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ORIGINAL ARTICLE

Rhythmic Spontaneous Activity Mediates the Age-Related Decline in Somatosensory Function

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Abstract

Sensory gating is a neurophysiological process whereby the response to a second stimulus in a pair of identical stimuli is attenuated, and it is thought to reflect the capacity of the CNS to preserve neural resources for behaviorally relevant stimuli. Such gating is observed across multiple sensory modalities and is modulated by age, but the mechanisms involved are not understood. In this study, we examined somatosensory gating in 68 healthy adults using magnetoencephalography (MEG) and advanced oscillatory and time-domain analysis methods. MEG data underwent source reconstruction and peak voxel time series data were extracted to evaluate the dynamics of somatosensory gating, and the impact of spontaneous neural activity immediately preceding the stimulation. We found that gating declined with increasing age and that older adults had significantly reduced gating relative to younger adults, suggesting impaired local inhibitory function. Most importantly, older adults had significantly elevated spontaneous activity preceding the stimulation, and this effect fully mediated the impact of aging on sensory gating. In conclusion, gating in the somatosensory system declines with advancing age and this effect is directly tied to increased spontaneous neural activity in the primary somatosensory cortices, which is likely secondary to age-related declines in local GABA inhibitory function.

Key words: aging, magnetoencephalography, somatosensory gating, spontaneous neural activity

Introduction

When 2 identical stimuli are presented in relatively rapid temporal succession, the neural response to the second stimulation is generally weaker than that observed for the first. The attenuated response to the second stimulus is a neurophysiological process often referred to as sensory gating. Sensory gating is thought to reflect the brain's ability to filter repetitive or irrelevant stimuli in order to more aptly utilize limited neural resources (Cromwell et al. 2008). Sensory gating has been extensively studied in the auditory system (Kisley et al. 2003; Brinkman and Stauder 2007), and substantial evidence suggests that patients with schizophrenia, bipolar disorder, and other psychiatric conditions have diminished auditory gating (Light and Braff 1999; Edgar et al. 2005; Cheng, Chan, Liu et al. 2016; Thoma et al. 2017; many others). There is also conflicting evidence in healthy older adults, with some studies showing impaired auditory gating (Cheng, Baillet et al. 2015) and others suggesting normal gating (Gmehlin et al. 2011). When present, these gating deficits are often argued to reflect impaired inhibitory function (Cheng, Baillet et al. 2015; Cheng, Chan, Liu et al., 2016).

While sensory gating in the auditory domain has been extensively studied over the past several decades, far less is known about gating in the somatosensory system. However, of the few somato-gating studies that exist, all have confirmed a

similar phenomenon to that observed in the auditory system. For example, studies using electrical paired-pulse stimulation paradigms have shown robust sensory gating following median nerve stimulation in healthy adults (Hsiao et al. 2013; Cheng, Chan, Niddam et al. 2016), as well as reduced sensory gating in healthy older relative to younger adults using the same paradigm (Lenz et al. 2012; Cheng and Lin 2013). Likewise, another healthy aging study found that older adults had reduced gating relative to younger adults when the paired electrical pulses were temporally separated by 100 ms or less, but that the 2 groups gated roughly equally when the pulses were 200 ms apart (Goto et al. 2015). These data may suggest that older adults have altered inhibitory function, which leads to aberrant gating when stimuli are presented in rapid succession and normal gating at longer temporal intervals. Of note, several distinct lines of evidence converge on the notion that advancing age is associated with a decline in intracortical inhibition (Schmidt et al. 2010; Levin et al. 2014), including a large-scale magnetic resonance spectroscopy (MRS) study showing strongly reduced GABA levels in frontal and parietal regions as a function of advancing age (Gao et al. 2013).

Interestingly, many recent somatosensory studies have implemented oscillatory analysis methods and found that electrical stimulation is associated with strong oscillations up to at least 75 Hz (e.g., 10–75 Hz; Cheng, Chan, Niddam et al. 2016; Wiesman et al. 2017). Examining high-frequency or gamma range neural responses (e.g., 30–75 Hz) are of major importance, as they could provide mechanistic insight into the source of age-related declines in somatosensory gating. Essentially, numerous cellular electrophysiology studies have shown that cortical gamma activity is critically dependent upon the integrity of local interneuronal networks, which function as GABA-gated pacemakers for neocortical oscillatory activity (Singer 1999; Bartos et al. 2007; Fries et al. 2007; Fries 2009, 2015; Uhlhaas et al. 2009; Uhlhaas and Singer 2012; Buzsaki and Wang 2012; Vinck et al. 2013; Salkoff et al. 2015). Thus, altered gamma activity during somatosensory processing and/or gating could reflect local GABA dysfunction, and thereby lend critical support to the notion that gating deficits with aging are due to impaired intracortical inhibition. Unfortunately, to date, somato-gating studies of aging have not evaluated gamma activity, and consequently the relationship between gamma activity, abnormal sensory gating, and advancing age remains unknown.

Although possible links between gamma and aging are not well established, several other neurophysiological parameters are known to be affected by healthy aging. For example, multiple animal studies have shown that visual cortical neurons have higher spontaneous firing levels, weaker directional and orientation sensitivity, and stronger responses to stimuli in older relative to younger adult cats and nonhuman primates (Schmolesky et al. 2000; Hua et al. 2006; Fu et al. 2013). Such increased spontaneous neural activity with advancing age has also been found in the human sensorimotor cortices (Rossiter et al. 2014; Heinrichs-Graham and Wilson 2016). Likewise, greater amplitude responses have been reported in the human somatosensory system, as at least 2 studies using magnetoencephalography (MEG) have found stronger activity following electrical stimulation in older relative to younger adults (Stephen et al. 2006; Hagiwara et al. 2014), although a third study with a much larger sample was unable to replicate this finding using EEG and a slightly different peak-to-peak approach (Lenz et al. 2012). Interestingly, in a follow-up investigation of the aging cats described above (Hua et al. 2006), Hua and colleagues (2008) found that the density of total neurons in each layer of striate cortex did not differ between older and younger animals, but that older animals had significantly reduced GABA-immunoreactive neurons, and an altered GABA-to-total neuron ratio in each layer of striate cortex. These findings are consistent with the human MRS data showing reduced GABA levels with aging (Gao et al. 2013), and other converging evidence linking altered intracortical inhibition and the functional declines seen in healthy aging (Schmidt et al. 2010; Levin et al. 2014).

In the current study, we used a paired-pulse electrical stimulation paradigm to examine the impact of healthy aging on gamma-frequency somatosensory responses, sensory gating in the somatosensory system, and spontaneous neural activity in the postcentral gyrus. Specifically, we collected high-density MEG from a large sample of healthy adults who were between the ages of 22 and 72 years old, and then applied advanced oscillatory analysis methods, which ultimately yielded voxel time series data for hypothesis testing. In addition, we did a time-domain analysis of these voxel time series data for comparison with previous event-related potential/field studies. Our primary hypotheses were 4-fold. We expected 1) all participants to exhibit strong gamma range somatosensory responses to both stimulations, 2) older adults to have impaired sensory gating, 3) for spontaneous neural activity during the baseline to be stronger in older adults, and 4) that these indices would be significantly correlated with age, and that the age-related decline in gating would be associated, and fully mediated, by changes in spontaneous neural activity within the same somatosensory cortices.

Materials and Methods

Participants

Sixty-eight healthy adults (36 males) participated in this study. The mean age was 42.81 years old (range: 22–72 years old). The mean education level was 18 years across the sample, and 58 participants were right-handed with the remainder being left-handed. Exclusionary criteria 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.

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 right 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 at least 80 paired-pulse trials with an inter-stimulus interval of 500 ms and an inter-pair interval that randomly varied between 4500 and 4800 ms. Each pulse generated 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.

MEG Data Acquisition

All recordings were performed in a 1-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 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 et al. 2005; Taulu and Simola 2006).

Structural MRI Processing and MEG Coregistration

Prior to MEG measurement, 4 coils were attached to the participant's head and the locations of these coils, together with the 3 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 3 T 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).

MEG Preprocessing, Time–Frequency Transformation, and Sensor-Level Statistics

Cardiac 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 3700 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, 72 trials per participant were used for further analysis.

Artifact-free epochs were transformed into the time–frequency domain using complex demodulation, 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 by dividing the power value of each time–frequency bin by the respective bin's baseline power, which was calculated as the mean power during the −700 to −300 ms time period. The resulting quotient was then multiplied by 100%.

The specific time–frequency windows used for source reconstruction were determined by statistical analysis of the sensor-level spectrograms across all participants and restricted to the entire array of 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 2 stage procedure was followed to control for Type 1 error. In the first stage, 1-sample *t*-tests 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 2, time–frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the threshold ($P < 0.05$), 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, at least 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.

MEG Beamformer Imaging and Statistics

Cortical networks were imaged through the dynamic imaging of coherent sources (DICS) beamformer (Gross et al. 2001), which employs spatial filters in the time–frequency domain to calculate source power for the entire brain volume. The single images are derived from the cross spectral densities of all combinations of MEG gradiometers averaged over the time–frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, we computed noise-normalized, source power per voxel in each participant using active (i.e., stimulation) and baseline periods of equal duration and bandwidth (Hillebrand et al. 2005). Such images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences (i.e., target versus control) per voxel. MEG preprocessing and imaging used the Brain Electrical Source Analysis (Version 6.1; BESA) software.

Normalized source power was computed for the selected time–frequency periods (see below) over the entire brain volume per participant at 4.0 × 4.0 × 4.0 mm resolution. 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 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 using the peak voxel in 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 time-domain average of the full bandwidth response, and the

envelope of the spectral power within the frequency range used in the beamforming analysis.

To examine the relationship between somatosensory processing and participant age, we conducted Pearson correlations and 2-tailed, independent-samples *t*-tests among somatosensory indices and chronological age (details below). These indices included the sensory gating ratio (the relative response power to stimulus 2 over the relative response power to stimulus 1), peak relative power of the first and second stimulus responses, absolute baseline power from −700 to −300 ms, and peak latency in response to the first and second stimulation. Finally, we conducted a mediation analysis using regression (SPSS Version 23.0, IBM Analytics, Armonk, New York, USA).

Results

All 68 participants were able to successfully complete the MEG and MRI aspects of study. However, 8 participants were excluded from the final analyses due to excessive artifacts in their MEG data and/or technical problems. The remaining 60 participants had a mean age of 43.83 years old, with a range of 22–72 years old.

Sensor-level Analysis

Significant increases were found in many sensors near the sensorimotor and parietal regions from about 10 Hz to 90 Hz during the first 100 ms after the onset of stimulus 1 and stimulus 2 ($P < 0.001$, corrected; Fig. 1). The higher-frequency responses (>20 Hz) were clearly much stronger in the initial 50 ms following stimulus onset, whereas activity in the lower frequency range (<20 Hz) was smeared across a longer time period. To evaluate the dynamics, we focused our beamformer analyses on the higher 20–75 Hz frequency range and utilized two 50 ms time intervals in which the neural response to stimulation was the strongest (0–50 ms and 500–550 ms). Note that we limited our main analyses to 20 Hz on the low end because this was the lowest frequency that we could precisely resolve using a 50 ms time window, and we restricted our analyses to 75 Hz on the high end because relative power sharply decreased thereafter, especially in response to the second stimulus. Note that for completeness, we also performed all analyses using a frequency band of 30–75 Hz, which is more consistent with the traditional definition of the gamma band. In all cases the same significant effects emerged, thus one can conclude that using 20–75 Hz versus 30–75 Hz would make no statistical difference in this study. Thus, to maintain consistency with the traditional definition of gamma activity, we have focused on the 30–75 Hz frequency band in the statistical analyses described below.

Voxel-based and Virtual Sensor Analyses

Beamformer images revealed peak responses in the contralateral somatosensory hand region, with virtually identical peak locations in response to the first and second stimulations (Fig. 1). Thus, to extract virtual sensors, we first averaged the beamformer images across both stimulations and all participants, and then utilized the resulting peak in this grand-averaged map to extract voxel time series data for each participant. Using these virtual sensor data, we next computed the baseline-normalized (i.e., relative) power envelope for the 30–75 Hz band, and these data revealed that peak responses were significantly weaker for the second stimulation (500–550 ms) compared to the first (0–50 ms) across all participants,

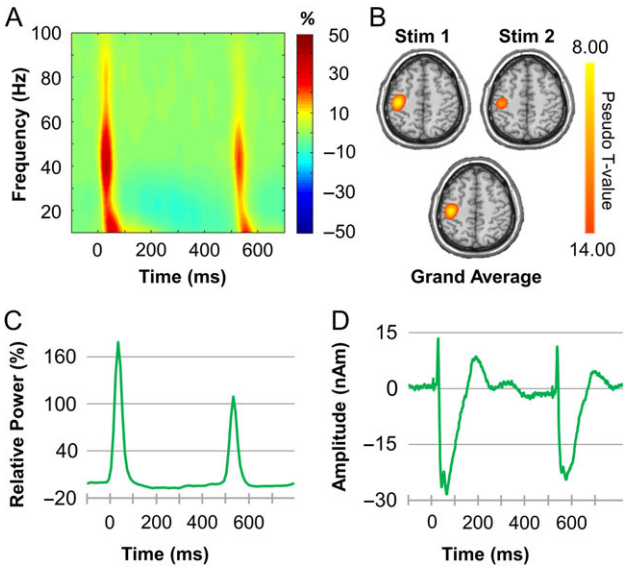

Figure 1. Neural Responses to Somatosensory Stimulation. (*A*) Time–frequency spectrogram from a MEG sensor near the sensorimotor cortices. The x-axis denotes time (ms) with the onset of the first stimulation beginning at time 0 ms, and that of the second stimulation beginning at 500 ms. The y-axis represents frequency (Hz). Power is shown in percentage units relative to the baseline period, with a color scale bar to the far right of the spectrogram. As can be discerned, there was a strong response following each stimulation, with the higher-frequency components being strongest during the first 50 ms after each stimulation. (*B*) Group-averaged beamformer images (pseudo-t) for stimulation 1 (left), stimulation 2 (right), and the grand-average (beneath). As shown, strong increases in power were observed in virtually identical areas of the contralateral hand region of the primary somatosensory cortex in response to each stimulation. These maps were grand-averaged and a virtual sensor (voxel time series) was extracted from the peak voxel and subjected to further analyses. (*C*) Baseline-normalized (i.e., relative) power envelope for the 30–75 Hz band. Voxel time series revealed a significantly weaker response to the second stimulation compared to the first, indicative of significant somato-gating in all participants. (*D*) Time-domain average of the somatosensory response. Again, gating can be clearly observed. Peak latency, power, and the gating ratio were derived to assess associations with age. M20 peak latency was significantly associated with age, such that older adults were slower to respond to the electrical stimulation. Significant gating was detected for the M20, M35 and M50 responses, but no associations with age were observed.

$t(59) = 6.59$, $P < 0.001$ (Fig. 1). Thus, we observed significant somato-gating in the relative power envelope.

Age-related Alterations in Somatosensory Processing, Spontaneous Activity, and Gating

To investigate how aging affects sensory gating, we first computed the gating ratio by dividing the peak relative power of the response to stimulation 2 by that of stimulation 1 in each participant. The resulting quotient, or gating ratio, reflects the individual's capacity to "gate" the second stimulus in an identical pair, with smaller values indicating stronger gating (i.e., better suppression of redundant stimuli). Next, we used a Pearson correlation to probe the relationship between age and the gating ratio, and this revealed a significant correlation, $r(58) = 0.28$, $P = 0.032$, such that as age increased, sensory gating was reduced (Fig. 2). To further examine age-related effects on these neurophysiological responses, participants were divided into an older and a younger group. Briefly, participants who fell within ±0.5 SDs of the full group's mean age were excluded from this aspect of the analysis, while those above 0.5 SD became

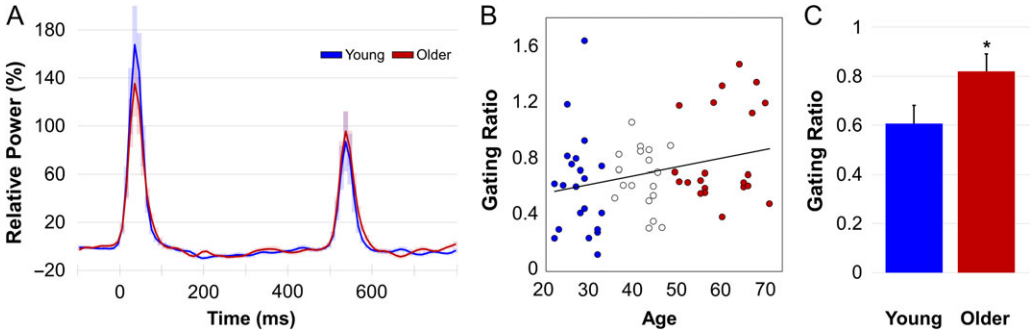

Figure 2. Aging and Somato-Gating (SG). (*A*) Age-related gating differences could be clearly seen in the relative power envelope for the 30–75 Hz band. The shaded area around each time series reflects the SEM. (*B*) Age was positively correlated with the SG ratio across all participants, and this reflected a higher gating ratio (i.e., impaired gating) in older participants. Given this finding, we divided the sample into age groups based on ±0.5 SDs of the full group's mean age, such that participants above 0.5 SDs were in the older group (red), and those below 0.5 SDs were in the younger group (blue). Participants within ±0.5 SD were not included in this aspect of the analysis. (*C*) Using the 2 groups, *t*-tests revealed a significantly higher gating ratio in the older group compared to their younger counterparts; *$P < 0.05$.

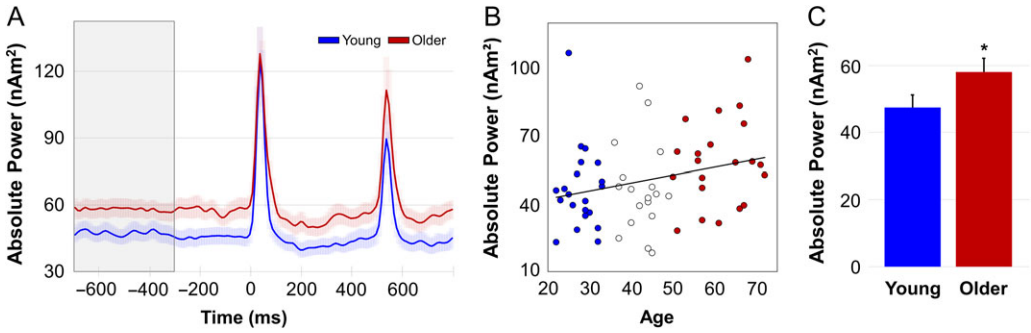

Figure 3. Aging and Spontaneous Neural Activity. (*A*) Absolute voxel time series extracted from the peak voxel of the contralateral hand region of the primary somatosensory cortex in the 30–75 Hz band revealed elevated spontaneous power during the baseline of older adults (shown in red) compared to younger adults (blue). Note that we have extended the time series in this plot to show the baseline period used in our analyses, which is shaded gray. The shaded area around each time series reflects the SEM. (*B*) Age was positively associated with absolute spontaneous power across all participants, such that, as age increased, spontaneous baseline power also increased. (*C*) When separated into distinct age groups following the 0.5 SD method (see Fig. 2), *t*-tests revealed that older adults had significantly higher spontaneous neural activity during the baseline relative to younger adults; *$P < 0.05$.

members of the older group and those below 0.5 SD became members of the younger group. This yielded 2 groups with the following age characteristics (Young: $N = 21$, $M = 27.9$ years old, $SD = 3.4$; Old: $N = 21$, $M = 61.0$ years old, $SD = 6.8$), and these 2 groups were examined using independent-samples *t*-tests. The results indicated that the gating ratio was significantly larger in older adults compared to their young counterparts, $t(41) = -2.05$, $P = 0.046$, indicating a reduced capacity to gate redundant stimuli in older adults (Fig. 2). In addition to the gating ratio, for completeness, we also evaluated age-related effects on the relative amplitude to each stimulation separately. However, these tests were both negative (both *P*'s > 0.526) indicating no differences between younger and older adults.

As mentioned in the introduction, recent MEG studies of aging have reported significantly elevated spontaneous activity during the baseline period in older relative to younger participants. To evaluate whether such spontaneous power differences were present in the current data set, and to identify any possible effects on somatosensory oscillatory responses and gating, we computed the absolute power time series (i.e., not baseline-corrected; Fig. 3) for the same voxels as was used in the relative analyses described above. Correlational analyses revealed a significant positive correlation between spontaneous neural activity during the baseline and chronological age, $r(58) = 0.27$, $P = 0.040$, such that as age increased, 30–75 Hz spontaneous activity also increased (Fig. 3). Next, we split the sample into older and younger groups following the same criteria used in the relative analyses described above and conducted an independent-samples *t*-test, which revealed that spontaneous power during the baseline period was significantly stronger in older relative to younger adults in the hand region of the contralateral somatosensory cortex, $t(41) = -2.00$, $P = 0.051$. For thoroughness, we also computed the gating ratio using the absolute values, which revealed significant gating across the whole group, $t(59) = 6.67$, $P < 0.001$, and a trend towards reduced gating in older adults, $t(41) = -1.94$, $P = 0.060$ (2-tailed test).

Spontaneous Baseline Activity Mediates the Age-related Decline in Gating

To date, few studies have investigated how spontaneous activity during the baseline period modulates neural oscillations following the onset of a stimulus, and no studies have probed the impact of spontaneous neural activity on somatosensory gating. To evaluate the relationship between such spontaneous activity and the age-related decline in somato-gating, a mediation analysis was conducted (Baron and Kenny 1986). For clarity, a mediation analysis using regression assumes a causal model by which the mediator variable elicits an outcome. Such analyses provide insight into the mechanisms through which a causal variable affects an outcome. In the current analysis, we hypothesized a full mediation of somato-gating on age through the mediator (i.e.,

baseline power). Our results indicated a full mediation of the relationship between somato-gating and aging by spontaneous baseline power (Fig. 4 and Table 1), which suggests that elevated spontaneous neural activity fully drives the observed age-related decline in sensory gating in the somatosensory system. Of note, we used the somato-gating ratios derived from the relative power time series for this mediation analysis, but for thoroughness we did the same analysis using the somato-gating ratios derived from the absolute time series and the results were virtually identical. Furthermore, during the review process, we also re-ran the mediation analysis using the response amplitude to the first stimulation in place of the gating ratio, and separately using the response amplitude to the second stimulation in place of the gating ratio. Neither of these models were significant, which suggests that spontaneous neural activity is not directly modulating response amplitude, but rather the relationship between the 2 responses in aging populations.

Time-domain Analysis

Finally, to facilitate comparison with previous studies, we conducted a time-domain average on the original virtual sensor time series extracted from the peak voxel. Briefly, these data were averaged across trials to derive the peak latency, power, and gating ratio in each participant. Analysis of these time series data using Pearson correlations revealed a significant association between M20 peak latency and age, such that the peak latencies were later in response to both stimulations in older compared to younger adults (first stimulation: $r = 0.47$, $P < 0.001$; second stimulation: $r = 0.41$, $P < 0.001$). The peak power of these responses were also examined, but no significant relationship with chronological age was observed. Finally, a significant gating response was detected for the M20, M35, and M50 components, but the gating ratio corresponding to these responses showed no relationship with participant age (all P's > 0.36).

Table 1 Mediation analysis using Baron and Kenny (1986) regression method of the sensory gating ratio on spontaneous neural power and age in the 30–75 Hz frequency band. A full mediation of sensory gating ratio on age through the mediator (i.e., spontaneous power) was determined

Model	*b*	SE	t	β	F	R^2	95% CI
Simple regression of spontaneous baseline power on age							
Intercept	35.22	7.71	4.57**		4.42*	0.27	[19.78, 50.65]
Age	0.35	0.17	2.10*	0.27			[0.02, 0.68]
Simple regression of sensory gating ratio on age							
Intercept	0.44	0.13	3.48**		4.83*	0.28	[0.19, 0.69]
Age	0.01	0.00	2.20*	0.28			[0.00, 0.01]
Multiple regression of sensory gating ratio on resting power and age							
Intercept	0.18	0.13	1.34		10.41**	0.52	[−0.09, 0.44]
Age	0.00	0.00	1.33	0.16			[−0.00, 0.01]
Resting power	0.01	0.00	3.85**	0.45			[0.00, 0.01]

Note: N = 60; *P < 0.05, **P < 0.01.

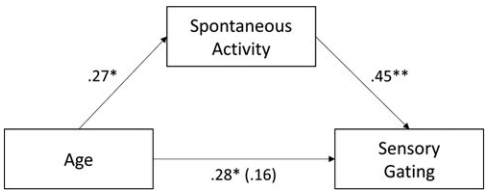

Figure 4. Mediation analysis of sensory gating ratio on spontaneous neural power and age in the 30–75 Hz frequency band. A full mediation of sensory gating ratio on age through the mediator (i.e., spontaneous power) was observed. Standardized regression coefficients are displayed; *P < 0.05.

Discussion

In the current study, we investigated the impact of healthy aging on sensory gating in the somatosensory system and the role of spontaneous neural activity in modulating these responses. Using advanced oscillatory analyses of voxel time series data, we observed robust responses in the gamma range (i.e., 30–75 Hz) following both stimulations. These oscillatory responses were used to calculate gating ratios, which indicated significant sensory gating across all participants. In addition, these gating ratios (relative and absolute) were positively correlated with chronological age, suggesting that older adults had inefficient processing of redundant stimuli (i.e., impaired gating). Finally, our analyses demonstrated that spontaneous gamma power during the baseline was significantly elevated in older adults, and that this modulated other components of the neurophysiologic somatosensory response. Importantly, these data revealed that spontaneous gamma activity during the baseline fully mediated the relationship between age and gamma-band somatosensory gating. Below, we discuss the implications of these novel findings for understanding how aging affects sensory gating, and the role of spontaneous activity.

Unlike previous studies of somatosensory gating, we focused on the dynamics of gamma responses to the first and second stimulations and found robust gating across our sample. Critically, we also found that such gating, whether calculated using the relative or absolute time series, was significantly modulated by age, with older adults exhibiting higher gating ratios, which suggests impaired gating and potentially a reduction in local inhibitory processing of incoming somatosensory signals. These results are consistent in principle with previous works using time-domain approaches (Lenz et al. 2012; Cheng and Lin 2013), although we did not observe such age-related effects in our time-domain analyses. Potentially, this difference reflects our use of MEG and not EEG (Lenz et al. 2012), our focus on voxel time series data and not dipole analysis (Cheng and Lin 2013), and/or other factors. Interestingly, a recent study of somato-gating and aging by the Cheng group used minimum norm estimates and did not find age-related differences in somato-gating either (Cheng, Chan, Baillet et al. 2015). Furthermore, the Lenz study used peak-to-peak differences (N20 to P25) to compute gating ratios, and a very short inter-stimulation interval of 30 ms, both of which are very different than the current study and those of Cheng and Lin (2013)and Cheng, Chan, Baillet et al. (2015). Finally, there is also data suggesting that age-related gating effects in the time-domain are only present when the inter-stimulation interval is less than 200 ms (Goto et al. 2015), which could explain our findings and those of Cheng, Chan, Baillet et al. 2015. Unfortunately, no studies to date have evaluated gamma range activity in the context of gating and aging, and thus we cannot comment on whether the inter-stimulation interval affects such gating responses. However, since time-domain responses are generally dominated by lower frequency activity (e.g., 9–12 Hz alpha and lower) and our oscillatory analyses focused on higher-frequency activity, major differences in the sensitivity of these responses to factors like inter-stimulation intervals would not be surprising. Thus, gamma range activity may be a more sensitive measure of sensory

gating phenomenon. Our emphasis on high-frequency gamma activity in this study was based on the literature showing that older adults have significant reductions in GABA inhibitory function (Schmidt et al. 2010; Levin et al. 2014), as such a focus allows us to uniquely monitor this and identify its impact on sensory gating. Essentially, as outlined in the introduction, previous studies have established that gamma oscillations are tightly linked to processing in local interneuronal networks (Singer 1999; Bartos et al. 2007; Fries et al. 2007; Fries 2009, 2015; Uhlhaas et al. 2009; Uhlhaas and Singer 2012; Buzsaki and Wang 2012; Vinck et al. 2013; Salkoff et al. 2015), and recent MRS studies have further connected GABA levels and MEG gamma activity. For example, Gaetz et al. (2011) showed that motor-related gamma responses were associated with GABA levels in the human motor cortex, and other studies have found similar gamma/GABA relationships in the visual system (Edden et al. 2009; Muthukumaraswamy et al. 2009). Finally, a large-scale MRS study of aging showed strongly reduced GABA levels in frontal and parietal regions with increasing age (Gao et al. 2013). Thus, while our study did not examine GABA levels directly, previous findings provide a mechanistic link between GABA and high-frequency gamma oscillations, and these relationships suggest that our age-related decline in somatosensory inhibition may be due to local GABA dysfunction. However, more work must be done in order to fully assess the role of GABA in somatosensory inhibition.

A central goal of the current study was to probe the impact of spontaneous neural activity during the baseline on event-related oscillations in the same cortical region, as only a few studies to date have examined this and none of these have focused on the somatosensory cortex. For example, a recent MEG study examined beta activity in the motor cortices during a hand grip task and found that spontaneous beta activity during the baseline period increased with increasing age, and that the strength of beta oscillations during movement followed a similar trajectory (Rossiter et al. 2014). However, this study did not evaluate possible dependencies between spontaneous and movement-related beta, nor the relationship(s) among beta indices and behavioral performance in the grip task. A more recent MEG study also found age-related increases in spontaneous beta activity within the motor cortices, as well as increases in the strength of peri-movement beta oscillations during a finger-tapping task (Heinrichs-Graham and Wilson 2016). Interestingly, this study found a direct relationship between these metrics, such that as spontaneous power increased, the strength of peri-movement beta oscillations also increased (i.e., became more negative), and both of these parameters impacted motor performance during the task (Heinrichs-Graham and Wilson 2016). In the current study, we also found that spontaneous, albeit higher frequency, neural activity increased with age, and further that older participants had significantly stronger absolute gamma activity relative to younger participants during the baseline period. This finding is specifically novel because it involves gamma activity and pertains to the somatosensory cortices, whereas previous studies focused on beta activity and the motor system (Rossiter et al. 2014; Heinrichs-Graham and Wilson 2016). However, most importantly, we found that spontaneous gamma levels in the somatosensory cortices fully mediated the age-related effects that we observed in sensory gating, regardless of whether the gating ratios were computed using relative or absolute data. Thus, we can conclude that spontaneous neural activity preceding the stimulation is an influential, and perhaps even a causal factor in the age-related decline that is observed in somatosensory gating.

Conclusion

In conclusion, the current study quantified age-related alterations in somatosensory gating and spontaneous activity in the somatosensory cortex. To date, few studies have probed sensory gating in the somatosensory system, and even fewer have evaluated the impact of aging. We found an age-related increase in the gating ratio, indicative of impaired gating in older participants and thus aberrant processing of redundant stimuli. This was true regardless of whether the gating ratio was based on the absolute or relative time series. While other studies have examined age-related declines in somato-gating (Lenz et al., 2012; Cheng and Lin 2013; Cheng, Chan, Baillet et al. 2015), our study was the first to focus on high-frequency gamma oscillations, and the first to evaluate spontaneous gamma activity preceding the stimulation. In that respect, we found that spontaneous gamma in the somatosensory cortex is significantly elevated in older participants, and critically that the strength of such spontaneous gamma fully mediates the age-related decline in somatosensory gating. One's ability to inhibit redundant information is essential to prioritizing environmental stimuli for adaptive behavior, and thus these findings show that this capacity declines with healthy aging. While our findings provide critical insight, they are not without limitations. For example, we only used 1 inter-stimulation interval (i.e., 500 ms), and future studies should evaluate multiple intervals both shorter and longer to identify any age-related effects. We also focused on adults age 22 years and older and future studies should map the trajectory of a developmental sample. Finally, we only used electrical stimulation of the somatosensory cortices and extending our findings to pneumatic stimulation will be important in future studies. To close, with an increasing number of studies evaluating the somatosensory processing of clinical pathologies such as cerebral palsy (Kurz and Wilson 2011; Kurz et al. 2012, 2014; Kurz et al., 2015; Kurz et al., 2015), adolescents with schizophrenia (Wilson et al. 2007, 2009), adults with posttraumatic stress disorder (Badura-Brack et al. 2015), and adults with HIV-related cognitive impairments (Wilson et al. 2015), it is important to further investigate the lifespan trajectory of somatosensory function in healthy participants, as well as spontaneous activity in these neocortices, to provide adequate context for interpreting reports of clinical decline and disease symptomatology.

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