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RESEARCH ARTICLE

Attention modulates topology and dynamics of auditory sensory gating

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Abstract

This work challenges the widely accepted model of sensory gating as a preattention inhibitory process by investigating whether attention directed at the second tone (S2) within a paired-click paradigm could affect gating at the cortical level. We utilized magnetoencephalography, magnetic resonance imaging and spatio-temporal source localization to compare the cortical dynamics underlying gating responses across two conditions (passive and attention) in 19 healthy subjects. Source localization results reaffirmed the existence of a fast processing pathway between the prefrontal cortex (PFC) and bilateral superior temporal gyri (STG) that underlies the auditory gating process. STG source dynamics comprised two gating sub-components, Mb1 and Mb2, both of which showed significant gating suppression (>51%). The attention directed to the S2 tone changed the gating network topology by switching the prefrontal generator from a dorsolateral location, which was active in the passive condition (18/19), to a medial location, active in the attention condition (19/19). Enhanced responses to the attended stimulus caused a significant reduction in gating suppression in both STG gating components (>50%). Our results demonstrate that attention not only modulates sensory gating dynamics, but also exerts topological rerouting of information processing within the PFC. The present data, suggesting that the cortical levels of early sensory processing are subject to top-down influences, change the current view of gating as a purely automatic bottom-up process.

KEYWORDS

attention, auditory gating generators, auditory sensory gating, dorsolateral prefrontal cortex, gating network, gating stream, magnetoencephalography, medial prefrontal cortex, neuroimaging, paired-click paradigm, sensory pathways

1 | INTRODUCTION

The fast inhibition or enhancement of the neural response evoked by sensory stimuli is cognitive abilities with an essential impact on everyday life. Sensory gating refers to the primordial feature of the neural system to adjust its response to subsequent stimuli; in a gating-out mode, the neural system selectively suppresses its responses to irrelevant or repetitive stimuli, while in a gating-in mode, the neural system reinforces its responses to task-relevant or novel stimuli (Boutros & Belger, 1992; Freedman et al., 1987; Gjini, Arfken, & Boutros, 2010). The neural mechanisms underlying the gating modulations by which the brain selects relevant sensory information for access in short-term memory while filtering out irrelevant information are still the subject of investigation.

The M50, the magnetic counterpart of the P50 event-related potential, is a middle latency component of the evoked neuromagnetic response elicited 40–85 ms following stimulus presentation. The P50/M50 component is modulated by the recency of previous sensory stimuli, providing a measure of the neural ability to gate a response to a subsequent stimulus. Thus, it is widely used to investigate sensory gating processing. The paired-click paradigm is the most often used protocol to study the auditory gating inhibition process (gating-out). It utilizes two identical clicks (first click = S1, second click = S2) separated by a time-window of 500 ms. Neural P50/M50 responses to repeated stimuli are normally attenuated relative to the response to the first stimulus. This phenomenon, also known as repetition suppression, has been observed both in single-unit recordings in

nonhuman primates (Desimone, 1996) and in electroencephalography (EEG) and magnetoencephalography (MEG) studies in humans (Boutros & Belger, 1992; Freedman, Adler, Myles-Worsley, Nagamoto, & Miller, 1996; Gjini et al., 2010; Weiland, Boutros, Moran, Tepley, & Bowyer, 2008). The suppression capacity is expressed as the gating ratio, that is, the percentage of amplitude decreases in response to the repeated stimulus (S2) compared to the first stimulus (S1).

It has been suggested that gating-out serves as a basic protective mechanism that prevents irrelevant information from recurrent sensory processing, while at the same time gating-in processing enables the recognition of relevant environmental inputs that are essential for survival (Boutros & Belger, 1992; Gjini et al., 2010; Venables, 1964). Consequently, the dysfunction of these gating mechanisms ultimately leads to cognitive dysfunction (Venables, 1964) and behavioral disorders that are related to many neuropsychiatric diseases and psychoses (Morales-Muñoz et al., 2016). Sensory gating deficits are associated with the pathophysiology of bipolar disorder (Wang et al., 2014), posttraumatic stress disorder (Neylan et al., 1999), Parkinson's disease (Teo et al., 1997), Huntington's disease (Uc, Skinner, Rodnitzky, & Garcia-Rill, 2003), and depression (Wang et al., 2009). Although abnormalities in extracranially measured auditory gating responses are recognized as a well-established trait in patients with schizophrenia (Adler et al., 1982; Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Patterson et al., 2008), recent studies have revealed gating source topology modulation to have a high potential to be an individual biomarker for the detection of Alzheimer's disease (Josef Golubic, 2018; Josef Golubic et al., 2017), which may provide a unique opportunity to detect physiological changes associated with the disease before symptoms occur.

To interpret the broad range of extracranially measured modulations of gating dynamics in different pathophysiologies, it is necessary to establish the topology and cortical dynamics of neural substrates underlying early sensory processing in healthy individuals. Such normative data provide the opportunity to identify changes in the gating network neurodynamics related to the various pathologies. MEG provides an excellent temporal and spatial resolution (Knösche, Nakasato, Eiselt, & Haueisen, 2007; Sander et al., 2010), thus allowing the detailed and systematic spatiotemporal analysis of cortical gating networks in the working human brain to better address underlying mechanisms (Desimone, 1996; Supek & Aine, 2014).

Numerous neurophysiological studies have explored the generators underlying gating mechanisms, but there is no agreement on the gating network (Garcia-Rill et al., 2008; Grunwald et al., 2003; Korzyukov et al., 2007; Thoma et al., 2003; Yvert, Crouzeix, Bertrand, Seither-Preisler, & Pantev, 2001). Range of brain regions have been proposed as the generators of P50/M50 auditory response; predominantly the bilateral superior temporal gyri (STG; Cacace, Satya-Murti, & Wolpaw, 1990; Edgar et al., 2003; Reite, Teale, Zimmerman, Davis, & Whalen, 1988; Thoma et al., 2003; Wang et al., 2014; Yvert et al., 2001), the frontal cortex only (Garcia-Rill et al., 2008; Korzyukov et al., 2007), the frontal cortex in addition to the parietal, temporal and cingulate areas (Boutros, Gjini, Eickhoff, Urbach, & Pfliegerd, 2013; Boutros, Gjini, Urbach, & Pflieger, 2011), but also the hippocampus, thalamus and frontal cortex along (Tregellas et al., 2007; Williams, Nuechterlein, Subotnik, & Yee, 2011). Proposed involvement of subcortical regions in the generation of P50/M50 response has been demonstrated with functional magnetic resonance imaging (fMRI; Tregellas et al., 2007) or with fMRI-guided EEG source-localization (Williams et al., 2011), although later attempts failed to replicate their results (Mayer et al., 2013). The amalgamation of the entire electrophysiological response to both S1 and S2 stimuli, due to the minute-range temporal resolution, limit hemodynamic sensitivity of fMRI to the P50/M50 response during sensory gating. Detected hemodynamic response more likely reflects neural generators associated with global inhibitory processing, not specifically P50/M50 gating response. A subcortical contribution to sensory gating has also been demonstrated in studies using depth electrodes with human epilepsy patients (Goff, Williamson, VanGilder, Allison, & Fisher, 1980; Wilson, Babb, Halgreen, Wang, & Crandall, 1984), although more recent studies found no evidence of the hippocampal contributions to the P50/M50 (Boutros et al., 2005; Grunwald et al., 2003; Rosburg et al., 2008). One constraint associated with these investigations is that they may not be representative of the normal processes in healthy individuals, relying on patients with hippocampal pathologies.

Oranje and colleagues reported activation of the bilateral STG and medial frontal areas in the P50 gating formation (Oranje, Geyer, Bocker, Leon, & Verbaten, 2006), still, modeling an interval that covered both the P50 event-related potential and the peak of the N100, in addition to usual methodological constraints associated with EEG spatial localization, yielded to reduced reliability of reported results. However, recent studies using data of modern whole-head MEG systems and advanced spatiotemporal source localization techniques (Josef Golubic et al., 2014; Weiland et al., 2008), provide strong evidence that the generators underlying auditory sensory gating consisted of a prefrontal (PFC) generator in addition to the anticipated generators in bilateral STG. In addition, Josef Golubic and colleagues, using an auditory oddball-paradigm that evoked both gating mechanisms, habituation to redundant information (standard stimuli) and preattentive memory-based comparison processes (deviant stimuli), provided evidence of a modulatory function of the medial PFC generator on bilateral auditory cortices that was activated during both gating-in and gating-out responses (Josef Golubic et al., 2014). This result implies the existence of a novel, early sensory processing stream that connects the medial prefrontal cortex (mPFC) to the auditory cortices, alongside well-affirmed dorsal and ventral sensory processing pathways. A novel, fast gating loop from the prefrontal cortex to primary sensory areas would allow for simultaneous top-down and bottom-up modulation of sensory inputs during early sensory processing, suggesting the possibility of an attentional influence at a relatively early stage of information processing (Josef Golubic, 2019).

A fundamental question in the cortical processing of sensory information concerns whether top-down control mechanisms from higher brain areas to primary sensory areas modulate the earliest sensory gating processing and are thus actively engaged in perception. The nature of the interaction between attention, a cognitive top-down process that selects and focuses brain resources on relevant sensory information, and bottom-up sensory gating mechanisms represents an important issue in understanding the elementary processing of external inputs. Since sensory gating appears very early in a sensory processing stream, it is conceptualized as a purely automatic, preattentional neural mechanism (Freedman et al., 1987). Automatic mechanisms are thought to be the basis by which the individual instinctively navigates through a

stimulus-loaded environment, ignoring trivial stimuli and selecting novel stimuli for further processing. Therefore, the effects of attention and psychological stressors on sensory gating have rarely been examined in healthy subjects. Neurophysiological studies predominantly acknowledge that early sensory processing lacks any attentional influence (Boutros et al., 2004; Braff & Light, 2004; Clark & Hillyard, 1996; Freedman et al., 1987; Freedman, Waldo, Bickford-Weimer, & Nagamoto, 1991; Guterman & Josiassen, 1994; Hillyard & Anllo-Vento, 1998; Jerger, Biggins, & Fein, 1992; Kho et al., 2003; Mangun et al., 2001; Rosburg, Trautner, Elger, & Kurthen, 2004; White & Yee, 1997). However, a few studies have found that attention exerts a small but significant modulatory influence on the dynamics of sensory responses that emerge within the first 100 ms (Gjini, Burroughs, & Boutros, 2011, but see Guterman & Josiassen, 1994; Guterman, Josiassen, & Bashore Jr, 1992; Woldorff et al., 1993; Yee et al., 2010). The recent discovery of a fast gating loop between a higher cognitive center (PFC) and primary sensory cortices that modulates gating processing (Josef Golubic et al., 2014) reaffirms the possibility of an attentional influence on the earliest repetition suppression of sensory responses. However, a conclusive test of this hypothesis requires the direct assessment of the interaction between the PFC and the auditory sensory cortex during attention.

In this work, we challenged the accepted model of auditory sensory gating as a preattentive, automatic inhibitory process by investigating whether voluntary attention directed to the second tone of a pair (S2) within a paired-click paradigm could compromise dynamics and/or topology of the gating-out phenomenon at the cortical level. We utilized a 306-channel whole-head MEG system and individual MR-scans and conducted individual multi-dipole spatiotemporal source localizations to identify the cortical generators underlying auditory gating-out responses recorded during passive and attended conditions of the paired-click paradigm. In addition, we systematically analyzed the auditory gating-out ratios of transient neuromagnetic responses (extracranial recordings) and of estimated cortical dynamics of gating generators in the primary auditory cortices.

Sensory gating impairments, in addition to deficits in the top-down regulation of attentional resources, have been found to be strongly involved in pathophysiological sensory processing in schizophrenia as well as several other neuropsychiatric disorders and diseases such as PTSD, bipolar disorder and ADHD. It has been shown that pharmacotherapy in these pathologies has a relatively low efficiency in treating symptoms, has insufficient stability of effects over time, and causes unacceptable side effects during therapy. If focused attention can measurably modulate early sensory gating processing, then cognitive training could be a promising complement or additional rehabilitation program that could normalize impaired gating functions in these disorders (Genevsky, Garrett, Alexander, & Vinogradov, 2010; Popov et al., 2011) and consequently lead to an attenuation of symptoms.

2 | METHODS

2.1 | Subjects

Nineteen healthy right-handed volunteers, 15 females and 4 males (mean age ± stdev = 29.7 ± 9.6; median 26), with normal hearing, participated in the study. Smoking was not allowed a minimum of 2 hr before measurements. According to the Declaration of Helsinki, all subjects were instructed verbally about all details of the experiment and their right to terminate participation at any time. They gave written informed consent prior to the experiment. The study was approved by the Ethics Committee of the Jena University Hospital and Friedrich Schiller University.

2.2 | Experimental design and paradigm

2.2.1 | Passive condition

The standard auditory paired-click paradigm utilized two subsequent tones, S1 and S2, separated by a 500 ± 1 ms interstimulus interval (ISI). A Poisson-distributed intertrial interval (ITI) ranged from 6.5 s to 8.5 s. Stimuli S1 and S2 were two identical 1,200 Hz sinusoidal tones with a Gaussian envelope and onset/decay phase of 4 ms. The tones were binaurally presented to the subjects. The overall tone duration was 20 ms, with an intensity of 65 dB above hearing threshold. Before the session, subjects were tested for the hearing threshold at 1,200 Hz for the S1 tone.

2.2.2 | Attention condition

The attention condition was characterized by the varying occurrence probability of a "deviant paired-click" stimulus between a series of repeated standard paired-click stimuli. This condition utilized the presentation of 70% standard paired-click (S1, S2) stimuli identical to the stimuli used in the passive condition and 30% "deviant paired-click" stimuli (S1, R). The "deviant paired-click" stimulus comprised a pair of nonidentical frequency tones, S1 at 1,200 Hz and R at 1,400 Hz. The tones were sinusoidal with a Gaussian envelope, had an onset/decay phase of 4 ms and had a 20-ms duration. Tone intensity was 65 dB SL above hearing threshold. The ISI and ITI were the same as in the passive (standard) paired-click condition. The attention condition required directing attention to the frequency deviation rarely presented in the second tone of a paired-click paradigm (R). Subjects were instructed to press a button in response to a deviant second tone R (paying attention to the S2 deviant stimuli). Subsequent analysis revealed that all participants had an accuracy of at least 95%.

2.2.3 | Design

The tones of the paired-click paradigm were presented using the sound editor CoolEdit (Syntrillium Software AG, Phoenix, AZ) and delivered to the subject's ear canals using Nicolet Eartips TIP-300 sound transducers with plastic tubing. Adjustments to the intensity of the tones were made for each subject individually based on the results of a hearing threshold test performed with the ear inserts in place in order to achieve an intensity that was 65 dB above threshold. Subjects were instructed to relax in a supine position and try to avoid head movements during recording sessions in a magnetically shielded room. The experiment included two runs (passive and attention conditions counterbalanced across subjects) that were approximately 20–35 min in duration. To avoid effects of circadian rhythms on attention, 9 subjects participated in the experiment from 10 to 14 hr, and 10 subjects from 14 to 18 hr. To prevent fatigue effects, two pauses of 1 min each were included in each run. The first pause was

set after 6.5 min and second after 13 min during the runs (conditions). The time window between runs was 1 min.

2.3 | MEG/MRI data acquisition

Auditory MEG data were acquired with a 306-channel whole-head (helmet-shaped) Elekta Neuromag Oy Vectorview system in a magnetically shielded room at the Biomagnetic Center, Friedrich Schiller University, Jena, Germany. Subjects were lying (supine position) comfortably with their head centered within the measurement helmet. For artifact elimination, EOG (electrooculography) signals were recorded simultaneously with the MEG signals. Electrodes were placed above and below the eyes to monitor eye blinks and eye movements. The subject's nasion and the left and right preauricular points were registered using a Polhemus head position device (3SPACE FASTRAK, Polhemus, Inc., Colchester, USA) to establish a 3D-coordinate head frame. An additional 150 points along the surface of the head were marked to determine head shape for later precise co-registration with anatomical MR images. For each subject, anatomical 3D volumetric T1-weighted magnetic resonance images were obtained from a Siemens Magnetom Vision 1.5T scanner. Neuromagnetic activity was continuously recorded at a sampling rate of 1,000 Hz and bandwidth from 0.1 to 330 Hz. MEG epochs that contained amplitudes exceeding a threshold of 3pT/cm and/or EOG signals greater than 150 μV were rejected from online averaging. The stimuli were repeated until 100 evoked responses were recorded online for each of the standard paradigm tones in each condition.

2.4 | Data processing and filtering

Additional spatial interference was removed from the data with MaxFilter Version 2.0.21 (Elekta Neuromag Oy, Finland) using the signal space separation (SSS) method (Taulu & Simola, 2006). Maxwell filtering transforms measured MEG data inherently to harmonic function amplitudes, which can be interpreted as virtual channels to compose interference-free brain signals and to transform data between different head positions. Normally, the program applies the virtual channels to convert the input data to idealized sensors. MaxFilter utilizes the inherent RMS noise levels of the sensors: three fT/sqrt(Hz) for magnetometers, three fT/cm/sqrt(Hz) for gradiometers. The default-scaling factor between magnetometer and gradiometer channels was 100.

All preprocessed raw data recorded for each stimulus (in both conditions) were used for later averaging. Averaged data were low-pass-filtered at 40 Hz to extract physiologically relevant activations. MEGAN (MEG ANalysis), a MEG data visualization and analysis tool developed by Elaine Best in the Biophysics group at Los Alamos National Laboratory was used to: (a) produce and display NetMEG files from the original .fif data format and (b) baseline correction (removing the baseline noise estimated from the −100 to 0 ms prestimulus interval).

Later, processing was performed using MRIVIEW (Ranken, 2014) for the following reasons: (a) to conduct the semi-automated segmentation of volumetric MRI data; (b) to identify the best-fitting sphere; (c) to reconcile the MRI coordinate system with MEG coordinate space; and (d) to obtain multi-dipole source estimates using a Calibrated Start Spatio Temporal (CSST) tool (Ranken et al., 2002) for multi-start, multi-dipole MEG inverse calculations.

2.5 | Source localization

The spatio-temporal localization of early sensory processing was determined assuming point current sources (Josef Golubic et al., 2011; Schimpf, Ramon, & Haueisen, 2002; Supek, K Stingl, Josef Golubic, Susac, & Ranken, 2006; Susac, Heslenfeld, Huonker, & Supek, 2014; Susac, Ilmoniemi, Pihko, Nurminen, & Supek, 2009; Susac, Ilmoniemi, Pihko, Ranken, & Supek, 2010). The cortical sources of the measured auditory evoked fields were modeled assuming multiple rotating current dipoles embedded in a spherical volume conductor (Huang et al., 1998). Using a semi-automated segmentation tool within MRIVIEW, individual cortical surfaces were derived and labeled from each subject's MRI data. 3D morphological operations were used to identify the gray/white matter boundary. Segmented cortical surfaces were used to estimate the best-fitting sphere for the individual head model of each subject and for subsequent inverse calculations using CSST algorithm.

Spatio-temporal source analyses of the empirical data acquired from all MEG channels were performed using the multi-dipole CSST algorithm and were not constrained to any preselected cortical locations. Source localization was conducted across the full 30–100-ms poststimulus time window for each tone in each condition. Estimates of the time invariant parameters (spatial locations) were derived first using nonlinear minimization and kept constant for the selected time window, while linear estimations of the associated time-varying parameters (source strength and orientation) were calculated for each time instance. CSST uses a semi-automated, nonlinear, multi-start downhill simplex minimization (Supek & Aine, 1993) of the reduced chi-square metric (Supek & Aine, 1997) to estimate the locations, strengths, and orientations of activated cortical sources.

CSST runs multiple nonlinear simplex calculations from the random selection of MRI-derived starting cortical locations to avoid local minima of the cost function (reduced chi-square error function). This algorithm minimizes a possible bias of the results toward anticipated areas of activity due to investigator selection of starting points. A two-stage simplex procedure utilizes a coarse convergence criterion in the simplex procedure to eject sub-optimal solutions at the first stage and then refines the remaining solutions using a fine convergence setting. In the present study, up to 10,000 starting points, randomly selected from the individual realistic segmented cortex (for each dipole source model), were used for the first stage of the simplex search, and the best 2,000 points were used in the second stage.

First, the minimum number of neuromagnetic dipole generators (minimum model order, n) was evaluated using singular value decomposition (SVD) of the spatiotemporal data matrix within the selected time interval. Inverse spatio-temporal calculations were conducted starting from the evaluated minimum model order n and continued by subsequently increasing the model order ($n + 1$, $n + 2$, etc.). The selection of the best-adequate solution was based on several parameters used during several subsequent steps. In obtaining the adequate solution for a given model order, first, we used normalized chi-square criteria. Performing calculations, we saved the 10 best-fitting solutions under the chi-square criterion for each model order. The selection of

the adequate solution from these statistically 10 best-fitting solutions required additional criteria: (a) the proportion of variance explained (PVE); (b) the comparison of dipole time-courses and residual field waveforms to assess whether additional neurophysiological signals remained; and (c) an visual inspection of neurophysiological acceptability of localized dipole solutions (dipoles localized within bones, in the center of the head, outside of the brain, etc. are indication for a solution rejection). Selection of an adequate solution for each model order was followed by a comparison between adequate solutions with different model order, to assess the best-adequate solution. In the selection of the best-adequate model, we first compared the reduced chi-square measures of goodness-of-fit of each selected solution with different model order. If adequate solutions had similar chi-square values, we applied additional criteria: the inspection of the PVE value, the visual inspection of dipole clustering to assess location scatter (an indication of over-modeling), the inspection of residual field waveforms to assess whether additional signals remained (an indication of under-modeling) and an inspection of the estimated source time courses (near-zero amplitudes across entire time interval are an indication of over-modeling).

In addition, Monte Carlo simulations were conducted to provide confidence regions for the best-fitting dipole solutions and to estimate the effect of the measurement noise. In the present calculations, 100 simulations were performed using the source locations from the best-fitting model as starting locations and adding noise determined by the sensor baseline noise variance (the −100-ms prestimulus signal).

2.6 | Anatomical locations

The anatomical locations of the best-fitting neuromagnetic dipole generators were assessed by reconciling the MEG head-centered coordinate system with participants' MRI coordinate system. The original individual MRI-derived head shapes were used to avoid distortion of brain characteristics, unlike the methods that remove size differences by scaling the structural data (i.e., spatially normalization to the Talairach stereotaxic system). The coordinate system used the following conventions: a positive *x*-axis denotes toward the nose, a positive *y*-axis denotes toward the left ear, and a positive *z*-axis denotes toward the top of the head. The primary auditory areas (STG in the right and left hemispheres) were manually identified on individual MRI scans (Brodmann areas [BA] 41/42). The anterior limit of the STG was identified using the first slice that showed the white matter tract (temporal stem) that connected the temporal lobe with the base of the brain. The posterior boundary of the STG was defined as the slice where the fibers of the crux of the fornix last appeared. The location of a dipole in the anterior polar portion of the medial prefrontal lobe (including frontopolar (BA 10) and orbitofrontal (BA 11) regions) was the criterion for the mPFC source relative to each individual subject's MRI. A dorsolateral prefrontal (dlPFC) generator implied a dipole source localized to the lateral part of middle frontal gyrus (lateral parts of BA 9, 10, and 46) relative to each individual subject's MRI.

2.7 | Statistical analyses

After baseline correction, the amplitudes (baseline-to-peak) and peak latencies of the transient auditory evoked neuromagnetic fields (AEF) in addition to the estimated cortical locations and source dynamics for each neuromagnetic dipole evoked by the paradigm tones were examined within the time window of 30–100 ms poststimulus across conditions and subjects. Data sets were tested for normality distributions and homogeneity of variances, that is, the assumptions of the analysis of variance (ANOVA). Kolmogorov–Smirnov tests were carried out to verify the normality of the distributions, and Bartellet-Box tests were used to determine the homoscedasticity of the variance. After the Kolmogorov–Smirnov and Bartellet-Box tests confirmed data normality, ANOVA was applied to assess differences in the amplitudes and maximum peak latencies of the transient neuromagnetic auditory responses that emerged within 30–100 ms, the estimated model order (number of localized dipole sources) and the accompanying cortical source dynamics within the 30–100-ms time window across subjects. Individual amplitudes and peak latencies of characteristic transient components were assessed from the root mean square (RMS) of responses recorded over magnetometers. Individual amplitudes and peak latencies of characteristic components in cortical dynamics of the primary auditory cortices were assessed from the time courses of the localized STG generators. The main factors submitted to ANOVA consisted of the following: Hemisphere (Left vs. Right STG); Tone (S1 vs. S2 tone); Condition (Passive vs. Attention condition). In the attention condition, the epochs obtained for the deviant second tone R (and corresponding S1) were rejected during analysis.

3 | RESULTS

During the passive condition, a total of 109 ± 7 and 107 ± 8 trials were acquired across subjects for the S1 and S2 tone, respectively, while 107 ± 7 and 104 ± 9 for the S1 and S2 tone during the attention condition. In the attention condition, there was only one missed hit across subjects (i.e., only one subject missed one hit), and one hit was inaccurate (different subject). The percentage of accurate responses was (99.65 ± 1.05)%, the percentage of the missed hits was (0.18 ± 0.77)%, the percentage of the inaccurate responses was (0.18 ± 0.77)% and the total percentage of the wrong hits was (0.35 ± 0.05)%.

3.1 | Auditory evoked fields

3.1.1 | Recorded data

Characteristic gating peaks, Mb1 and Mb2, in AEF responses to S1 and S2 tones were observed across all subjects during both conditions of a paired-click paradigm. Figure 1 shows the RMS of AEF responses to S1 and S2 of a representative subject within a 20–100-ms poststimulus window as well as the grand average responses to the tones in both paradigm conditions.

Panels A and B of Figure 2 show the spatial magnetic field distributions evoked by the S2 tone at the peak latencies of the Mb2 component across conditions. The component showed a multi-dipolar pattern topography in both conditions. The strongest dipolar-field amplitudes were recorded at the temporal sensors over both hemispheres across conditions and subjects. In addition, lower but detectible dipolar AEF distributions were recorded at the frontal sensors across subjects. Tones of the passive paradigm elicited frontal dipolar-like patterns

predominantly over the dorsal sensors in the majority of subjects (18/19), while the attention condition shifted the peak field distributions to the medial frontal sensors (19/19). AEF responses elicited by S1 and S2 tones were generally stronger to the S1 tone throughout the entire recording time for all subjects and both conditions.

3.1.2 | Passive paired-click paradigm condition

Two AEF components within a 30–100 ms poststimulus window, identified from the MEG recordings to S1 and S2 tones in a passive paradigm condition with high reproducibility across subjects (19/19), are shown in Figures 1 and 2 for representative subjects. The first component in the RMS grand average response to the S1 tone, Mb1, peaked at 49 ± 6 ms and the second response, Mb2, peaked at 73 ± 8 ms. The first component in response to the S2 tone peaked at 53 ± 6 ms (Mb1) and the second at 72 ± 9 ms (Mb2). There were no significant differences between the peak latencies of the corresponding components (Mb1 and Mb2) in response to the paradigm tones (S1 and S2), Mb1: $F(1,36) = 1.14$, $p = 0.29$; Mb2: $F(1,36) = 1.74$, $p = 0.2$.

3.1.3 | Extracranial gating-out during the passive condition

Table 1 presents the mean gating ratios and corresponding standard deviations in addition to individual gating-out ratios across subjects for both gating components evoked by a passive paired-click paradigm. The gating ratio was calculated as the ratio of amplitudes in response to the repeated stimulus (S2) compared to the first stimulus (S1). The amplitudes of both subcomponents in the M50 response to S1 were significantly larger than the corresponding response amplitudes to S2 (Mb1, $F(1,36) = 33.35$, $p < 0.001$; Mb2, $F(1,36) = 31.46$, $p < 0.001$). The first component of the M50 auditory response (Mb1) had a tendency toward a more efficient repetition suppression, showing a decreased gating-out ratio in comparison to that of the Mb2, although this effect did not reach statistical significance.

3.1.4 | Attention paired-click paradigm condition

AEF recorded during conditions with voluntary attention directed to the second tone did not show changes in the morphology of responses evoked by either paradigm tone in comparison to the responses in the passive condition (Figure 2). Two stable AEF components, found within a 30–100-ms poststimulus window in response to S1 and S2 tones, with high reproducibility across subjects (19/19), are representatively shown in Figures 1 and 2. The first component in response to the S1 tone, Mb1, peaked at 42 ± 9 ms on average, and the second, Mb2, peaked at 73 ± 9 ms. The first component in the response to the S2 tone peaked at 36 ± 7 ms (Mb1) and the second at 74 ± 7 ms (Mb2), across subjects. There were no significant differences between the peak latencies of the corresponding components (Mb1 and Mb2) in

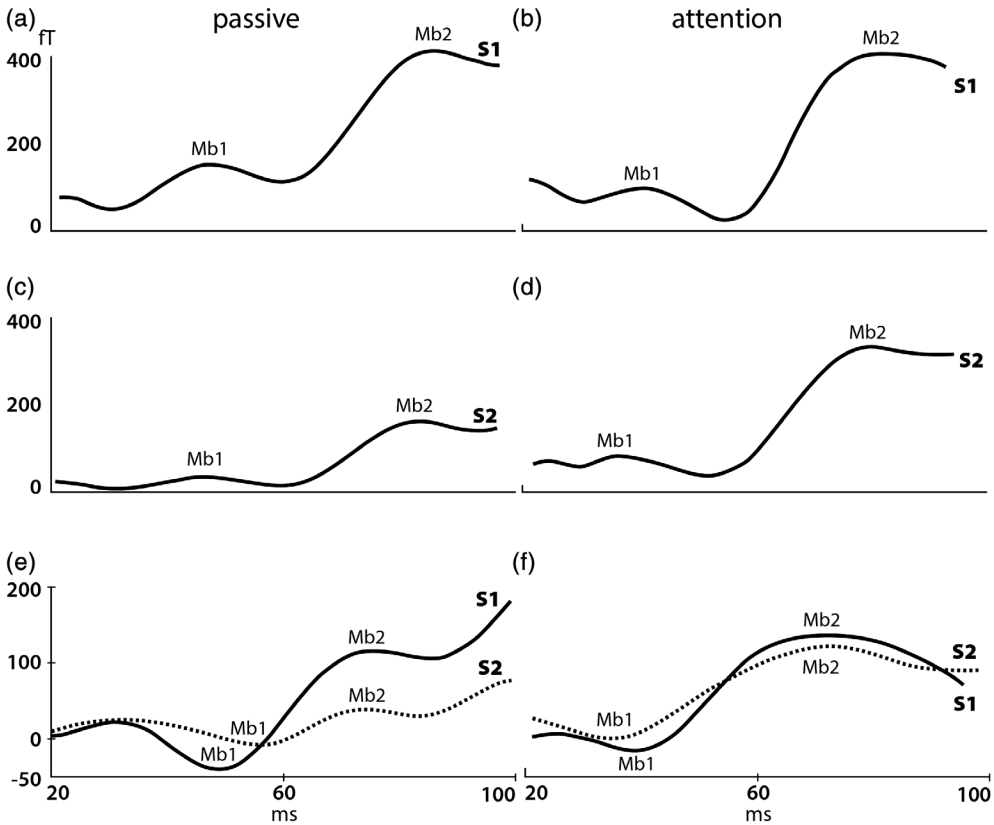

FIGURE 1 AEF gating responses evoked by both conditions of a paired-click paradigm. AEF responses within a 20–100-ms poststimulus time window in passive and attention conditions of a paired-click paradigm. RMS of responses to S1 and S2 tones evoked in passive (panel a and panel c) and attention (panel b and panel d) conditions, recorded by all magnetometers, are shown for a representative subject. Grand averages (GA) of AEF responses (individually across magnetometers, then across subjects) to S1 and S2 for the two conditions are shown in panels e and f. GA demonstrates the high robustness of both characteristic gating responses (Mb1 and Mb2) and an attention effect across subjects

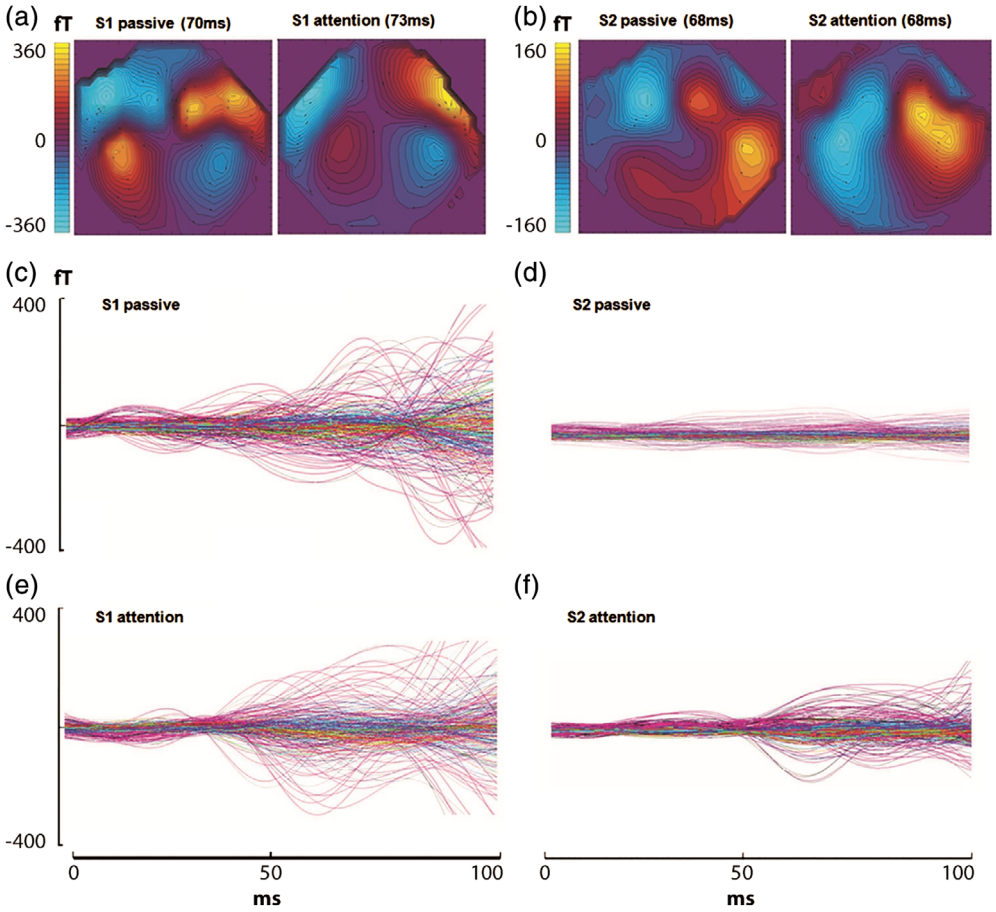

FIGURE 2 Spatio-temporal distributions of AEF evoked by the two conditions of a paired-click paradigm. Spatial magnetic field distributions evoked by S1 and S2 tones at the RMS peak latencies of the Mb2 component across paradigm conditions are shown in panels a and b. Iso-field color-coded maps of the AEF obtained from all magnetometers are shown for a representative subject. Black iso-field lines were constructed by the interpolation from the amplitudes measured at the selected peak latency. The magnitudes of positive fields (flux emerging from the head) are displayed in shades of yellow-red, and those of negative fields are displayed in shades of blue. Scale values are indicated to the left of the maps. The AEF responses within the first 100 ms poststimulus to the S1 and S2 tones evoked in passive (panel c and panel d) and attention (panel e and panel f) conditions, recorded by all sensors, are shown for a representative subject. Each tracing represents an average of 100 individual neural responses [Color figure can be viewed at wileyonlinelibrary.com]

response to the paradigm tones, Mb1: $F(1,36) = 0.20$, $p = 0.67$; Mb2: $F(1,36) = 0.06$, $p = 0.80$.

3.1.5 | Extracranial gating-out during the attention condition

Individual gating-out ratios, mean values and corresponding standard deviations of the responses to the tones in an attention paired-click paradigm are shown in Table 1. The amplitudes of both M50 subcomponent responses to the S1 were significantly larger than the corresponding amplitudes of responses to the S2 (Mb1, $F(1,36) = 9.76$, $p = 0.003$; Mb2, $F(1,36) = 4.74$, $p = 0.04$). As in a passive condition, the first component of the M50 auditory response (Mb1) showed a tendency toward a more efficient repetition suppression compared to that of the Mb2, but the effect was not statistically significant.

3.1.6 | Effect of attention on the extracranial gating-out

The amplitudes of both M50 components (Mb1 and Mb2) in response to the S1 did not show statistically significant differences as an effect of condition (Mb1: $F(1,36) = 2.22$, $p = 0.14$; Mb2: $F(1,36) = 2.21$, $p = 0.15$). The amplitudes of both M50 components in response to the S2 in the attention condition (when the focus of attention was directed at S2) were significantly larger compared to responses in the passive condition (Mb1: $F(1,36) = 31.79$, $p < 0.001$; Mb2, $F(1,36) = 27.35$, $p < 0.001$). Consequently, attention directed to the second tone in the pair revealed a gating-out reduction, that is, both gating-out ratios in the attention condition were significantly increased (23% Mb1 and 37% Mb2) in comparison to those of the passive condition (Mb1: $F(1,36) = 48.72$, $p < 0.001$; Mb2, $F(1,36) = 44.63$, $p < 0.001$) due to the larger responses to S2 in the attention condition. However, there were no significant differences between the peak latencies of the corresponding components (Mb1 and Mb2) in response to the paradigm tones (S1 and S2) as an effect of condition: $F(3,18,54) = 1.53$; 1.76; $p > 0.12$).

3.2 | Topology of auditory sensory gating generators

To identify the cortical generators underlying auditory gating-out responses, multi-dipole spatio-temporal localizations of AEF data were conducted for the 30–100-ms poststimulus time interval for both paradigm tones and both experimental conditions. Localization analysis of cortical generators revealed three cortical regions underlying the components of the M50 auditory sensory gating response across subjects

TABLE 1 Extracranial gating-out ratios[a]

	Passive		Attention	
Subject	Mb1[b]	Mb2[b]	Mb1	Mb2
P1	0.52	0.55	0.96	0.65
P2	0.26	0.88	0.74	0.94
P3	0.51	0.55	0.71	0.96
P4	0.38	0.55	0.73	0.90
P5	0.81	0.82	0.72	0.67
P6	0.64	0.56	0.71	0.96
P7	0.65	0.66	0.80	0.90
P8	0.67	0.46	0.83	0.83
P9	0.71	0.35	0.82	0.57
P10	0.51	0.55	0.69	0.75
P11	0.52	0.58	0.73	0.79
P12	0.56	0.57	0.77	0.74
P13	0.68	0.59	0.68	0.73
P14	0.55	0.51	0.82	0.76
P15	0.54	0.57	0.77	0.93
P16	0.43	0.54	0.80	0.85
P17	0.47	0.54	0.77	0.89
P18	0.54	0.58	0.85	0.94
P19	0.54	0.55	0.88	0.92
Mean ± *SD*	0.55 ± 0.12	0.58 ± 0.11	0.78 ± 0.07	0.81 ± 0.14

[a]Gating ratio: Amplitude S2/amplitude S1.
[b]Mb1, Mb2—Sub-components of the M50 auditory gating response.

(19/19). Two subjects showed activation of an additional generator localized in parietal areas for both tones and both conditions. However, the estimated dynamics of this parietal generator (not shown) were evident only during the last 20 ms (80–100 ms) of the localization interval, suggesting the activation of a cortical generator contributing to later AEF activity (M100).

3.2.1 | Passive paired-click paradigm condition

Panel (a) of Figure 3 shows the three identified brain regions underlying M50 auditory sensory gating evoked by the tones of the passive paired-click paradigm. The bilateral STG generators were localized in 19/19 subjects for both tones of the paradigm. Prefrontal activity was identified in 19/19 subjects. The right dorsolateral prefrontal area (dlPFC) was the region where the prefrontal generator occurred in the majority of subjects (18/19). Only one subject revealed a more medial prefrontal source location. There were no significant within-subject differences in the spatial positions of the identified gating generators evoked by the paradigm tones (RM ANOVA; left STG, right STG, dlPFC, mPFC: $p > 0.14$).

3.2.2 | Attention paired-click paradigm condition

Panel (b) of Figure 3 shows the three identified brain regions underlying the M50 auditory sensory gating evoked by the tones of the paired-click paradigm when attention was directed to the second paradigm tone. Bilateral STG activation was localized in 19/19 subjects for both paradigm tones. Prefrontal activity was identified in 19/19 subjects. The medial prefrontal area (mPFC) was the region where the prefrontal generator was localized for all subjects (19/19). There were no significant within-subject differences in the spatial localization of the identified gating generators evoked by the paradigm tones (RM ANOVA; left STG, right STG, mPFC: $p > 0.25$).

3.3 | Cortical gating-out ratios

Kolmogorov–Smirnov tests confirmed that none of the data distributions (amplitudes and peak latencies of the estimated cortical dynamics of the generators underlying M50 auditory sensory gating) were significantly different from a normal distribution. STG generators were localized bilaterally across subjects without systematic differences

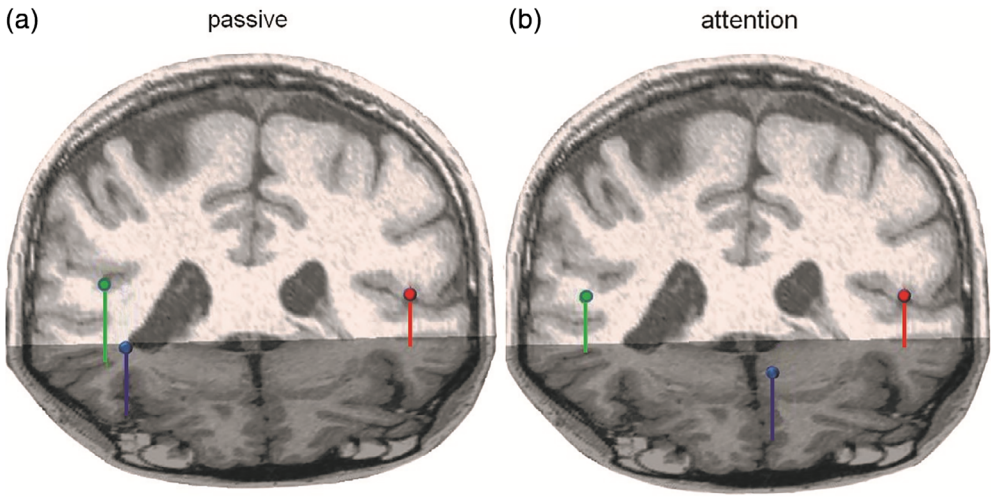

FIGURE 3 Localization of auditory gating generators estimated in the 30–100-ms time interval evoked by the tones of the paired-click paradigm in a representative subject across conditions. The best-fitting source locations were superimposed on individual volumetric MRI head data to achieve a spatial (3D) rendering of the auditory gating topology. Panel (a) shows the gating topology evoked by the passive paradigm condition where the right dlPFC (blue dot) in addition to bilateral STG sources (green and red dots; right and left STG generators, respectively), were active in processing both paradigm tones (18/19 subjects). Panel (b) shows the attention-alerted gating network, characterized by a topological change in the prefrontal generator. Instead of a gating generator in the dlPFC region, an mPFC (blue dot) generator was activated in the processing of both paradigm tones (19/19)

between hemispheric activations during paradigm tones and conditions (RM ANOVA, the main effect of the hemisphere; latency, amplitude, $p > 0.1$); hence, the estimated STG time-courses were averaged across hemispheres for each subject.

3.3.1 | Passive paired-click paradigm condition

Panel (a) of Figure 4 reveals two identifiable components within the cortical dynamics of the STG generators underlying auditory sensory gating. These components of the cortical activity of the gating generators were anticipated to be the origins of the Mb1 and Mb2 components of the M50 gating response found in the extracranially recorded AEF responses. The cortical Mb1 and Mb2 components were consistently identified within the 30–100-ms poststimulus window in the time courses of the generators localized in the primary auditory cortices with high reproducibility across subjects (19/19). Comparisons between the paradigm tones showed significantly stronger STG responses to the first paradigm tone than to the second for both cortical gating components (Mb1, $F(1,36) = 119.41$, $p < 0.001$; Mb2, $F(1,36) = 105.61$, $p < 0.001$).

The gating-out ratios revealed from the cortical dynamics analysis of the STG generators are shown in Table 2. There was no statistically significant difference between the corresponding gating-out ratios of the Mb1 and Mb2 cortical components ($p > 0.5$). Gating-out effects in the dynamics of the dlPFC generator were not observed across subjects.

3.3.2 | Attention paired-click paradigm condition

Panel (b) of Figure 4 shows two identifiable components, Mb1 and Mb2, within the cortical dynamics of the generators underlying auditory sensory gating when attention was targeted to the second paradigm tone S2. These components were consistently identified within the 30–100-ms poststimulus window in the activity of the STG generators evoked by the tones of the attention paradigm condition, showing high reproducibility across subjects (19/19). The first paradigm tone S1 evoked significantly stronger STG responses in comparison to the second tone S2 (Mb1, $F(1,36) = 12.48$, $p = 0.001$; Mb2, $F(1,36) = 21.47$, $p < 0.001$).

3.3.3 | Effect of attention on the cortical gating-out ratios

The effect of attention was prominent in the STG amplitudes of both gating components to the second paradigm tone S2. The gating components Mb1 and Mb2 evoked by the second tone S2 were significantly larger in the attention condition than in the passive condition (Mb1, $F(1,36) = 49.51$, $p < 0.001$; Mb2, $F(1,36) = 50.84$, $p < 0.001$). The amplitudes of both cortical gating components in response to S1 did not show a statistically significant difference as an effect of condition ($p > 0.95$). Attention directed to the second paradigm tone caused significant cortical gating-out reductions in the Mb1 (55%) and Mb2 (50%) gating components (Mb1, $F(1,36) = 113.27$, $p < 0.001$; Mb2, $F(1,36) = 78.66$, $p < 0.001$) due to the larger responses of the STG generators to the second paradigm tone (Table 2). Gating-out effects in the dynamics of the mPFC generator were not observed across subjects.

4 | DISCUSSION

In the present study, neuromagnetic, MEG, and structural MR imaging techniques were combined to identify the functional and anatomical effects of attention on sensory gating processing of a paired-click paradigm. Our results provide the first evidence that auditory attention not only modulates gating dynamics within the first 100 ms after stimulus presentation, but also exerts a robust influence on the topology of the neural substrates underlying the gating-out phenomenon. Here, we show that attention directed to the second tone of a simple paired-click paradigm changed the gating generators topology by switching a prefrontal source from the right dlPFC region, which was active in the passive condition, to an mPFC region, active in an attention condition. This topological change in the generators underlying the gating responses was accompanied by a reduction in the gating-out efficiency in the cortical dynamics of the STG generators caused by enhanced responses elicited by the attended tone S2.

Since the long intertrial time intervals are an inherent part of the setup of P50/M50 sensory gating paradigms, attention cannot be directed to other, task-irrelevant auditory stimuli. Thus, in sensory

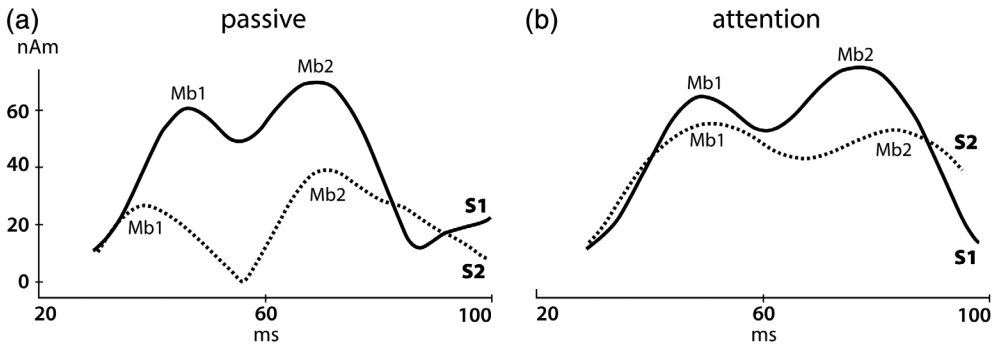

FIGURE 4 Estimated cortical dynamics of the gating generators in the primary auditory cortices across paradigm tones and conditions. Time courses of STG activity were individually averaged across hemispheres then across subjects and are displayed for the 30–100-ms time window. The cortical sub-components Mb1 and Mb2 of the auditory sensory gating response are marked on the estimated cortical dynamics of STG generators. Panel a shows the estimated cortical responses in the primary auditory cortices to the S1 tone and a significantly reduced response to the redundant S2 tone during the passive listening of a paired-click paradigm. Panel B shows the estimated cortical activity in the primary auditory cortices when attention is directed to the second tone S2 of the paired-click paradigm. The cortical response to the S2 tone in the attention condition was significantly enhanced in comparison to the response to the same tone in the passive condition

TABLE 2 Cortical gating-out ratios[a]

	Passive		Attention	
Subject	Mb1[b]	Mb2[b]	Mb1	Mb2
P1	0.45	0.42	0.85	0.82
P2	0.45	0.44	0.80	0.84
P3	0.53	0.50	0.75	0.76
P4	0.37	0.51	0.85	0.71
P5	0.59	0.84	0.85	0.87
P6	0.45	0.63	0.73	0.77
P7	0.65	0.68	0.85	0.81
P8	0.30	0.30	0.71	0.67
P9	0.44	0.41	0.77	0.82
P10	0.42	0.40	0.81	0.80
P11	0.76	0.70	0.86	0.92
P12	0.52	0.48	0.87	0.83
P13	0.58	0.55	0.78	0.71
P14	0.46	0.53	0.79	0.89
P15	0.41	0.46	0.89	0.88
P16	0.58	0.48	0.75	0.85
P17	0.54	0.57	0.87	0.87
P18	0.54	0.54	0.83	0.75
P19	0.67	0.51	0.86	0.81
Mean ± *SD*	0.51 ± 0.11	0.52 ± 0.12	0.81 ± 0.05	0.81 ± 0.07

[a]Gating ratio: Amplitude S2/amplitude S1.
[b]Mb1, Mb2—Sub-components of the M50 auditory gating response.

gating experiments attention cannot be controlled in a similar way as in dichotic listening tasks and, therefore, attention has to be regarded as a potential confound in a paradigm. In our experimental design, to ensure paying attention to the second tone of a paired-click paradigm, subjects were instructed to press a button in response to a deviant second tone R. In the attention condition, the epochs obtained for the deviant second tone R (and corresponding S1) were rejected during analysis and were not included in the respective averages to avoid any sensorimotor or other possible overlapping activity beside attention. Single cell recordings from animal studies (Eliades & Wang, 2003; Poulet & Hedwig, 2002) and human neuroimaging studies (Blakemore, Wolpert, & Frith, 1998; Martikainen, Kaneko, & Hari, 2005) confirmed that there is an attenuated response in the primary auditory cortex after a motor response.

Expectation facilitates sensory perception by restricting interpretation based on the prior likelihood, while attention relieves processing burden by prioritizing of that sensory information deemed to be of the highest relevance to the subject. Attention and expectation, despite similar behavioral effects, influence neural responses differently, whereas attention typically enhances evoked responses, expectation reduces them (Auksztulewicz & Friston, 2015; Friston, 2010; Friston & Kiebel, 2009). Increased M50 response to the attended tone S2 only, (i.e., without amplitude modulation of response to accompanied tone S1), provides evidence of an attention effect in our experiment. This result is in line with the predictive coding framework, which formalizes attention as optimal updating of sensory precision, where more precise sensory prediction errors induce stronger evoked responses (Feldman & Friston, 2010).

The present results suggest the neural architecture of early top-down control of information processing, once again affirming the existence of a fast sensory gating loop (Josef Golubic et al., 2014) that links the prefrontal cortex to primary sensory areas. Here, we show that the sensory gating loop could operate as a dynamic mechanism that monitors and modulates neural adaptation to environmental demands including selective attention to a simple sensory input. Our results are in line with the recent modeling efforts of sensory gating using individualized canonical microcircuits (Kunze, Peterson, Haueisen, & Knösche, 2017). In addition, we demonstrated that the requirement of selective attention may evoke early (i.e., within the first 100 ms post-stimulus) rerouting of information processing within the prefrontal cortex by shifting activity from the dlPFC to the mPFC region.

It has been shown that a nonattention auditory oddball paradigm evokes an mPFC generator in addition to STG sources (Josef Golubic et al., 2014), the same gating generator topology localized here in the attention paired-click condition. Conversely, the nonattention paired-click condition evoked a different gating topology, consisting of a dlPFC source in addition to the STG generators. Passive (i.e., not requiring any behavioral response or directed/focused attention) paired-click and oddball paradigms activate a different prefrontal generator within the auditory gating network. This result indicates that medial and dorsal prefrontal regions serve different functions involved during the earliest gating processing of simple sensory stimuli.

Passive paired-click stimulation, characterized by the constant repetition of both short-term and long-term patterns (S1-500 ms; S2-8 s), could result in long-term repetition suppression produced by the dorsolateral prefrontal region. On the other hand, an oddball paradigm, characterized by the varying occurrence probability of a deviant stimulus between a series of repeated standard stimuli, could put the neural stream into a state of expecting novel stimuli (perceptual expectation; gating-in) while simultaneously suppressing redundant stimuli (perceptual adaptation; gating-out). This effect may be interpreted as the automatic, stimulus-driven initiation of attentional involvement in sensory processing (Knudsen, 2007; Summerfield & Egner, 2009). Similarities in the auditory gating networks activated by the nonattentional oddball paradigm and the attentional paired-click paradigm (voluntary attention directed to the redundant paradigm tone) give strong support to our interpretation concerning the automatic/voluntary (bottom-up/top-down) switching-on of attentional control by the medial prefrontal region. Regional specificity in the prefrontal cortex due to differences in which the same information is processed, here observed as an effect of attention (nonattentional vs. attentional paired-click paradigm), was introduced by Petrides (Petrides, 1998) but is not yet widely accepted.

With regard to more distal connections, the medial and lateral regions of the prefrontal cortex could likely be a part of distinct networks. Medial regions admit a sparse number of direct sensory-related inputs compared to the lateral regions (Carmichael & Price, 1996). It is interesting that the major afferents to the mPFC arrive from the dlPFC and STG in addition to the temporal pole and cingulate and parieto-temporal cortices (Barbas, Ghashghaei, Dombrowski, & Rempel-Clower, 1999). Traditionally, the mPFC has been strongly associated with decision making, attention control, error monitoring, and working memory (Euston, Gruber, & McNaughton, 2012). Recent evidence emerging

from invasive studies of animal models indicates that mPFC lesions strongly impair attention but not working memory maintenance (Chudasama & Muir, 2001; Kahn et al., 2012; Passetti, Chudasama, & Robbins, 2002). This is consistent with our results, presented here and in a previous study (Josef Golubic et al., 2014), showing that the mPFC region is highly associated with both voluntary (endogenous) and stimulus-driven (exogenous) attention. It seems that in the endogenous attention mode, the mPFC provides a top-down bias signal that influences the stimulus response in the primary sensory areas of the brain while exogenous attention provides a bottom-up impact on the stimulus-response mappings that encompass the mPFC as an executive brain center. There is strong evidence for a modulatory role of the mPFC region on the gating produced by the primary auditory generators during oddball stimulation (Josef Golubic et al., 2014). Significantly enhanced amplitudes of M50 responses to a standard tone seen in the cortical dynamics of the STG generators are found in all patients who lack an mPFC gating generator compared to healthy controls who successfully activated the mPFC during gating processing. Additionally, the modulatory function of frontal areas on the primary auditory region has been suggested by Alho and colleagues, who observed that P50 amplitudes are increased in patients with frontal lesion (Alho, Woods, Algazi, Knight, & Näätänen, 1994).

The dorsal sensory processing pathways primarily terminate in the dlPFC, which is the convergence point of many cortico-cortical pathways, suggesting its function as a cross-modal area of association (Fuster, Bodner, & Kroger, 2001). A crucial aspect of the dlPFC is that it is highly interconnected with sensory and motor cortices and especially with all PFC areas. These interconnections not only allow indirect communication to the spectra of brain networks that are linked to other PFC areas, but also ensure a way for other systems to be indirectly wired together through this central point. It has been shown that the dlPFC is involved in selection, planning, and volition, implying that its function cannot be limited to only working memory as is widely suggested (D'Esposito, Postle, & Rypma, 2000). In line with our results, there is evidence that the dlPFC is responsible for the repetition suppression of the function of early sensory processing areas (Ehlis et al., 2009). Impairments in inhibitory control to sensory inputs are also found in neurological patients with dorsolateral prefrontal damage, in the same cortical area seen in schizophrenic patients (Knight, Staines, Swick, & Chao, 1999; Yoon et al., 2008). The inability of the dlPFC to automatically inhibit irrelevant inputs could result in increased neural noise, which may disturb intercommunication with the mPFC region responsible for the recognition and expectancy of novel input, that is, voluntary and stimulus-driven attentional control. This indirect involvement in attentional processing could be a reason for the impaired sustained attention seen in neurological patients with focal dlPFC lesions along with observed abnormalities in the detection of novel events and inability to inhibit irrelevant input (Knight, Hillyard, Woods, & Neville, 1981; Woods & Knight, 1986).

Another important result emerged during the analysis of the neural dynamics underlying auditory sensory gating responses evoked by the two-condition paired-click paradigm. We found a complex composition of M50 gating components, as demonstrated in earlier studies (Bramon et al., 2004; Yvert et al., 2001). In the analysis of both AEF and the estimated dynamics of cortical generators, two components Mb1 and Mb2, elicited within 30–100 ms after stimulation across paradigm tones and conditions, were consistently identified. The observed cortical gating dynamics of the STG generators is in agreement with the auditory EPs recorded intracerebrally in Herschel's gyrus. Invasive measurements have identified P50 (45–50 ms) and N75 (70–80 ms) as auditory gating components (Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001). Both M50 components exerted a significant gating-out effect, which strongly suggests the existence of two different gating-out ratio values within what has been so far been considered one P50/M50 gating ratio.

The present results offer an explanation concerning the resounding problem of inconsistent reports about attentional influence on the initial stages of auditory sensory processing. First, the existence of two distinct M50 gating components within the narrow time window might contribute to resolving earlier inconsistencies and, thus, to a better understanding of the functional significance of the P50/M50 component. The use of specific frequency filters could have contributed to masking latency differences between the relatively weak components of the P50/M50 complex, producing a single peak with several composite amplitudes. Second, our results draw attention to the importance of paradigm selection. The two paired-click and oddball paradigms, which are often used to challenge sensory gating effects, evoke different gating generator topologies even though they are both passive for subjects, that is, do not require the use of voluntary attention. In addition, a complex M50 network that encompasses a PFC generator in addition to generators in the primary sensory areas, which are often the only ones presumed, provides an explanation for the top-down influences observed within the first 100 ms of sensory information processing during more elaborate paradigms such as one-back discrimination tasks (Goetz et al., 2017).

A limitation of our study is the use of a spherical volume conductor model. More realistic volume conductor models will improve source localization accuracy (Stenroos, Hunold, & Haueisen, 2014).

In conclusion, the results of our spatio-temporal localization of generators underlying auditory sensory gating contribute to resolving fundamental questions concerning when and where in the auditory pathway stimulus processing is first modulated by attention. Here, we support the existence of a fast sensory processing pathway (sensory gating stream) that links primary auditory areas with executive PFC regions within the first 30–100 ms after stimulation. This fast connection is likely to enable both the application of top-down attentional control from the PFC during the earliest stages of sensory processing and the rapid initiation of bottom-up stimulus-driven attentional involvement. Voluntary assignment of auditory attention produces alterations in gating topology by rerouting the processing stream from the dlPFC to the mPFC frontal region, in addition to significantly reduced gating-out ratios of both gating components Mb1 and Mb2 in the cortical dynamics of the primary auditory areas. These results could challenge the central hierarchical paradigm of sensory processing, with the stream of information from higher- to lower-order cortical areas having a role equal in significance to the feed-forward pathways. Our study suggests that perception could comprise both feed-forward and top-down information. This coordination between bottom-up and top-down processing very early in the sensory stream may have an important role in perceptual learning and plasticity. We argue that the

role of top-down information is to provide behavioral context from an internal brain state, contrary to the feed-forward stimulus context from the environment.

In addition, the establishment of the gating network topology and dynamics in healthy individuals provides a referent basis for the further understanding of compromised sensory processing in gating-related neuropsychiatric diseases/disorders, such as schizophrenia, ADHD, or PTSD.

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AUTHOR CONTRIBUTIONS

SJG developed the hypothesis, designed the study, collected the MEG data with the assistance of Tina Radtke, performed spatio-temporal source localization, analyzed and interpreted data, and wrote the manuscript. MJJ participated in MEG measurements, performed the neuroanatomical localization of estimated neural generators and discussed the results. AS participated in the MEG measurements and was involved in the coregistration of MRI and MEG data. RH implemented the task paradigm; RH and TG collected the study volunteers, organized MRI and MEG recordings and were involved in measurements and data collection. JH was involved in the design, planning, and organization of the study. All co-authors were involved in editing the manuscript. All authors read and approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors report no biomedical financial interests or potential conflict of interests.

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