen in animal studies by displaying defining characteristics of LTP, such as duration, input-specificity and NMDA receptor dependency (Kirk et al., 2010). The close resemblance between the synaptic plasticity seen with high-frequency sensory stimulation and hippocampal LTP has led to the former being suggested to represent a LTP-like synaptic plasticity effect (Cooke & Bear, 2010).

1.3 | Modality-specificity in stimulus response modulation

Although human research using SRM paradigms shows considerable promise, as of today no consensus exist on what paradigm parameters elicit the most robust measure of LTP-like synaptic plasticity. Certain key elements, such as simple sensory stimulus presentation, a high-frequent or prolonged stimulation block and several post-stimulation recordings, are present across paradigms, but there is considerable variation in both stimulus design and parameters thought to induce the LTP-like effects (Sanders, Thompson, Corballis, Maslin, & Searchfield, 2018). Most SRM research has focused on eliciting visually evoked potentials, as using visual stimuli has yielded the most potent effects (e.g. Cooke & Bear, 2012). A few studies have utilized AEPs, reporting significant, but somewhat more modest, modulation effects (e.g. Clapp, Kirk, et al., 2005).

In order to replicate, this study model the research paradigms utilized in the first known successful demonstrations of LTP-like synaptic plasticity in the visual (Teyler et al., 2005) and auditory (Clapp, Kirk, et al., 2005) cortex respectively. Both studies used high-frequency (9 Hz) stimulation to induce the modulation effect, and subsequent studies have successfully utilized these paradigms for inducing increased amplitude of sensory evoked potentials post-modulation (e.g. Abuleil, Mcculloch, & Thompson, 2019; Smallwood et al., 2015; Spriggs, Cadwallader, Hamm, Tippett, & Kirk, 2017). Other studies have utilized low-frequent (2 Hz), prolonged (10 min) stimulation to successfully induce modulation of the VEP (Elvshagen et al., 2012; Normann, Schmitz, Fürmaier, Döing, & Bach, 2007). The high-frequency visual stimulation was designed as an analogue to the high-frequency electrical stimulation used to induce synaptic plasticity in rodents, and is referred to as a ‘visual tetanus’ (Teyler et al., 2005). Thusly, it is not the stimulation protocols in themselves that are LTP-like, the response in the visual
cortex is. Accordingly, the duration and frequency are secondary to the timing when inducing either LTP or long-term depression (LTD). Bliss and Cooke (2011) refer to animal studies demonstrating that if an action potential is repeatedly evoked before pre-synaptic stimulation, a depression of synaptic strength will follow given that the interval is brief enough. If the pre-synaptic activation precedes the post-synaptic spike, triggering an action potential, then LTP would be induced (Bliss & Cooke, 2011). Study paradigms using tetanic sensory stimulation to induce VEP or AEP modulation have shown similar component-specific increase of the visual N1b and the auditory N1 component respectively (Clapp, Kirk, et al., 2005; Teyler et al., 2005). Studies coupling the high-frequency SRM paradigms with functional magnetic resonance imaging (fMRI) demonstrated increased BOLD responses to the sensory stimulation localized in the respective sensory cortices post-HFS (Clapp, Zaehle, et al., 2005; Zaehle, Clapp, Hamm, Meyer, & Kirk, 2007). These fMRI studies complement the original EEG studies showing the locus of the modulation to be the extrastriate visual cortex for modulation of the VEP, and the primary auditory cortex for the modulation of the AEP (Sanders et al., 2018).

Finding a cross-modal association between modulation of amplitudes after both visual and auditory HFS would indicate possible common underlying mechanisms for LTP-like SRM plasticity expressed in the two modalities. This would provide further evidence that the SRM effect potentially reflect common mechanisms underlying LTP-like synaptic plasticity in the brain rather than being limited to what presently may be characterized as inadequately understood modality-specific cortical effects.

To our knowledge, the current study is the first study to integrate high-frequency visual and auditory stimulation within the same SRM paradigm. The aim of the current study is firstly to replicate and confirm previous studies showing robust modulation effects using high-frequency stimulation in a larger healthy sample across different age groups. Secondly, if SRM indeed provides a robust measure of LTP-like synaptic plasticity in humans, we should expect significant within-subject correlation of modulation magnitudes. Consequently, an overlap in intra-individual responder rates (i.e. participants with observable amplitude modulations) across sensory modalities should be evident, that is individuals displaying LTP-like synaptic plasticity should theoretically display this effect in both the visual and auditory modality.

2  |  MATERIALS AND METHODS

2.1  |  Participants

One hundred and one healthy subjects provided informed consent and participated in the study. Due to unsatisfactory data quality (n = 5) and technical issues during recording (n = 3), eight subjects were excluded, leaving a total of 93 participants (61 females, 32 males; mean age 35.9 years, SD 13.62, range 17–71) available for statistical analyses. Normal or corrected-to-normal vision, normal hearing and absence of any psychiatric or neurological condition were required. Regarding auditory integrity, all participants were screened using a basic audiometry protocol. Participants were recruited through social media platforms (Facebook and Instagram), in addition to local advertisement. All procedures were approved by the regional ethics committee (ref. no: 2016/2003).

2.2  |  Experimental setup

The experimental protocol consisted of two individual ERP paradigms, run sequentially, in addition to a period of resting-state EEG recording and a loudness-dependent auditory evoked potential (LDAEP) paradigm. The LDAEP paradigm, not included in the current analyses, was run between post-stimulation blocks 4 and 5 of the visual stimulus-selective response modulation (V-SRM) paradigm. Likewise, the resting-state EEG recording is not included in the current analysis. A total of 8 min of resting was recorded between post-stimulation blocks 4 and 5 of the auditory stimulus-selective response modulation (A-SRM) paradigm. The whole session lasted approximately 50 min (see Figures 1 and 2 for...
the protocol layout). This paper reports results from the visual and the auditory stimulus-selective response modulation paradigms.

Participants were comfortably seated 70 cm from a 24” LCD screen (BenQ, model ID: XL2420-B) on which visual stimuli were presented. Both visual and auditory stimuli were programmed in the Psychtoolbox-3 environment (Kleiner et al., 2007) and run on the MATLAB platform (version 2015a; MathWorks, Natick, MA, USA). The auditory stimuli were delivered binaurally through Etymotic ER-1 in-ear earphones (Etymotic Research, Inc.). Instructions were given to the participants verbally prior to the start of the experimental session, and written paradigm-specific reminders were given on-screen before the onset of each paradigm. When not reading instructions, participants were required to fixate on a red circular dot centrally positioned on the screen.

Both SRM paradigms featured two pre-HFS blocks (baseline), one HFS block and five post-HFS blocks identical to the baseline blocks. Each pre-/post-HFS block consisted of 40 trials, including five target trials. In the visual SRM paradigm (V-SRM), a trial corresponds to one reversal of a black and white checkerboard texture (check size approximately 1.0°), whereas in the auditory SRM paradigm (A-SRM), the equivalent is the playback of a tone (frequency = 1,000 Hz; duration = 50 ms; intensity = 70 dB SPL; edge trim = 5 ms ramp). The tones presented in the LDAEP paradigm did not overlap in intensity with the tones presented in the A-SRM to avoid possible interference effects. Target trials in the V-SRM refer to trials cueing the participants, by switching the colour of the fixation dot briefly to green, to press a response button. Target trials were included to ensure attention and prevent fatigue and drowsiness, but were not included in the ERP analyses. Trials in the pre-/post-HFS blocks in the V-SRM paradigm were separated by a stimulus onset asynchrony (SOA) value in the 500–1,500 ms range. There is no clear consensus regarding what represent the optimal SOA value in V-SRM experiments, and the range chosen in the current experiment encompasses SOA values reported in related experiment paradigms (Jahshan, Wynn, Mathalon, & Green, 2017; Teyler et al., 2005). The corresponding SOA range in the A-SRM pre-/post-HFS blocks was 1,800–2,600 ms, in line with previous paradigms (Clapp, Zaehle, et al., 2005). Consequently, each probing block (pre- and post-HFS blocks) had a duration of approximately 40 s in the V-SRM paradigm, and approximately 88 s in the A-SRM paradigm. The HFS block was 120 s in both paradigms. In the visual paradigm, the post-HFS blocks were recorded after approximately 2, 4, 6, 8 and 19 min respectively. In the auditory paradigm, the post-HFS blocks were recorded after approximately 2, 4.5, 8, 10.5 and 20 min respectively.

2.3 Data acquisition

Electroencephalographic data were recorded using a 64-channel (Ag-AgCl electrodes) BioSemi ActiveTwo system (BioSemi B.V., Amsterdam). The electrodes were spatially positioned according to the international 10–20 system. Four additional external electrodes were positioned around the eyes; laterally, and inferior/superior to the right eye (approximately corresponding to the 10–20 system locations of LO1, LO2, IO2 and SO2) and at the earlobes (locations A1 and A2). The raw data were recorded at a sampling rate of 1,024 Hz. Aside from the hardware anti-aliasing filter, no online filters were applied. Event markers were passed from the MATLAB platform to the EEG data through a 25-pin serial port.

2.4 EEG preprocessing

The EEG data were preprocessed in the EEGLAB (version 2019.1) environment (Delorme & Makeig, 2004) on the MATLAB platform (version 2019b). Continuous EEG data were re-referenced to the average of the 64 EEG channels and resampled to half of the original sampling rate. The EEG segments containing V-SRM and the A-SRM data were extracted, and data not relevant to these paradigms were discarded from further preprocessing.
First, a high-pass filter (EEGLAB default, lower bound 1 Hz, with data edge padding) was applied to remove the DC offset and low-frequency drifts. Channels with an amplitude SD outside the interval 1–25 µV were then iteratively removed from the reference signal. The ZapLine tool (de Cheveigné, 2020) and a low-pass filter (EEGLAB default, upper bound 30 Hz, with data edge padding) were used to suppress line noise and high-frequency noise respectively. Portions of the data with significant noise in >50% of the channels were rejected. Remaining channels with excessive noise in >10% of the remaining data points were removed. Signal artefacts attributable to eye blinks and movements were removed using independent component analysis (Delorme & Makeig, 2004). The EEGLAB implementation of the second-order blind separation algorithm (Belouchrani, Abed-Meraim, & Cardoso, 1993) was used for component decomposition. Ocular components were identified with the ICLabel tool (Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019). A final removal of noisy channels was conducted with tools from the PREP pipeline toolbox (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015). All the removed channels were then spherically interpolated.

V-SRM and A-SRM epochs were extracted into separate files from the cleaned data. The epochs were time-locked to the onset of the stimuli (epoch length: 500 ms, including a 100-ms pre-stimulus period for baseline correction). Epochs containing signals above/below ±50 µV in channels spatially relevant to the subsequent ERP measurement were rejected. Prior to peak measurements, the signals were re-referenced to AFz and the mean of T7 and T8 for VEP and AEP respectively.

2.5 | Statistical analyses

VEP components C1, P1 and N1 and AEP components N1 and P2 were identified individually for each subject by visual inspection. This was done by defining a time window from the modality-specific grand average for each subject. Block-specific peaks were then defined as the minimum/maximum amplitude data points inside this time window. All peak identifications were visually verified independently by three viewers. Amplitude was measured at these subject-specific latencies for each block separately. An additional difference component was computed for each modality; visual P1-N1 peak-to-peak amplitude and auditory N1-P2 peak-to-peak amplitude.

The measurements were obtained from an occipital electrode cluster (mean amplitude of O1, Oz and O2) for the VEP waveforms, and from a frontocentral electrode cluster (mean amplitude of FC1, Fz, FC2, FCz and Cz) for the AEP waveforms. These electrode clusters were selected in order to capture the maximum difference between baseline and post-HFS blocks, as revealed by the topographic amplitude maps at the time points of the mean component peak latencies (see Figure 3a,b for topographic amplitude maps).

For enhanced readability, the VEP and AEP components are labelled with the prefixes V and A respectively. For both the V-SRM and the A-SRM data, the two pre-modulation blocks were averaged into one block, labelled baseline (BL). Post-HFS blocks were analysed separately and labelled Post-HFS 1, 2, 3, 4 and 5 respectively.

To assess the main effect of the modulation block on the component amplitudes, each component was tested using separate repeated measure ANOVAs with block (BL versus Post-HFS 1 versus Post-HFS 2 versus Post-HFS 3 versus Post-HFS 4 versus Post-HFS 5) as within-subject factor. Each component was subjected to post hoc paired samples t tests comparing each post-HFS block amplitude to the associated BL block amplitude separately.

To examine the rate to which subjects displayed a modulation effect, the difference between each post-modulation block and BL was computed for all components for each subject separately. Each difference score was then categorized as indicating either a responder or non-responder based on whether it reflected amplitude increase or reduction.

In an effort to assess between-modality effects, difference scores were computed by subtracting BL amplitudes from the average of all post-HFS blocks for the two peak-to-peak components; V-P1-N1 and A-N1-P2. Subsequently, the scores of subjects who fulfilled the criteria of responder in both modalities were selected and correlated across modalities.

For all statistical analyses, a two-tailed p-value of <0.05 was considered significant. Greenhouse–Geisser corrections were applied to all analyses of variance with repeated measures. Effect sizes are written as Eta-squared ($\eta^2$). Pearson’s correlation, corrected for multiple comparisons, was employed to analyse age effects on amplitude modulation and between-modality effects. Statistical analyses were performed using MATLAB (version 2019b).

3 | RESULTS

3.1 | Visual HFS modulation

3.1.1 | Main effect of block

A significant main effect of HFS on amplitudes was observed in all VEP components; V-C1 [$F(5.802) = 4.420, p < 0.001, \eta^2 = 0.059$], V-P1 [$F(4.254) = 11.593, p < 0.001, \eta^2 = 0.244$], V-N1 [$F(4.606) = 8.991, p < 0.001, \eta^2 = 0.089$] and V-P1-N1 [$F(4.035) = 29.633, p < 0.001, \eta^2 = 0.244$]. See Figure 4a for grand average VEP waveforms.
3.1.2 | Block-wise effect of visual HFS

For all VEP components, each post-HFS block was separately compared to the associated BL block (Figure 5a). For the V-C1 component, Post-HFS 1 \[ t(92) = -3.304, p < 0.001 \], Post-HFS 2 \[ t(92) = -5.323, p < 0.001 \], Post-HFS 3 \[ t(92) = -2.257, p = 0.026 \] and Post-HFS 4 \[ t(92) = -3.887, p < 0.001 \] displayed reduced amplitudes compared to baseline, whereas Post-HFS 5 did not \[ t(92) = -1.375, p = 0.173 \]. Similarly, for the V-P1 component, significant

**FIGURE 3** (a) Topographical voltage maps of the VEP components. Time points are defined by the average peak latencies across all subjects. The difference maps (bottom row) are computed by subtracting the baseline voltage from the post-HFS average. (b) AEP components equivalent to a
increases in amplitude from BL were observed in Post-HFS 1 \(t(92) = -4.961, p < 0.001\), Post-HFS 2 \(t(92) = -4.681, p < 0.001\), Post-HFS 3 \(t(92) = -3.484, p = 0.001\) and Post-HFS 4 \(t(92) = -5.804, p < 0.001\) but not in Post-HFS 5 \(t(92) = 0.445, p = 0.657\). Likewise, the V-N1 amplitude showed a significant increase compared to BL in Post-HFS 4 \(t(92) = -5.804, p < 0.001\) but not in Post-HFS 5 \(t(92) = 0.445, p = 0.657\). Likewise, the V-N1 amplitude showed a significant increase compared to BL in Post-HFS.
As seen in Table 1, the visual component displaying the highest responder rate was the V-P1-N1 peak-to-peak component in post-HFS blocks 1–4. Generally, the fraction of subjects defined as responders to high-frequency stimulation were lower in the latest post-HFS block (Post-HFS 5), and the fraction of responders were generally higher in the temporally later components (V-N1 and V-P1-N1 peak-to-peak).

### 3.2 Auditory HFS modulation

#### 3.2.1 Main effect of block

Of the AEP components, a significant main effect of block on amplitude was evident for both A-P2 [F (4,523) = 8.896, p < 0.001, ηp² = 0.088] and A-N1-P2 [F (4,665) = 10.430, p < 0.001]. The effect was not significant in A-N1 [F (4,431) = 1.189, p = 0.313, ηp² = 0.013]. See Figure 4b for grand average AEP waveforms.
3.2.2 | Block-wise effect of auditory HFS

For the AEP components, each post-HFS block was separately compared to the associated BL block (Figure 5b). For the A-N1 component, no post-modulation blocks were significantly different from baseline. In contrast, the A-P2 component displayed a significant amplitude increase in all post-HFS blocks compared to baseline, Post-HFS 1 $[t(92) = -4.228, p < 0.001]$, Post-HFS 2 $[t(92) = -2.983, p = 0.004]$, Post-HFS 3 $[t(92) = -5.023, p < 0.001]$, Post-HFS 4 $[t(92) = -3.283, p = 0.001]$ and Post-HFS 5 $[t(92) = -7.700, p < 0.001]$. A similar pattern was observed for the peak-to-peak component (A-N1-P2); an increase in amplitude compared to baseline was evident in all post-stimulation blocks with the exception of Post-HFS 4. Post-HFS 1 $[t(92) = -5.045, p < 0.001]$, Post-HFS 2 $[t(92) = -3.318, p = 0.001]$, Post-HFS 3 $[t(92) = -4.005, p < 0.001]$ and Post-HFS 5 $[t(92) = -7.096, p < 0.001]$.

3.2.3 | Responder rates

As seen in Table 1, the auditory component displaying the highest responder rates was the N1-P2 peak-to-peak component in post-HFS block 5. Similar to the visual component, the fraction of subjects defined as responders to high-frequency stimulation increase with later components.

3.3 | Latency differences

3.3.1 | Main effect of block

A significant main effect of HFS on latency was observed in all VEP components; V-C1 $[F (3.677) = 4.900, p = 0.001, \eta^2 = 0.051]$, V-P1 $[F (4.303) = 3.798, p = 0.004, \eta^2 = 0.040]$ and V-N1 $[F (3.937) = 3.498, p = 0.008, \eta^2 = 0.037]$. There were no significant effects of modulation block on latency in any of the AEP components.

3.3.2 | Block-wise effect of HFS modulation

For all VEP components, each post-HFS block was separately compared to the associated BL. For the V-C1 component, only Post-HFS 5 displayed a significant increase in latency compared to baseline $[t(92) = -3.789, p < 0.001]$. For the V-P1 component, significant increases in latency compared to the baseline block were observed in Post-HFS 3 $[t(92) = 2.739, p = 0.007]$, Post-HFS 4 $[t(92) = -3.622, p < 0.001]$ and Post-HFS 5 $[t(92) = 3.513, p = 0.001]$. For the V-N1 amplitude, significant increases in latency compared to BL were observed in Post-HFS 3 $[t(92) = 3.083, p = 0.003]$ and Post-HFS 4 $[t(92) = 4.520, p < 0.001]$. No significant latency effects were found for any of the AEP components.

3.4 | Effects of age and sex

After correcting for multiple comparisons (Bonferroni corrected $\alpha = 0.008$), we found a modest significant correlation showing a decrease in the modulation score of the V-C1 component in Post-HFS 3 $[r(93) = -0.294, p = 0.004]$ and 4 $[r(93) = -0.357, p < 0.001]$ with increasing age as well as a significant correlation showing a decrease in the modulation score of the A-N1-P2 peak-to-peak component in Post-HFS 4 $[r(93) = -0.303, p = 0.003]$ and 5 $[r(93) = -0.301, p = 0.003]$ with increasing age respectively. The repeated measures ANOVA showing main effect of block was still significant when corrected for age. Independent samples $t$ tests were conducted to compare mean modulation scores across all post-HFS blocks between sexes. There were no significant sex differences in modulation scores for any of the visual or auditory ERP components (all uncorrected $p$ values $>0.103$).

After correcting for multiple comparisons (Bonferroni corrected $\alpha = 0.002$), there was no significant correlation between age and latency difference from baseline to post-HFS (baseline latency values subtracted from post-HFS latency values) in the visual modality (all $r < 0.158$ all $p > 0.130$). Likewise, there were no significant correlations in the auditory modality between age and latency difference in the A-N1 component. We did, however, find a significant correlation between age and latency difference in the A-P2 component in Post-HFS 4 $[r(93) = 0.333, p = 0.001]$, indicating longer latencies with increasing age. There were no significant differences between sexes regarding latency differences in either modality.

3.5 | Between-modality correlation

Between-modality effects were assessed using a hierarchical two-layer operation on the two peak-to-peak component measures. In the first stage, subjects displaying a positive modulation effect from baseline in both modalities were identified separately for each post-modulation block (Post-HFS 1 = 60.2%, Post-HFS 2 = 53.8%, Post-HFS 3 = 53.8%, Post-HFS 4 = 45.2% and Post-HFS 5 = 40.9% of the total subjects). In the second stage, the selected subjects’ block modulation scores were correlated across modalities using Pearson’s $r$. The analysis yielded no significant between-modality relationships (all $r$ values $<0.130$, all $p$-values $>0.215$). According to power analyses (G*power v. 3.1.9.4), a $r$ value $>0.203$ is defined as the critical $r$ for our sample size (Erdfelder, Faul, Buchner, & Lang, 2009). See Figure 6 for a scatterplot showing between-modality correlations.
In the present study, we integrated high-frequent visual and auditory stimulation within the same SRM session, with the aim of assaying within-subject associations between LTP-like synaptic plasticity in the visual and auditory domains respectively. In line with previous studies, we demonstrated a significant effect of the HFS in both modalities, evident as amplitude changes post-modulation. This modulation effect induced by high-frequent sensory stimuli is robust in all temporal components in the visual domain, though more modest and limited to later temporal components in the auditory domain. In contrast to our main hypothesis, no significant correlations were found across sensory modalities.

4.1 | Replication of previous studies of visual and auditory SRM

A principal aim of the current study was to replicate and confirm previous studies using high-frequency sensory stimulation (HFS) to demonstrate LTP-like synaptic plasticity by the modulation of visual and AEPs within the same experimental session, within a large sample of healthy subjects across age groups. A replication of previous findings on the VEP was evident, supporting the majority of previous work using similar paradigms (e.g. Clapp, Zaehle, et al., 2005; Normann et al., 2007), including the first study demonstrating the effect of visual HFS on subsequent amplitude changes using the same stimulation parameters as the current study (Clapp, Zaehle, et al., 2005). The amplitude changes seen in all components of the VEP add to previous reports on this phenomenon and lend support to the notion that visual HFS indeed is a viable probe into LTP-like synaptic plasticity in the human visual cortex.

The AEPs did not fully replicate previous work, as there were no significant amplitude change of the N1 component from baseline to post-stimulation blocks, an effect that was expected given that the auditory paradigm in the present study was modelled after the initial report on the phenomenon (Clapp, Kirk, et al., 2005). However, we did find a significant increase of all P2 post-HFS amplitudes, as well as most of the N1-P2 peak-to-peak amplitudes with the exception of Post-HFS 4, a finding in accordance with previously reported increased N1-P2 amplitude 25 minutes post-HFS (Teo et al., 2014). Little is known about the functional relevance and neural generators of the auditory P2 (Tremblay, Ross, Inoue, McClannahon, & Collet, 2014), but it is often defined together with the N1 as a long-latency response wave given their temporal proximity. The long-latency responses are thought to be influenced by attention and arousal (Luck, 2014) and both components are thought to originate in the primary and secondary auditory cortex bilaterally (Lightfoot, 2016).

4.2 | Latency differences

The current study found significant increases in latency from baseline to post-HFS blocks, though these effects were restricted to the visual components and the effect sizes were generally small.

4.3 | Effects of age and sex

As age-related reductions in neuroplasticity may play a central role in the cognitive decline of older adults, the underlying mechanisms behind such possible reductions should be further investigated. Some evidence from animal models indicate that visual plasticity is indeed higher in early childhood and gradually decline with age (Abuleil et al., 2019). Most human SRM studies have, however, used samples with younger adults, leaving room for uncertainty regarding whether the LTP-like plasticity changes seen after tetanic stimulation persist into old age (de Gobbi Porto et al., 2015). In the current study, we found some significant effects of age on modulation, related to the early visual component C1 and the auditory peak-to-peak N1-P2 composite respectively. Previous studies using similar tetanic visual stimulation protocols in older adults have shown conflicting results as some have found modulation of later visual components, such as the N1b (de Gobbi Porto et al., 2015), some have not found this N1b amplitude enhancement (Spriggs et al., 2017) and others found no significant amplitude change in older adults after visual tetanic stimulation (Abuleil et al., 2019). These studies did, however, use samples that skewed older compared to the current sample. Though a general assumption

FIGURE 6  Scatterplots with least-squares lines of the between-modality correlations of modulation scores
has been that LTP-like plasticity is gradually reduced with increasing age, clearly this needs to be further investigated in future studies.

The current study found no significant sex differences in modulation of visual or AEPs.

We found no significant correlations between age and the slightly prolonged latencies in the visual components post-HFS, neither were there any significant correlations regarding sex and visual latency differences. There were, however, one significant correlation between age and latency changes in the Post-HFS 4 block on the auditory P2 component. This finding is in accordance with previous research reporting correlations between older age and delayed latency on later ERP components such as the P3 (Dujardin, Derambure, Bourriez, Jacquesson, & Guieu, 1993).

4.4 Cross-modality effects

Contrary to our hypothesis, the current investigation did not identify any significant within-subject cross-modality association between post-HFS modulation in the visual and the auditory domain. There might be several reasons for this lack of association between modalities. Primary among these are uncertainties regarding the efficiency of the auditory paradigm, reflected in modulation of the late components only and lower responder rates compared to V-SRM. There are considerably fewer prior publications exploring the effect of HFS in the auditory compared to the visual modality, and the available reports vary with regard to how modulation of AEPs is measured. There are some dissimilarities in the design of the original Clapp, Kirk, et al. (2005) and Clapp, Zaehle, et al. (2005) report and the current experiment that might explain why the original findings were not replicated. Most notably, collection of the current AEP data took place within a multimodal framework with the addition of another auditory experimental paradigm (a Loudness-Dependent Auditory Evoked Potential [LDAEP] protocol). Although the LDAEP stimuli were presented within the V-SRM paradigm and the auditory stimuli in the LDAEP and the AEP protocol were not overlapping in intensity (dB SPL), the stimuli were presented in the same frequency (1 kHz), potentially increasing the likelihood of later interference and/or habituation effects. In addition, the AEP protocol was routinely administered after the VEP protocol, approximately 30 min after the initiation of the experimental protocol. This passage of time might introduce fatigue as a possible interfering factor.

Beyond characteristics of the current experimental design, there might be potential larger issues in the induction and measurement of AEPs. The apparent discrepancy in the quantity of publications concerning modulation of visual versus AEPs, and the magnitude of the observed effects, might indicate that modulation of AEPs by HFS is not as readily replicable as modulation in the visual domain. In addition, there is still a considerable amount of uncertainty related to how subject-related characteristics such as physical activity (Smallwood et al., 2015), age (Abuleil et al., 2019; de Gobbi Porto et al., 2015; Spriggs et al., 2017) and sex (Sharma, 2015) potentially affect aspects of sensory-induced LTP-like effects. Several other factors, such as arousal level and phase of circadian cycle, may also influence ERP reliability by causing confounding variations in neural activity (Luck et al., 2011). Though these more general considerations theoretically should affect both modalities, the AEP might be more sensitive to such factors for hitherto unknown and unexplored reasons.

4.5 Early versus late LTP

LTP is usually segregated into phases based on the cellular processes that occur, specifically whether or not new proteins are produced (Bliss & Collingridge, 1993; Malenka, 1991). The first phase, short-term potentiation, only involves existing proteins and the effect of decays after 15–30 min post-induction. The second and third phases, so-called early and late LTPs, last from a couple of hours up to several weeks, and both involve protein synthesis (Kung, 2016). The current study only consider the short-term to early-phase effects of stimulation, and may therefore not be reflective of long-lasting LTP effects. The effects of stimulation in the current study show certain modality-specific results regarding the duration of post-HFS modulation effects. The N1 was the only visual component displaying a modulation effect approximately 20 min post-stimulation. Interestingly, the auditory P2 component, and the auditory N1-P2 peak-to-peak component, displayed modulation effects in the late post-HFS block. Hence, the auditory effect might potentially be longer lasting and reflecting of early or late LTP effects rather than short-term potentiation.

4.6 Strengths and limitations

The number of participants in the present study exceeds most comparable SRM studies indicating more statistical power than previous work. A weakness in the current paradigm is that the presentation of the visual and auditory paradigms was not randomized, and these paradigms were presented in a fixed order for all participants. By randomizing the order of the modalities presented, we may have avoided potential effects of fatigue and/or habituation affecting the AEPs and possibly observed a stronger modulation effect in the auditory components.
4.7 Considerations for future research/methodological development

Though both modalities displayed some modulation effects following HFS, albeit a considerably stronger effect in the visual domain, the effect gradually dissipated in the VEP paradigm towards the later post-stimulation blocks. Conversely, a strengthening of the effect was evident in the later post-modulation blocks of the AEP paradigm. An important question is whether this difference reflects underlying different phenomena when using HFS paradigms stimulating different sensory systems and cortices, or whether the limitation of not randomizing the sequence of the modality-specific stimulation possibly concealed relevant cross-modal effects. Another possibility is that these measures of LTP-like cortical plasticity represent different basic mechanisms, explaining why modulation in one sensory domain of cortical plasticity does not necessarily translate to, or show within subject concordance to, measures of cortical plasticity in another sensory domain.

The available literature on HFS modulation of AEPs is scarce and often characterized by a limited number of participants and consequently low statistical power. Though responder rates are rarely reported in SRM studies, Klöppel et al. (2015) reported a visual responder rate of approximately 75% (Klöppel et al., 2015). Assuming that this ratio of responders to non-responders translates to auditory responder rates, the auditory LTP-like phenomenon is a considerably vulnerable phenomenon that might be challenging to capture in smaller samples, and successful assessment of AEPs will demand robust power estimates. Given the relatively high number of participants in the present study, we would expect to see stronger effects of the auditory HFS than what is reflected in the current results.

Another possible reason for the modulation effect being considerably more accessible in the visual domain relative to the auditory domain relates to how human visual SRM paradigms have parallels in animal research. Intracranial electrophysiological recordings in the V1 in the rodent cortex after the presentation of a sinusoidal grating stimuli have demonstrated an amplitude increase of average VEPs (Cooke & Bear, 2010). To our knowledge, no similar studies have been carried out using intracranial recording from the auditory cortex in animals.

Based on results from the present study, we argue that developments in modulation of sensory evoked potentials mainly should focus on developing and optimizing paradigms within the visual domain. Modulation of VEP using either prolonged or high-frequency visual stimulation consistently shows robust effects (e.g. Elvssahlen et al., 2012; Smallwood et al., 2015; Teyler et al., 2005), making it a promising candidate as an index of LTP-like cortical plasticity.

Developing a robust and valid biomarker of sensory-induced human LTP-like synaptic plasticity is of potential importance for clinical research and practice. Both animal models and human SRM research have suggested that impaired synaptic plasticity might add knowledge to the pathophysiology and monitor treatment response in affective disorders (Elvssahlen et al., 2012; Normann et al., 2007) and schizophrenia (Cooke & Bear, 2012; Jahshan et al., 2017). As of now, however, the specificity of such biomarkers is low. Improving and optimizing current visual SRM paradigms should therefore be a priority within this field of research in the years to come.

In summary, we found that visual HFS produces robust modulation effects in healthy adults, whereas auditory HFS produces more modest modulation effects. In contrast to our initial hypothesis, no within-subject correlations between modalities were found, suggesting that auditory and visual SRM may depend on different mechanisms of neocortical plasticity. The current results indicate that the focus within the field of stimulus-specific response modulation research should be on optimizing paradigms within the visual domain.

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CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

SA, CH, TE and TM designed the experiment; TWR collected data; CH designed the MATLAB script and preprocessed the data; CH and TWR analysed data and wrote the manuscript under supervision of SA and revisions from TM.

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DATA AVAILABILITY STATEMENT

All data are available from the corresponding author upon request.

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