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# Methodological considerations for a better somatosensory gating paradigm: The impact of the inter-stimulus interval

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## Abstract

Sensory gating (SG) is a neurophysiological phenomenon whereby the response to the second stimulus in a repetitive pair is attenuated. This filtering of irrelevant or redundant information is thought to preserve neural resources for more behaviorally-relevant stimuli and thereby reflect the functional inhibition of sensory input. Developing a SG paradigm in which optimal suppression of sensory input is achieved requires investigators to consider numerous parameters such as stimulus intensity, time between stimulus pairs, and the inter-stimulus interval (ISI) within each pair. While these factors have been well defined for the interrogation of auditory gating, the precise parameters for eliciting optimal gating in the somatosensory domain are far less understood. To address this, we investigated the impact of varying the ISI within each identical pair of stimuli on gating using magnetoencephalography (MEG). Specifically, 25 healthy young adults underwent paired-pulse electrical stimulation of the median nerve with increasing ISIs between 100 and 1000 ms (in 100 ms increments). Importantly, for correspondence with previous studies of somatosensory gating, both time-domain and oscillatory neural responses to somatosensory stimulation were evaluated. Our results indicated that gating of somatosensory input was optimal (i.e., best suppression) for trials with an ISI of 200–220 ms, as evidenced by the smallest gating ratios and through statistical modeling estimations of optimal suppression. Importantly, this was true irrespective of whether oscillatory or evoked neural activity was used to calculate SG. Interestingly, oscillatory metrics of gating calculated using peak gamma (30–75 Hz) power and frequency revealed more robust gating (i.e., smaller ratios) than those calculated using time-domain neural responses, suggesting that high frequency oscillations may provide a more sensitive



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**Rachel K. Spooner:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition. **Jacob A. Eastman:** Investigation. **Alex I. Wiesman:** Methodology, Software, Writing - review & editing. **Tony W. Wilson:** Conceptualization, Methodology, Supervision, Resources, Funding acquisition, Writing - review & editing.

Appendix A. Supplementary data

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measure of SG. These findings have important implications for the development of optimal protocols and analysis pipelines to interrogate SG and inhibitory processing with a higher degree of sensitivity and accuracy.

**Keywords**

Magnetoencephalography; Somatosensory; Oscillatory activity; Time-domain; Inter-stimulus interval

## 1. Introduction

Sensory gating (SG) is a neurophysiological phenomenon whereby the response to the second stimulus in an identical pair is attenuated. This weakened response to stimuli presented in rapid succession is thought to reflect the brain's capacity to filter irrelevant information to preserve neural resources for more behaviorally relevant stimuli (Adler et al., 1982, 1998; Cromwell et al., 2008; Nagamoto et al., 1989, 1991; Venables, 1964). SG has been examined in many clinical populations and across multiple sensory modalities (e.g., auditory and somatosensory) and broadly is known to be aberrant in aging, as well as many psychiatric and neurological conditions (e.g., schizophrenia, bipolar disorder, cerebral palsy, neuroHIV (Brinkman and Stauder, 2007; Cheng et al., 2015a; Cheng et al., 2016a; Cheng et al., 2015b; Cheng and Lin, 2013; Kisley et al., 2003; Kurz et al., 2017; Light and Braff, 1999; Spooner et al., 2018; Spooner et al., 2019; Thoma et al., 2017)). Historically, SG paradigms have used a paired-stimulus presentation design, whereby pairs of auditory tones or electrical stimulations are administered in close temporal proximity to evaluate gating in the auditory or somatosensory domain, respectively. Such gating is generally quantified as a ratio or difference score between the response pairs. For example, a higher gating ratio (response to stimulation 2/response to stimulation 1) is indicative of worse suppression of redundant information, while a higher gating difference score (response to stimulation 1 - response to stimulation 2) reflects better gating. The ratio approach is the most common as it is less affected by individual differences in response amplitude across both stimulations. Importantly, regardless of the tested modality or clinical population, aberrations in SG are thought to reflect alterations in functional inhibitory processing (Cheng et al., 2016b; Cromwell et al., 2008; Gao et al., 2013; Spooner et al., 2018, 2019), making the application of such protocols in human neurophysiology extremely desirable.

While the overall paired-pulse design of SG experiments has been in place for decades, there are a host of other experimental parameters that must be considered during task design, such as stimulus intensity, time between the individual stimuli, and time between the pairs. For example, it is exceedingly common for SG protocols to present the identical stimuli in rapid succession separated by a fixed, relatively short inter-stimulus interval (e.g., 500 ms), while the pairs of identical stimuli are separated by larger temporal windows (e.g., 5000 ms) that can be randomly jittered to eliminate anticipatory responses (Cheng et al., 2016b; Kurz et al., 2017; Spooner et al., 2019; Wiesman et al., 2017). These pairs of stimuli are always presented at identical intensities within the same person, to ease the interpretation of any experimental effects, and these intensities are often determined by individual-specific

thresholds. Importantly, the experimental parameters that best elicit the SG response have received considerable attention. In the auditory domain, there are numerous reports of optimal inter-stimulus and inter-pair intervals for eliciting robust gating responses. Rentzsch et al. (2008) tested the effect of inter-pair interval (IPI; i.e., time between trials) on auditory gating of the P50 response and found that, regardless of whether the time between stimulus pairs was long (i.e., 8 s) or short (i.e., 2.8 s), gating and response amplitudes were equivalent across all participants and both protocols (Rentzsch et al., 2008). Further, the effect of inter-stimulus interval (ISI), or the time between identical stimuli in a trial, has been extensively studied in the context of auditory gating. For example, Adler et al. (1982) demonstrated very strong SG in controls using a 500 ms ISI, with reduced SG at longer ISIs ranging from 1000 to 2000 ms; of note, SG was reduced at all ISIs in patients with schizophrenia (Adler et al., 1982). Other studies evaluating the effect of ISI on auditory gating have largely replicated Adler et al.'s findings, showing that SG is strongest when stimuli are presented 500 ms apart, slightly reduced for stimuli greater than 1000 ms apart, and undetectable for stimuli closer than ~50–150 ms from one another (Adler et al., 1998; Nagamoto et al., 1989, 1991). Surprisingly, while these experimental parameters have been well studied and optimized in the context of auditory gating, they have not been widely tested in the context of somatosensory gating, despite their frequent direct extension to this modality.

The most common method for characterizing changes in SG in human neurophysiology is through analysis of auditory and somatosensory event-related potentials (ERP). This includes analysis of time-domain neural responses to the first and second stimulus in the pair to derive metrics of basic sensory processing (e.g., response amplitude and latency) and gating. However, several recent studies of SG have employed advanced oscillatory analysis methods and found rich, multi-spectral recruitment of neural populations following the paired stimuli. For example, in the context of the somatosensory system, recent studies have shown that electrical stimulation of the median nerve elicits robust oscillatory activity up to 90 Hz (e.g., 20–90 Hz; (Cheng et al., 2016b; Spooner et al., 2018; Spooner et al., 2019; Wiesman et al., 2017). These high-frequency or gamma oscillations (>30 Hz) are critical to the basic processing of fine stimulus features across modalities and may ultimately provide mechanistic insight into intracortical inhibitory processing. Essentially, gamma oscillatory activity has been shown to critically rely on GABA-ergic inhibitory architecture and functionality, and thus alterations in high-frequency oscillatory gating may be a more direct link to intracortical inhibition (Bartos et al., 2007; Buzsáki and Wang, 2012; Fries, 2009, 2015; Fries et al., 2007; Salkoff et al., 2015; Singer, 1999; Uhlhaas and Singer, 2012; Vinck et al., 2013), making neural oscillations an attractive avenue for probing SG deficits in the context of clinical populations.

In the current study, we utilized magnetoencephalography (MEG) and a paired-pulse electrical stimulation paradigm to investigate how an essential SG task parameter (i.e., ISI) affects somatosensory gating metrics and inhibitory processing in 25 healthy young adults. Specifically, we tested the impact of ISIs ranging from 100 to 1000 ms, in 100 ms increments, using advanced oscillatory and time-domain analysis methods and curve estimation to derive optimal gating at the millisecond timescale. Our primary hypotheses were that (1) shorter ISIs would lead to better suppression of redundant somatosensory input

and (2) oscillatory and time-domain analysis approaches would suggest different ISIs for optimal gating.

## 2. Methods

### 2.1. Participants

Twenty-five healthy young adults (12 females, $M_{age}$ = 25.34 years, range 21–32 years old) participated in this study. All participants were right-handed. Exclusionary criteria were assessed via self-report and included any medical illness affecting the CNS (e.g., HIV/AIDS), neurological or psychiatric disorder, history of head trauma, current substance abuse, and the MEG Laboratory's standard exclusion criteria (e.g., ferromagnetic implants). After a full description of the study was given to participants, written informed consent was obtained following the guidelines of the University of Nebraska Medical Center's Institutional Review Board, which approved the study protocol.

### 2.2. Experimental paradigm

Participants were seated in a nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. Electrical stimulation was applied to the left median nerve using external cutaneous stimulators connected to a Digitimer DS7A constant-current stimulator system (Digitimer Ltd, Garden City, UK). For each participant, we collected 500 paired-pulse trials (i.e., 50 trials of each condition) with an ISI that varied from 100 to 1000 ms in 100 ms increments for a total of 10 conditions, and an inter-pair interval that randomly varied between 2700 and 3000 ms across all 10 conditions. Each pulse consisted of a 0.2 ms constant-current square wave that was set to a limit of 10% above the motor threshold that was required to elicit a subtle twitch of the thumb. The amplitude of the pulse was held constant across the 10 conditions in each participant.

### 2.3. MEG data acquisition

All recordings were performed in a one-layer magnetically shielded room with active shielding engaged for environmental noise compensation. With an acquisition bandwidth of 0.1–330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta/MEGIN MEG system (Elekta, Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. Throughout data acquisition, participants were monitored using a real-time audio-video feed from inside the magnetically shielded room. MEG data from each participant were individually corrected for head motion and subjected to noise reduction using the signal-space separation method with a temporal extension (tSSS; (Taulu and Simola, 2006; Taulu et al., 2005)).

### 2.4. Structural MRI processing and MEG coregistration

Prior to MEG measurement, four coils were attached to the participant's head and the locations of these coils, together with the three fiducial points and scalp surface, were determined with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the

sensors throughout the recording session. Since coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered with T1-weighted structural magnetic resonance images (sMRI) prior to source space analyses using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany). All sMRI data were acquired with a Philips Achieva 3T X-series scanner using an 8-channel head coil (TR: 8.09 ms; TE: 3.7 ms; field of view: 240 mm; slice thickness: 1 mm; no gap; in-plane resolution: 1.0 × 1.0 mm). All sMRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space, along with the functional data, after beamforming (see below).

### 2.5. MEG preprocessing, time-frequency transformation, and sensor-level statistics

Cardiac and ocular artifacts were removed from the data using signal-space projection (SSP) and the projection operator was accounted for during source reconstruction (Uusitalo and Ilmoniemi, 1997). Epochs were of 2700 ms duration, with 0 ms defined as the onset of the first stimulation and the baseline being the −700 to −300 ms window. Of note, we shifted our baseline away from the period immediately preceding stimulus onset to avoid potential contamination by any anticipatory responses, although there was no evidence of such anticipatory responses in our final analyses. Epochs containing artifacts were rejected based on a fixed threshold method, supplemented with visual inspection. On average, 45.8 trials per participant and condition remained after artifact rejection (i.e., 46.3 for 100 ms ISI, 46.0 for 200 ms ISI, 45.7 for 300 ms ISI, 45.4 for 400 ms ISI, 46.7 for 500 ms ISI, 45.8 for 600 ms ISI, 45.0 for 700 ms ISI, 46.1 for 800 ms ISI, 45.4 for 900 ms ISI, and 46.2 for 1000 ms ISI). Importantly, the number of trials used for final analyses did not significantly differ between conditions ($F(9,207) = 1.67$, $p = .13$).

Artifact-free epochs were further processed following two parallel pipelines. For the time domain (i.e., evoked) analyses, all epochs per condition and participant were averaged with respect to stimulus onset for each sensor in the array and normalized using the baseline. For the oscillatory analyses, all epochs were transformed into the time-frequency domain using complex demodulation (Kovach and Gander, 2016), and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density. These sensor-level data were normalized using the respective bin's baseline power, which was calculated as the mean power during the −700 to −300 ms time period.

For the oscillatory analyses, the specific time-frequency windows used for source reconstruction were determined by statistical analysis of the sensor-level spectrograms across all participants' trials, task conditions, and gradiometers. Each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired sample $t$-tests against baseline were conducted on each data point and the output spectrogram of $t$-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally

neighboring bins that were also significant, and a cluster value was derived by summing all of the *t*-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster values and the significance level of the observed clusters (from stage 1) were tested directly using this distribution (Ernst, 2004; Maris and Oostenveld, 2007). For each comparison, 10,000 permutations were computed to build a distribution of cluster values. Based on these analyses, the time-frequency windows that contained significant oscillatory events across all participants were subjected to the beamforming analysis.

### 2.6. MEG source imaging

Cortical oscillatory networks were imaged through the dynamic imaging of coherent sources (DICS) beamformer (Gross et al., 2001), which uses the cross-spectral density matrices to calculate source power for the entire brain volume. These images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences (i.e., active vs. passive) per voxel. Following convention, we computed noise-normalized, source power per voxel in each participant using baseline periods of equal duration and bandwidth (Hillebrand et al., 2005). MEG preprocessing and imaging used the Brain Electrical Source Analysis (Version 7.0; BESA) software. Further details of our analysis pipeline can be found in Wiesman and Wilson (2020).

Normalized source power was computed over the entire brain volume per participant at 4.0 × 4.0 × 4.0 mm resolution for the time-frequency periods identified through the sensor level analyses. Prior to statistical analysis, each participant's MEG data, which were coregistered to native space structural MRI prior to beamforming, were transformed into standardized space using the transform previously applied to the structural MRI volume and spatially resampled. The resulting 3D maps of brain activity were averaged across all participants, both stimulations and task conditions (i.e., ISI) to assess the neuroanatomical basis of the significant oscillatory responses identified through the sensor-level analysis, and to allow identification of the peak voxels per oscillatory response.

Voxel time series data (i.e., "virtual sensors") were extracted from each participant's data individually per condition using the peak voxel from the grand-averaged beamformer images. To compute the virtual sensors, we applied the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series for the specific coordinate in source space. Note that virtual sensor extraction was done per participant, once the coordinates of interest were known. Once the virtual sensor time series were extracted, we computed the envelope of the spectral power within the frequency range used in the beamforming analysis. From this time series, we computed the relative (i.e., baseline-corrected) response time series of each participant per task condition.

In regard to the time domain analyses, source images were computed using standardized low-resolution brain electromagnetic tomography (sLORETA; regularization: Tikhonov 0.01%; (Pascual-Marqui, 2002)). The resulting whole-brain maps were 4-dimensional estimates of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the units are arbitrary. Using the temporal clusters identified in the sensor-level

analysis, these maps were averaged over time following each somatosensory stimulation (e.g., 0–50 ms and 500–550 ms for the 500 ms ISI condition) for all ISI conditions. The resulting maps were then grand-averaged across the two stimulations to determine the peak voxel of the time-domain neural response to the stimuli across participants. From this peak, sLORETA units were extracted per stimulation and ISI condition to derive estimates of the time-domain response for each participant.

### 2.7. Statistical analysis

To examine the effect of ISI on gating metrics (e.g., amplitude and frequency) across participants, we conducted polynomial regression analyses to find a model estimate of the best somatosensory gating (i.e., smallest numerical ratios). Briefly, a linear, quadratic and cubic term of ISI was entered into the model and change in $R^2$ was assessed for model fit of increasing ISI on somatosensory neural indices. These indices included the oscillatory sensory gating ratio (relative response power to stimulus 2/relative response power to stimulus 1), peak oscillatory frequency in response to stimulation, and the gating ratio in the time domain. Further, model estimates demonstrating significantly better fit to our data were then used to derive the ISI necessary to elicit optimal gating at the millisecond timescale. Finally, to compare the sensitivity of these oscillatory and evoked gating metrics, paired sample t-tests were conducted between these measures for neighboring ISIs.

## 3. Results

### 3.1. Sensor-level time-frequency analyses

Robust increases in response to electrical stimulation of the left median nerve were found in many sensors near the sensorimotor and parietal regions from about 10 to 90 Hz following the first and second stimulation ($p < .001$, corrected; Fig. 1). To evaluate the oscillatory dynamics in the gamma range, we focused our beamformer analyses on the higher 30–75 Hz frequency range and the 50 ms time interval immediately following each electrical stimulation (e.g., 0–50 ms and 500–550 ms for the 500 ms ISI condition), as the neural responses were strongest during this period. Note that we limited our analyses to 75 Hz on the high end because relative power sharply decreased thereafter, especially following the second stimulus.

### 3.2. Source-level analyses

Beamformer images revealed peak gamma activity in the contralateral primary somatosensory cortex, with virtually identical peak locations in response to the first and second stimulation for all ISIs (Fig. 1). As described in the methods, these images were grand-averaged across all participants, ISIs, and both stimulations, and virtual sensor data were extracted from the peak voxel. The resulting baseline-corrected (i.e., relative) power envelope for the 30–75 Hz band was used in the subsequent statistical analyses.

### 3.3. Oscillatory profiles of somatosensory gating depend on ISI

To investigate how the ISI duration (i.e., time between stimulations within a trial) impacted sensory gating, a polynomial regression of ISI on the somatosensory gating ratio was conducted and curve estimation was used to derive the ISI for which optimal gating may be

achieved based on our data. Of note, higher gating ratios are indicative of worse suppression of redundant somatosensory input (i.e., reduced gating). First, pairwise t-tests between stimulation response power revealed that the response to the second stimulation was significantly reduced compared to the first for each ISI, revealing significant gating across all ISI conditions (i.e., 100–1000 ms ISI; $p$s < .05). Interestingly, optimal gating was seen during trials where the ISI between electrical stimulations was 200 ms, as evidenced by the overall smallest numerical ratios (i.e., better suppression, Fig. 2). In addition, polynomial regression of linear, quadratic and cubic terms of ISI on somatosensory gating in the gamma band were conducted to assess model fit. These analyses revealed that the cubic model of ISI on oscillatory gating ratios yielded significantly better model fit than linear or quadratic terms, as evidenced by a significant change in $R^2$ ($F(3,9) = 128.89$, $p < .001$; $\Delta R^2 = .09$, $p = .001$) when the cubic term was entered into the model. Further, using the cubic model equation derived from our regression analysis, we estimated the local minima of the curve, which is indicative of the best suppression of somatosensory input. This analysis suggested that an ISI of 220 ms would elicit optimal gating ratios (i.e., better suppression), which corresponds well with the overall smallest ratios evident in the 200 ms ISI condition (Fig. 2). Importantly, to ensure that our gating ratio differences as a function of varying ISIs were not due to changes in response power to the first stimulation in the identical pair, we conducted pairwise analyses between neighboring ISI conditions (e.g., 100 vs. 200 ms, 200 vs. 300 ms). This indicated no significant differences in oscillatory response power to the first stimulation between any neighboring ISI conditions, suggesting that our changes in gating were not attributable to differences in the neural response to the first stimulation ($p$s > .153).

Given recent data suggesting that the peak frequency is a key parameter of oscillatory responses, especially in the gamma range, paired sample t-tests between response frequency for each ISI were conducted to evaluate the impact of ISI on the spectral information comprising somatosensory gating. This analysis revealed significant elevations in the peak gamma frequency for the second stimulation in the pair compared to the first for trials with an ISI of 200, 300 and 400 ms ($p$s < .003; Fig. 2).

### 3.4. Somatosensory gating in the time domain

To facilitate comparison with previous studies of evoked somatosensory processing, we computed time-domain sLORETA source images to derive phase-locked response estimates for each participant. Time series data were then extracted in each participant from the grand-averaged peak voxel of the sLORETA source images to derive the somatosensory gating ratio. Similar to our oscillatory analysis, time-domain response amplitudes were significantly weaker in response to the second stimulation compared to the first in all ISI conditions ($p$s < .041). Interestingly, gating ratios were the smallest (i.e., best suppression of redundant information) in trials with an ISI of 200 ms. For correspondence with our analysis of the oscillatory sensory gating, a polynomial regression of linear, quadratic and cubic terms of ISI on time-domain somatosensory gating ratios was conducted to assess model fit. These analyses revealed no significant improvement in model fit (i.e., change in $R^2$) with subsequent addition of polynomial terms, suggesting that neither linear, quadratic nor cubic models were significantly better at estimating our data ($\Delta R^2 = .002$, $p$s > .841). Thus, optimal gating in the time-domain was restricted to the overall smallest ratios as seen in the

200 ms ISI condition, while gating during trials with ISIs of 300 ms and above abruptly flattened and changed only slightly with increasing ISI (Fig. 3). Finally, similar to our analysis of oscillatory power, we conducted pairwise t-tests to evaluate whether varying ISI modulated the response power to the first stimulation in an identical pair. Importantly, we observed no significant changes in sLORETA source power to the first stimulation between neighboring ISI conditions ($p$s > .127), suggesting that our changes in sensory gating as a function of ISI were not confounded by changes in the response power to the first stimulation.

### 3.5. Sensitivity of time and spectral components for detecting optimal gating

Finally, to evaluate the sensitivity of our analysis pipelines (i.e., oscillatory versus evoked) for detecting gating, we conducted paired t-tests between the gating ratios derived from our analyses of oscillatory gamma power and sLORETA time-domain responses. Interestingly, these analyses revealed more robust gating (i.e., smaller ratios) of oscillatory compared to time-domain responses for trials with an ISI ranging from 100 to 600 ms (all $p$s < .003, Fig. 4). This suggests that the spectro-temporal profile of high frequency gamma oscillations may be a more sensitive index of somatosensory gating (i.e., elicits more robust gating) compared to time-domain approaches alone.

## 4. Discussion

The goal of the current study was to evaluate the impact of different ISIs on the gating of somatosensory responses using two established signal processing pipelines. Specifically, we used a paired-pulse electrical stimulation paradigm and MEG to derive metrics of gating in the time-and oscillatory domains using advanced source imaging techniques. These evoked and oscillatory responses were used to calculate gating ratios, which indicated significant sensory gating across all participants at each ISI. Across both oscillatory and time domain analyses, our results indicated that gating of somatosensory input was optimal when identical stimuli were presented 200 ms apart. Further, these results were validated through cubic fit curve estimations derived from regression analyses, which estimated that optimal oscillatory gating ratios would be elicited at an ISI of 220 ms, corresponding well with the current data. Interestingly, our gating curves as a function of ISI indicated that oscillatory activity was more robustly gated compared to evoked activity, suggesting that high frequency oscillations (>30 Hz) may be a more sensitive measure of sensory gating. Importantly, this study is the first to directly test for optimal SG task parameters in the somatosensory system, which may ultimately aid in experimental design and functional interpretations. The implications for these novel findings are discussed below.

In line with the most recent studies of somatosensory gating, we evaluated the effect of ISI on the dynamics of high-frequency gamma (>30 Hz) oscillations in response to the first and second stimulation (Cheng et al., 2016b; Kurz et al., 2017; Spooner et al., 2018, 2019; Wiesman et al., 2017). Critically, we found that the gating of somatosensory input was optimal (i.e., smaller gating ratios) when stimulations were presented 200 ms apart from one another, irrespective of whether this ratio was calculated using peak oscillatory power or peak frequency. Interestingly, gating ratios calculated using peak oscillatory power were

found to follow a significant cubic trend, such that ratios during trials with ISIs greater than 300 ms were significantly higher and would eventually plateau around 700 ms, compared to the local minima seen at an ISI of 200 ms. Further, this cubic model fit was used to estimate the best suppression of somatosensory information on the millisecond timescale. Specifically, the model derived from our data suggested that 220 ms is the ISI necessary for eliciting optimal gating of high frequency oscillatory power, which corresponded well to the overall smallest ratios seen in the 200 ms ISI condition. Notably, these results align well with our hypothesis that shorter intervals would result in better suppression of redundant information compared to longer ones, with the exception of the 100 ms ISI condition where gating ratios were generally higher (i.e., worse suppression) compared to stimulations separated by 200 ms. This finding was not totally surprising, as previous studies evaluating even shorter temporal windows separating identical auditory stimuli (e.g., ~50–100 ms) found either a complete lack of gating or, alternatively, no discernable deficits in gating among patients with psychiatric disorders that had previously been linked to gating aberrations (Nagamoto et al., 1989, 1991). Thus, from an experimental design standpoint, our findings suggest that paired-pulse somatosensory stimulation paradigms using an ISI of 200 ms are likely to see the strongest gating, and that ISIs greater than ~400–600 ms may not yield optimal gating.

In regard to peak oscillatory frequency, we observed similar findings, such that significant elevations in peak gamma frequency to the second stimulus in a redundant pair were seen for ISIs ranging from 200 to 400 ms. These results were not surprising, as our previous study evaluating somatosensory gating in the context of HIV infection revealed that peak gamma frequency was significantly elevated in response to the second stimulation compared to the first across all participants and further, this elevation was accentuated in HIV-infected adults, despite relatively equivalent gating ratios across groups (Spooner et al., 2018). The current findings, and those observed in our previous study, may suggest that elevation of peak oscillatory frequency in response to the second stimulation may serve as a mechanism to attenuate oscillatory power to the second stimulation (given the inverse relationship between oscillatory power and frequency), thereby contributing to effective gating in the somatosensory cortex and, potentially, serving as a compensatory mechanism for clinical populations exhibiting alterations in sensory processing. Thus, it is not surprising that we observed this change in peak gamma frequency for ISIs ranging from 200 to 400 ms, as this aligns well with ISIs exhibiting optimal gating of oscillatory power (i.e., better suppression) in the same participants. However, these interpretations are speculative and further studies are necessary to disentangle these relationships.

Sensory gating is the “filtering” of repetitive, peripheral information, and this preservation of neural resources is ubiquitous across sensory systems. Our focus on high-frequency gamma activity was based on numerous prior studies of somatosensory gating from our laboratory and others (Cheng et al., 2016b; Kurz et al., 2017; Spooner et al., 2018, 2019, in press; Wiesman et al., 2017), as well as the extensive literature linking GABAergic inhibitory function and gamma oscillatory activity. Many previous electrophysiological studies have provided direct evidence that GABAergic inhibitory drive modulates local pyramidal synchrony, and that this modulation is reflected in higher frequency (>30 Hz) oscillatory activity (Bartos et al., 2007; Buzsáki and Wang, 2012; Fries, 2009, 2015; Fries et al., 2007;

Salkoff et al., 2015; Singer, 1999; Uhlhaas et al., 2009; Uhlhaas and Singer, 2012; Vinck et al., 2013). This relationship has also extended to recent human studies. For example, using GABA magnetic resonance spectroscopy (MRS), Muthukumaraswamy and colleagues showed a positive association among peak gamma frequency in the visual cortex during visual grating presentation and total resting GABA concentration in the same region (Muthukumaraswamy et al., 2009). A later study replicated this finding and, in addition, showed that both increased GABA concentration and elevated peak gamma frequency in the primary visual cortex were predictive of better visual orientation discrimination (Edden et al., 2009). Similar studies of gamma oscillatory activity and GABA concentrations have been conducted in the motor system and these also replicated the established gamma-GABA link described in the visual cortex of humans (Gaetz et al., 2011), and in some cases have extended this relationship to other spectral components of movement (Hall et al., 2011; Muthukumaraswamy et al., 2013). However, of note, not all studies have replicated this gamma-GABA relationship in sensory systems (Cheng et al., 2017; Cousijn et al., 2014). For example, a recent study by Cheng and colleagues evaluated the relationship between GABA concentration in the sensorimotor cortex and somatosensory gating ratios. They observed no significant association among the two variables, suggesting that at least some measures of sensory gating are not related to changes in GABA concentration (Cheng et al., 2017). However, importantly, this study used the P35 time-domain response to compute gating ratios and the degree to which this response reflects gamma-frequency activity is unclear. Thus, while this study did not observe a significant relationship among GABA and time-domain gating responses, it is unclear how informative this negative finding is in regard to the linkage among GABA levels and oscillatory gamma-based metrics of SG. Despite these discrepancies, the majority of relevant cellular and cortical neurophysiological studies have provided a mechanistic link between GABA levels and gamma oscillatory activity throughout the cortex and, while our study did not directly measure levels of GABA, our findings of altered SG as a function of important task parameters may be due to sub-second changes in local intracortical inhibition. Thus, future studies of sensory gating in the gamma range and GABAergic inhibition will be paramount to further the field’s understanding of the role of local inhibition in somatosensory gating.

For comparison with previous studies of SG, an analysis of evoked neural activity in response to various ISIs was conducted, and the results were incredibly informative. Essentially, similar to the oscillatory data, we found that gating was optimal (i.e., smaller ratios) for trials where stimulations were separated by 200 ms compared to longer (300–1000 ms) temporal windows. This finding is especially important as it indicates that regardless of the analysis pipeline implemented in a particular study, a 200 ms ISI is likely to generate the strongest gating effects and thus be the parameter of choice. Interestingly, a previous study evaluating the impact of varying ISI on BOLD and MEG neural responses to somatosensory stimulation showed robust gating of the P35 time-domain component with an ISI of 500 ms, but not with ISIs of shorter (e.g., 250 ms) or longer (e.g., 750–2000 ms) intervals (Stevenson et al., 2012). However, comparing these findings to the current data is difficult, as there were no empirical comparisons between neighboring ISI conditions in the previous study to evaluate whether the gating at 500 ms was in fact “optimal” (i.e., elicited best suppression) above and beyond other tested ISI conditions. Further, shorter ISIs of 250

ms employed in the previous study yielded qualitatively similar gating ratios to the 500 ms ISI condition, albeit with larger variability than other conditions, suggesting that gating of evoked neural responses could also be effectively elicited at ISIs less than 500 ms, which would align well with the current findings. One possible explanation for the lack of significant gating at the other ISIs could be the rather small sample size used in the earlier study (i.e., eight participants (Stevenson et al., 2012)). Nevertheless, the current study empirically determined that the degree of gating of evoked neural activity was relatively similar for trials with ISIs greater than 200 ms, and this was especially true for trials with ISIs from 300 to 700 ms, as neither linear, quadratic nor cubic model estimates produced adequate model fit of increasing ISI on time-domain gating ratios. Finally, our analysis of gating across signal processing methods revealed more robust gating (i.e., better suppression) to the different ISIs for gating ratios based on gamma oscillations compared to those derived from time-domain analyses, which may suggest that measures of gamma activity provide a more sensitive (i.e., dynamic range of gating) index of inhibitory processing in the somatosensory cortex. Beyond increased sensitivity to task parameters, some studies have found that gating based on oscillatory indices is also more sensitive to participant characteristics. For example, in a previous study of healthy aging, our laboratory observed significantly decreased somatosensory gating, based on gamma oscillatory activity, with increasing age (Spooner et al., 2019). While our results were consistent with previous studies of SG and aging using time-domain approaches (Cheng and Lin, 2013; Lenz et al., 2012), in our study the effect sizes for the time-domain analysis were smaller than the oscillatory and consequently the aging effect did not reach significance for the time domain component (Spooner et al., 2019). In short, the findings of the current study and previous work suggest that evoked and oscillatory analyses may have different sensitivities to SG deficits in particular populations, as well as unique task parameters.

In conclusion, this study was the first to examine the impact of various ISIs on SG in the somatosensory system. To date, paradigms used to study SG in the somatosensory domain have largely relied on the early, seminal work evaluating gating of auditory information, which has broadly suggested that an ISI of 500 ms is optimal for maximizing SG and distinguishing clinical populations from their healthy counterparts compared to shorter (e.g., 50–100 ms) and longer (e.g., 1000 ms) intervals (Adler et al., 1998; Adler et al., 1982; Nagamoto et al., 1989; Nagamoto et al., 1991). In contrast, we found that gating in the somatosensory system is optimal (i.e., best suppression) when the time between identical stimuli is 200 ms, compared to both shorter and longer intervals and further, cubic model estimation found this optimal temporal window to be 220 ms. This optimal gating was seen regardless of whether time-domain or oscillatory analyses were used to derive gating ratios. However, gating ratios computed from gamma oscillatory power were significantly lower (i.e., better suppression) compared to those calculated from phase-locked time-domain data, suggesting that high frequency oscillatory activity may provide a more sensitive measure of SG in the somatosensory system. Ultimately, the data described herein provide novel insight into the effect of various ISIs on the filtering of redundant somatosensory information and may dramatically influence the design, analysis, and interpretation of future studies of SG. With numerous clinical conditions known to be associated with altered somatosensory processing, gating, and functional inhibition (e.g., HIV, posttraumatic stress disorder,

cerebral palsy, schizophrenia; Badura-Brack et al., 2015; Spooner et al., 2018; Wilson et al., 2015; Wilson et al., 2019; Wilson et al., 2007; Wilson et al., 2009), the current study recommends that the use of paired-pulse paradigms with an ISI of ~200–220 ms may be ideal for eliciting optimal gating (i.e., best suppression of redundant information), and this may be most effective for distinguishing clinical populations from their healthy counterparts. However, previous studies have shown that the ISI optimal for distinguishing deficits in clinical populations (e.g., 500 ms) may differ from the ISI eliciting the best suppression (e.g., 100 ms) in the same patient group, suggesting that the two may serve dissociable mechanisms for sensory gating (Nagamoto et al., 1991). Further, work has shown that schizophrenia-related SG deficits in one modality (e.g., auditory) do not always extend to other modalities (e.g., somatosensory; (Edgar et al., 2005)). Thus, further investigation of SG task parameters and signal processing methods within clinical populations will be incredibly important to derive the optimal analytical approach for distinguishing different patient groups and detecting optimal gating.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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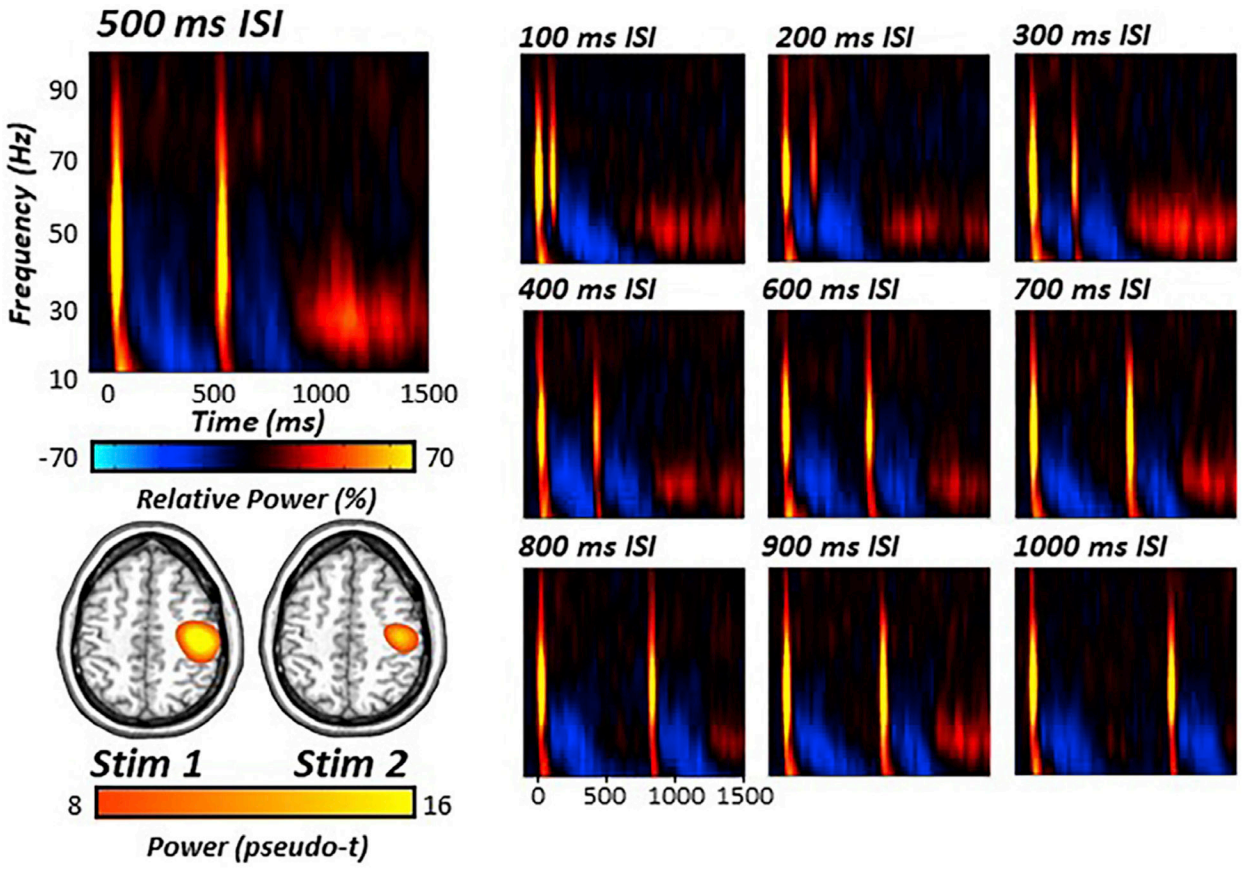


**Fig. 1. Neural Responses to Paired-Pulse Electrical Stimulation of the Left Median Nerve.**

(Top Left): Grand-averaged time-frequency spectrogram of a MEG sensor near the sensorimotor cortices illustrating the somatosensory spectral responses to paired-pulse electrical stimulation with an inter-stimulus interval of 500 ms. Time is shown on the x-axis (ms) and frequency is denoted on the y-axis (Hz). All signal power is expressed as a percent change from baseline (−700 to −300 ms), with the corresponding color scale bar displayed below the graphic. (Right): Time-frequency spectrograms of the same MEG sensor illustrating the somatosensory responses at each of the tested inter-stimulus intervals (ISIs) ranging from 100 to 1000 ms, respectively. Note that all axes and scales are held constant across the time-frequency spectrograms. (Bottom Left): Grand-averaged beamformer images (pseudo-t) for stimulation 1 and stimulation 2 across all participants and ISIs. Strong increases in power were found in the contralateral hand region of the somatosensory cortex in virtually identical locations across both stimulations and all ISIs.

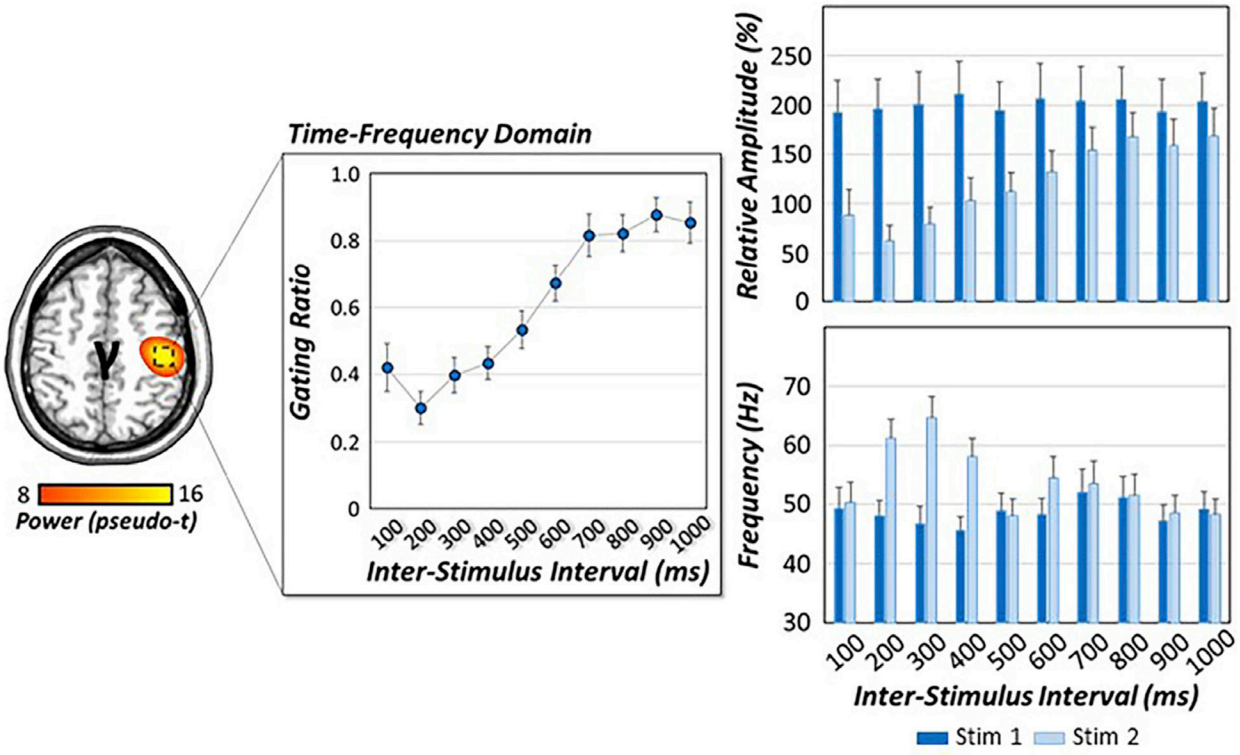


**Fig. 2. The Effect of ISI on Oscillatory Sensory Gating.**

(Left): Virtual sensor data were extracted from the contralateral primary somatosensory cortex of each participant using the peak voxel in the grand-averaged image. (Middle): From these time series, gating ratios (response power to stimulus 2/response power to stimulus 1) were computed and subjected to statistical analysis with temporally-neighboring ISIs. Trials with electrical stimulations separated by 200 ms exhibited the smallest gating ratios (i.e., better gating), with larger ratios evident for trials with other ISIs. (Right): Relative amplitude of the response to the first and second stimulation separately is shown for each ISI at the top, with dark blue reflecting responses to the first stimulation and light blue reflecting the same for the second stimulation. The spectral specificity of sensory gating (i.e., peak gamma frequency) is shown at the bottom, with significant elevations in peak gamma frequency in response to the second stimulation compared to the first for trials with an ISI of 200–400 ms.

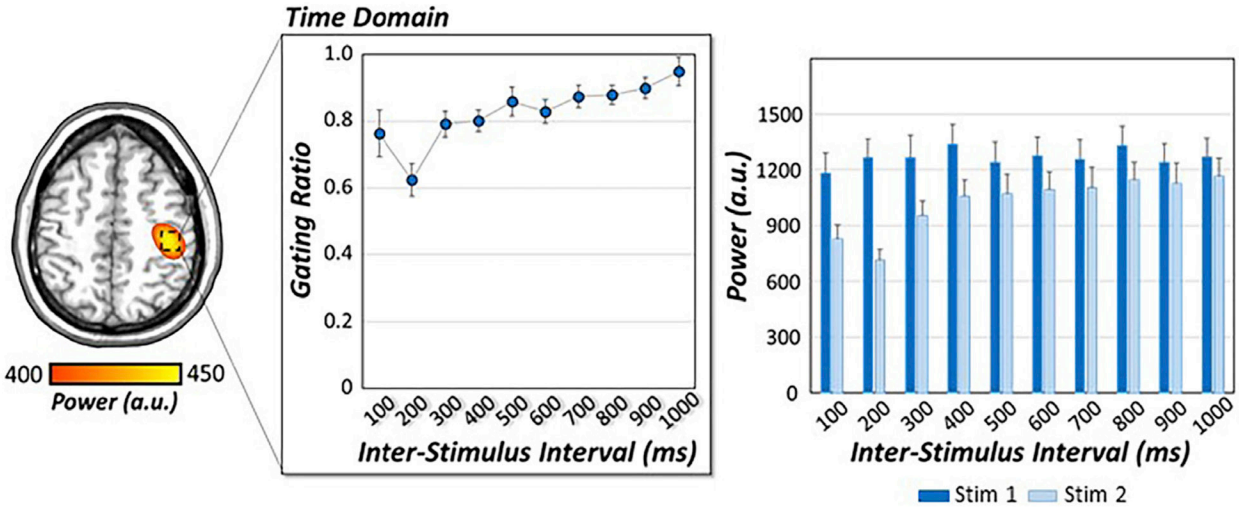


**Fig. 3. The Effect of ISI on Evoked Sensory Gating.**

(Left): Peak voxel sLORETA source image estimates were extracted from grand-averaged time-domain images to derive gating ratios for each ISI (Middle): Gating ratios were smallest (i.e., better suppression) for trials with an ISI of 200 ms. Electrical stimulations separated by 300 ms or greater revealed no discernable differences in gating. (Right): Power of the response to the first and second stimulation separately is shown for each ISI, with dark blue reflecting responses to the first stimulation and light blue reflecting the same for the second stimulation. For a time series depicting traditional somatosensory components, see Fig. S1 in supplementary materials.

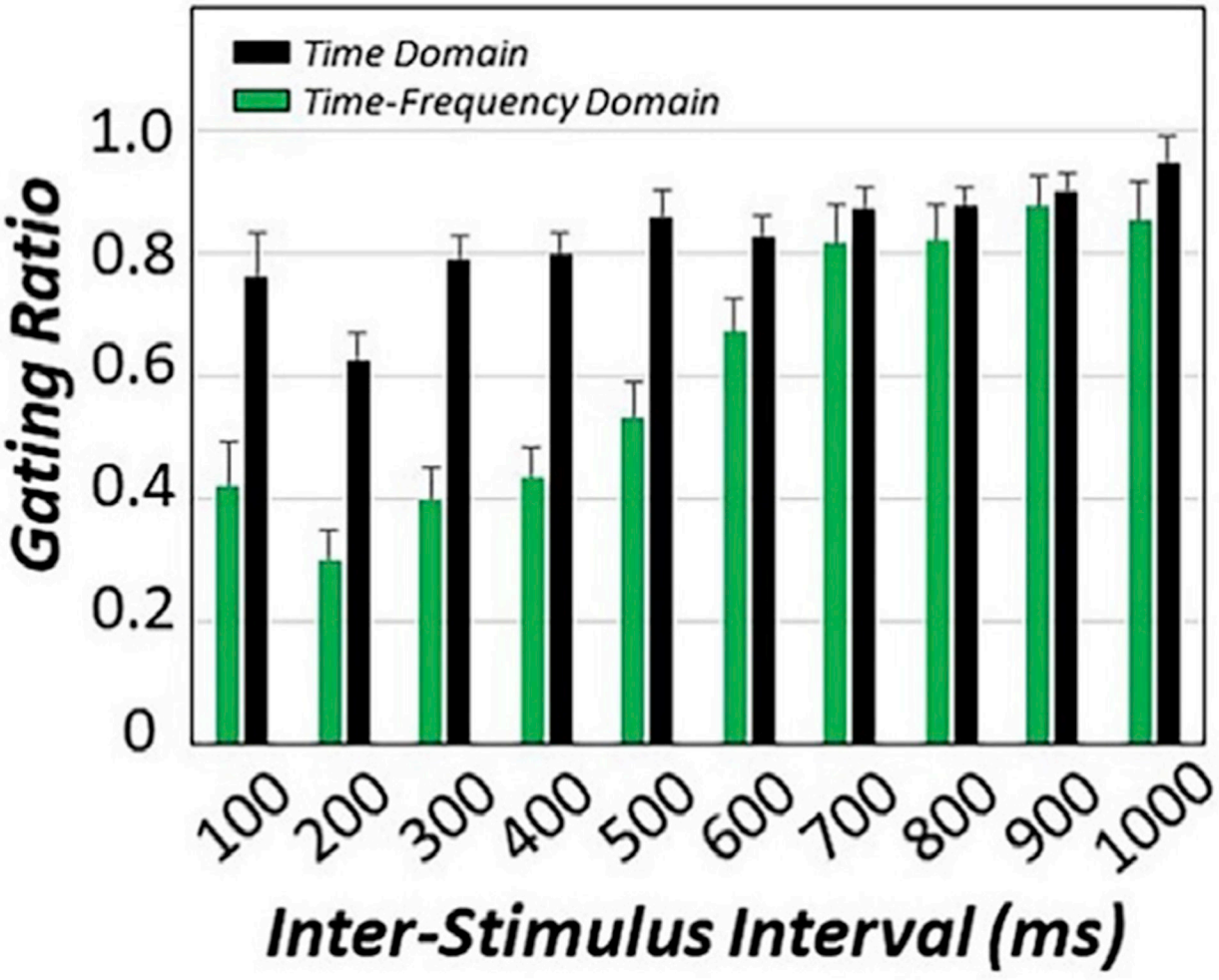


**Fig. 4. Sensitivity of Time-Domain and Oscillatory Responses to Gating.**

Paired sample t-tests of time-frequency domain (i.e., oscillatory) compared to time-domain gating ratios at each ISI revealed more robust gating (i.e., smaller ratios) in the oscillatory domain compared to time-domain evoked approaches for ISIs separated by 100–600 ms.