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Aging changes and gender differences in response to median nerve stimulation measured with MEG

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Abstract

Objective: The current study uses magnetoencephalography (MEG) to characterize age-related changes and gender differences in the amplitudes and timing of cortical sources evoked by median nerve stimulation.

Methods: Thirty-four healthy subjects from two age groups: 20–29 and >64 years of age were examined. After measuring the MEG responses, we modeled the data using a spatio-temporal multi-dipole modeling approach to determine the source locations and their associated timecourses.

Results: We found early, large amplitude responses in the elderly in primary somatosensory (~20 ms) and pre-central sulcus timecourses (~22 ms) and lower amplitude responses in the elderly later in primary somatosensory (~32 ms) and contralateral secondary somatosensory timecourses (~90 ms). In addition, females had larger peak amplitude responses than males in the contralateral secondary somatosensory timecourse (~28 and 51 ms).

Conclusions: These results show that the median nerve stimulation paradigm provides considerable sensitivity to age- and gender-related differences. The results are consistent with the theory that increased amplitudes identified in the elderly may be associated with decreased inhibition.

Significance: The results emphasize that an examination of two discrete age groups, collapsed across gender, cannot provide a complete understanding of the fundamental changes that occur in the brain across the lifetime.

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Keywords: Magnetoencephalography; Somatosensory; Median nerve; Aging; Gender; Source modeling

1. Introduction

The characterization of the somatosensory system in response to median nerve stimulation as a function of age has primarily been performed using somatosensory evoked potentials (SEPs). These studies have identified increases in amplitude of the P20, N27 and N40 components with increasing age (Desmedt and Cheron, 1980, 1981; Ferri et al., 1996; Hume et al., 1982; Kakigi and Shibasaki, 1991; Kazis et al., 1983; Liberson, 1976; Lüders, 1970; Touge et al., 1997). Many of the studies have focused on latency changes with age and have identified increases in latency of some of the somatosensory components as a function of age (Adler and Nacimiento, 1988; Akyuz et al., 1996; Chu, 1986; Dorfman and Bosley, 1979; Huisman et al., 1985; Kazis et al., 1983; Mervaala et al., 1988; Shagass and

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Schwartz, 1965; Shaw, 1992; Simpson and Erwin, 1983; Strenge and Hedderich, 1982; Tanosaki et al., 1999). Some of these studies have also identified a gender effect with women having shorter latencies than men for the earliest components. The correlation between latency and height found by some of these investigators suggested that the average shorter conduction pathway in women relative to men is the source of this latency difference. No other gender-related differences have been reported in previous studies.

The changes in amplitude with age have largely been attributed to decreases in the level of inhibition found in the elderly (Drechsler, 1978; Dustman et al., 1985, 1996; McDowd and Oseas-Kreger, 1991). This decrease in inhibition leads to larger amplitude cortical responses due to the lack of damping of the incoming signal. As mentioned by Drechsler (1978), an additional reason the SEP amplitudes could be larger in the elderly is related to a decrease in variability of the responses with age. The SEP and MEG waveforms require $>100{,}000$ synchronously activated neurons to generate a measurable signal. However, if the neuronal responses are not well synchronized, the opportunity for response summation is reduced. Therefore, more synchronous activity can lead to larger amplitude responses. Although Drechsler (1978) partially tested this possibility, most other studies did not look at variability to determine if this might be an additional cause of the increased amplitude measured in the elderly.

Although the SEP studies have provided a good framework with which to identify age-related changes in the somatosensory system, identifying changes in the peaks of the surface recorded waveforms does not provide an equivalent amount of information as identifying and characterizing the changes related to the cortical generators of those waveforms. Previous MEG studies describing the somatosensory response to median nerve stimulation have identified a number of cortical areas that are active during the first 100 ms post-stimulus (Forss and Silen, 2001; Inui et al., 2004; Kitamura et al., 1996; Liu et al., 2003; Nakano and Hashimoto, 1999; Tesche, 2000). These areas include primary somatosensory cortex, contralateral and ipsilateral secondary somatosensory cortex, posterior parietal cortex and a source located on the pre-central gyrus (Huang et al., 2000; Inui et al., 2004; Kawamura et al., 1996). Although the MEG response to median nerve stimulation is well characterized, most of these studies did not examine differences related to age. The MEG study by Huttunen et al. (1999) performed a single dipole fit at three time points corresponding to the first three peaks of the somatosensory response and then compared the age-related changes of the source latency and amplitude to the previously reported SEP results. In general, modeling the waveforms to obtain the source location and amplitude has a number of advantages. First of all, some of the SEP studies mention changes in the topography of the maximum somatosensory response with age. Therefore, although one electrode may be an appropriate comparison within an age-group, across electrode comparisons may be more appropriate for between-group comparisons. Identifying the sources of activity eliminates the difficulty of pre-determining which electrode to use to perform age-related comparisons. As mentioned by Huttunen et al. (1999), SEP results are also affected by changes in the reference electrode as well as possible differences in conductivity between the comparison groups. Therefore, MEG studies are ideal for extending these studies to identify changes in the somatosensory system as a function of age.

The current study adds to previous SEP and MEG aging results by using a multi-dipole spatio-temporal modeling approach (Huang et al., 1998; Ranken et al., 2002), rather than a single dipole model. In addition, we tested whether the variability of the individual responses could, in part, account for the amplitude difference hypothesized between the young and the elderly age-group. Based on the previous results, we hypothesized a larger amplitude initial peak for the S1 source in the elderly compared to the young. In addition to the small latency increase often reported for the first peak of the S1 response in the elderly, we hypothesized that the peak latency of the S2 source would be delayed relative to the young due to central slowing observed in elderly subjects.

2. Methods

Thirty-four healthy normal young (22; 12 female) and elderly subjects (12; 6 female) were recruited from the Albuquerque area to participate in the MEG study. All subjects signed a consent form approved by the Human Research Review Committee at the University of New Mexico and the Research and Development Committee at the Albuquerque VA Healthcare System prior to participation. Initially, the subjects underwent a neurological exam performed by a Board Certified Neurologist. This exam was used to confirm the self-reported normal status of the subjects. Subjects were also screened for potential artifacts (e.g. metal clips) that could interfere with the MEG signal.

2.1. Data acquisition

The MEG data were acquired using a whole-head 122-channel Neuromag biomagnetometer located within a magnetically shielded room (IMEDCO, Switzerland). Anatomical MRIs were obtained for each subject using a 1.5 T Picker Edge MRI scanner to allow for registration of the dipole locations to the respective anatomical source locations. Prior to MEG data collection three head position coils were attached to the subject's head. The position of these coils relative to three fiducial points (left- and right-pre-auricular points and nasion) was determined using a Polhemus head position device. Subsequently, the coil locations relative to the MEG sensor locations were

determined, allowing for direct determination of the position of MEG data measurements relative to the fiducial points. After data collection the fiducial points were identified on the subject's MRI allowing for co-registration of the MEG data and source locations with respect to brain anatomy.

The median nerve was stimulated using two surface electrodes placed on the forearm. A 0.5 ms current pulse was applied using a Grass Constant Current Stimulator. The electrodes and voltage were adjusted until a thumb twitch was obtained in each hand. Across subjects the current ranged from 1 to 15 mA. The right and left median nerves were stimulated randomly with a mean ISI of 1.25 s and a minimum ISI of 0.5 s. The subjects were instructed to relax and close their eyes, but not to fall asleep. Head position was maintained with foam wedges inserted between the helmet and the head. At least 300 epochs were collected for each averaged response for left and right median nerve stimulation. The data were digitized at 1 kHz with the online filters set to 0.03 – 330 Hz. An interval of 100 ms pre-stimulus and 400 ms post-stimulus was evaluated. The following describes how the data were pre-processed using MEGAN (an MEG ANalysis tool developed by E. Best at Los Alamos National Laboratory). An offline 58–62 Hz bandstop filter was applied to eliminate 60 Hz line noise. The baseline noise was estimated from the −100 to −5 ms pre-stimulus interval. Any DC shift identified in the baseline was removed by determining the mean amplitude and subtracting it from the entire epoch for each channel. Channels with flux jumps or large amplitude responses found in only one channel were removed. Due to the close proximity of the channels in the 122-channel array, a large response in a single channel is necessarily non-physiological.

2.2. Measuring standard error in the responses

The intrasubject variation in responses from trial to trial was measured using the Neuromag program, Graph. Using the unaveraged data, the standard error of the averaged responses was calculated for each channel for the time interval (−100, 400 ms, relative to stimulus onset). The maximum value in the standard error plots was found for three intervals of time 15–25, 25–35 and 35–70 ms post-stimulus using MEGAN. These time intervals corresponded to the onset of the somatosensory response and the later activity. Peaks in the standard error curves correspond to consistent variations in either the amplitude or timing of the response that are larger than those seen in the background brain activity. Differences in the amplitude of the standard error were tested in an age by gender ANOVA. Fisher's PLSD post hoc test was used to determine the source of any significant interactions and main effects.

2.3. Dipole modeling

Each subject's MRI was imported into MRIVIEW (Ranken and George, 1993; Ranken et al., 2002), an MRI and MEG data analysis program. Once the MRI was imported, the MEG data was registered to the MRI by identifying the fiducial points on the MRI and performing the automated transformation of the coordinate space. Following registration of the MEG and MRI data, the cortical surface was identified and labeled using the automated segmentation tool. This cortical surface was used as the set of starting locations of the dipole fitting procedure described below. In addition, the surface of the cortical geometry was used to estimate the best fitting sphere for the modeling procedure. However, the cortical surface was not used to constrain the final dipole locations in the dipole fitting procedure described below.

Once the data were pre-processed, a cortical-start multi-dipole spatio-temporal modeling technique was used (Ranken et al., 2002; Stephen et al., 2003a,b) similar to that used by Aine et al. (2000, 2003, 2005), Huang et al. (1998), and Stephen et al. (2002) to determine the sources of the measured activity. Activity was modeled using a multi-source, rotating, current dipole model. The time interval, 15–200 ms post-stimulus, was analyzed for the median nerve responses. Thousands of independent fits using random starting locations from the cortical surface for each fit (2000–8000 fits were performed for each model order, e.g. 2000 fits for a 1-dipole model, 4000 fits for a 2-dipole model, etc.) were performed in an attempt to obtain a more complete search of the head volume without user bias and to help ensure that a global minimum was reached. For each independent fit, the dipoles (number determined by the operator), were fit simultaneously to the data using the Nelder–Meade minimization procedure to obtain the best source parameters (locations and orientations) given the initial starting parameters. First a high tolerance criterion was used for the minimization procedure to obtain approximate source parameters for a given set of random starting parameters. A goodness-of-fit was determined using the reduced chi square statistic. The best 10% of the original coarse grain fits, based on the reduced chi square (χ^2) values, were started at their final locations and a fine-grain search was performed, again using the Nelder–Meade minimization procedure, to determine the final parameters for each set of starting locations. This two-stage process allows one to eliminate solutions with high reduced χ^2 values without spending a significant amount of time performing a fine-grain search with these starting parameters. The best five solutions of the fine-grain search, based on a descending order sort of the reduced χ^2 values of all fine-grained fits, were displayed. As discussed in Huang et al. (1998), the random starts also help to identify cases where the data is overmodeled—one of the potential pitfalls of multi-dipole modeling. In the overmodeled case, the final best solutions do not cluster well.

The goodness-of-fit of each model was determined by (1) the value of the reduced χ^2 of the best fits compared to other model orders (Supek and Aine, 1993); (2) the residual signal left between the modeled and measured data; and (3) the spatial clustering of the best five fits to the data. See previous results for a more detailed description of this analysis technique (Stephen et al., 2003a,b). The location and timecourse information for the best five solutions were averaged and saved for further analysis. The timecourse refers to the amplitude of the response for a particular cortical location, whereas waveform refers to the raw signal measured at the sensor locations. Further analysis was performed on sources that replicated across subjects and were identified in at least half of the subjects. Source locations were reported based on the individual subject's head-centered coordinate system with the origin defined by the pre-auricula and nasion points with $+x$ directed out the right ear, $+y$ directed out the nose and $+z$ directed out the top of the head. Although using the subject's head-centered coordinate system does not control for normal variation in head shape between subjects, it does allow one to identify approximate variations in source location across different sources.

In addition to applying multi-dipole spatio-temporal modeling to all data sets, the time interval 15–35 ms was modeled with a single dipole model using the same dipole modeling program described above. This allowed us to compare the source locations and timecourses of the S1 activity between the single and multi-dipole models during a time interval where we expect primarily S1 activity and a single dipole should adaquately model the data. This provided information on the robustness of the source and timecourse information in the multi-dipole model.

The timecourses between groups were compared by identifying peaks in the timecourses and characterizing those peaks by identifying peak amplitude, peak latency and peak duration. This approach was chosen over the alternative approach of comparing timecourse differences on a time-point by time-point basis for the following reasons. First, comparison of timecourses by timepoints can only provide one with information on amplitude differences for each time-point comparison. In the current experiment we expected time differences between groups and considered the peak latency comparison to be the most appropriate method to present these timing differences. In addition, the time-point comparison method requires a very large data set to properly control for multiple comparisons. Since the current data set was divided up by both gender and age, the sparse comparison approach was most appropriate for the current data set. Although it can be difficult to determine which peaks correspond across categories, by focusing on the earliest peaks (results are only reported for the first three peaks), we feel we have minimized this problem.

The peaks for each subject's source timecourses were characterized using a semi-automated peak characterization routine created in MATLAB. The timecourses were smoothed with a low-pass 50 Hz filter and the local minima were automatically identified and plotted on the timecourse of interest. The investigator then identified the beginning and ending of the peaks of interest based on the local minima provided. The routine found the maximum amplitude in the chosen time interval (peak amplitude), the time of the maximum amplitude (peak latency), and the duration of the peak. The peak duration was defined as the full width at half-maximum for the peaks that began and returned below half of the peak amplitude. In the case when the peak did not begin or return to below half-maximum, the user-identified onset or offset time of the peak was used, respectively. Due to the high frequency of the N20 response, this peak was characterized without any digital filters applied. The remainder of the timecourse was analyzed as described. The information was then compiled across subjects. Peaks of similar onset/offset and peak latencies were grouped across subjects and identified sequentially as peak 1, peak 2, etc. for each of the sources of interest. The data were tested for outliers to eliminate the possibility that the results would be skewed by individual subject results. This allowed direct comparison of peak amplitude, latency and duration for similarly timed peaks across groups. Statistical comparisons were performed using an ANOVA in an age by gender design.

Signal-to-noise ratio (SNR) was calculated for left and right median nerve conditions for each subject using the MEG waveforms. The maximum SNR is reported. The ratio was calculated by estimating the noise level from the baseline time interval (-100, -5 ms) and finding the maximum signal in the analyzed time interval 10–200 ms. The SNR was calculated for each channel and the channel with the largest SNR was reported as the SNR for the condition. This calculation was performed only on channels that did not contain artifact as described in the pre-processing of MEG data section.

3. Results

As expected, the responses to median nerve stimulation provided very good signal-to-noise ratio (SNR). The SNR was equivalent across the age and gender categories and provided a mean SNR of 27.2. Example waveforms from one subject, displaying the expected lateralization of response, are shown in Fig. 1(a). Fig. 1(b) shows the standard error of the mean (SEM) waveforms from the same subject. The channels with the maximum amplitude in the SEM waveforms also generally corresponded to the channels with the maximum averaged evoked response. The correspondence between the averaged and SEM waveforms can clearly be seen in Fig. 1.

Fig. 2 shows overlaid waveforms of representative young and elderly subjects to demonstrate similar SNR as well as some qualitative differences that one can see in

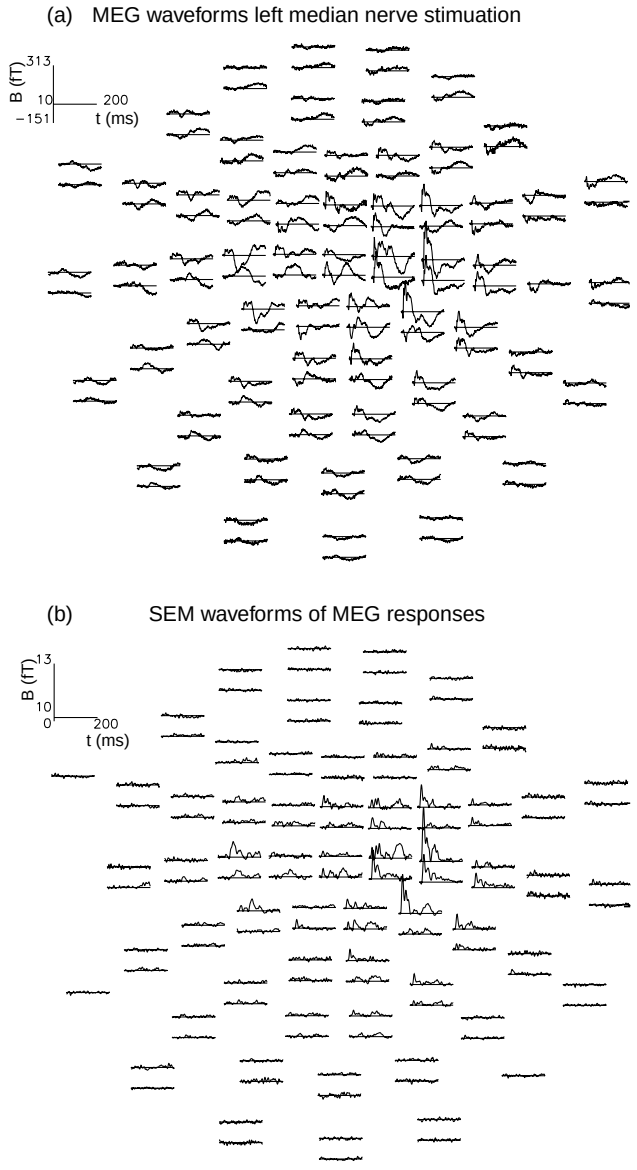

Fig. 1. (a) MEG waveforms to left median nerve stimulation from a young female subject. The waveforms are presented in a top-down view of the MEG sensors with the front of the head at the top of the plot and the left hemisphere shown on left. The scale in the upper left denotes the *x*- and *y*-scale of the individual channel waveform plots. Notice the expected right hemisphere lateralization in response to left median nerve stimulation. It also demonstrates the high SNR generally obtained in response to median nerve stimulation. (b) This plot shows the standard errors associated with the waveforms in (a). It demonstrates the distribution and timing of the variability of the median nerve response associated with the ~300 presentations of the median nerve stimulus. Notice the maximum standard error is associated with the maximum somatosensory response.

the waveforms in the two groups. A dashed line placed at 20 ms allows for a comparison between the initial peaks in the four subjects presented. Similar patterns are identified in the averaged timecourses presented below. In general, the earliest peak of the response occurs sooner in female and young subjects relative to male and elderly subjects, respectively.

The modeling of the waveforms provided the reliable localization of five areas across subjects: contralateral primary somatosensory cortex (S1), contralateral precentral gyrus, contralateral secondary somatosensory cortex (cS2), ipsilateral secondary somatosensory cortex (iS2), and bilateral posterior parietal cortex (see Table 1 for relevant number of sources identified across subjects). Representative source locations can be seen in Fig. 3 with the average source coordinates shown in Table 2. Notice the good correspondence in the source locations between the single dipole model (15–35 ms) and the source location of S1. S1 was identified in all subjects (we could not obtain an S1 source from one side of four subjects—the data from this side was eliminated from further processing). The remaining sources were not modeled as reliably as S1; however, they were obtained in the majority of the subjects. Since left and right median nerve were stimulated in each subject, there were potentially twice as many occurrences of sources as there were subjects. These locations agree well with previously published results.

3.1. S1 results

Once the sources were identified on the individual subject's MRI, the timecourses were compiled across subjects to determine any significant differences in the latency or amplitude of the responses. The timecourses were collapsed across the left and right stimulation conditions due to the lack of significance of any difference in left versus right responses. Representative timecourses for two young and two elderly males are shown in Fig. 4. To present the overall results obtained for this region we plotted the averaged timecourses (across subjects) for the four different subject groups: young males/females and elderly males/females. The averaged S1 timecourses can be seen in Fig. 5. Although the peak latency of the initial peak did not correlate with height for the subjects included ($r=0.2$, $N=55$, $P=0.13$), the onset of the initial peak did correlate with height ($r=0.47$, $N=55$, $P=0.0003$). The significance was determined by performing an ANOVA on the measured peak latencies and amplitudes of the individual timecourses as described in Section 2. There was a small but significant difference in peak latency with age for the first peak with height as a covariate, with the elderly having a peak latency of 24.1 ms versus the young at 20.6 ms ($P=0.045$, $F=12.2$, df$=51$). This result can be seen in the individual timecourses of Fig. 4. There was no significant difference in the initial peak latency between males (22.9 ms) and females (21.0 ms) when height was taken into consideration.

In addition, we found a significant age effect for the amplitude of the first peak of the S1 response ($P=0.013$, $F=6.5$, df$=55$) with the elderly showing a larger amplitude response than the young (see Fig. 5a). Although the averaged timecourse for the young females does not show a distinct peak around 20 ms, an individual peak was identified in the individual subjects and, presumably, the

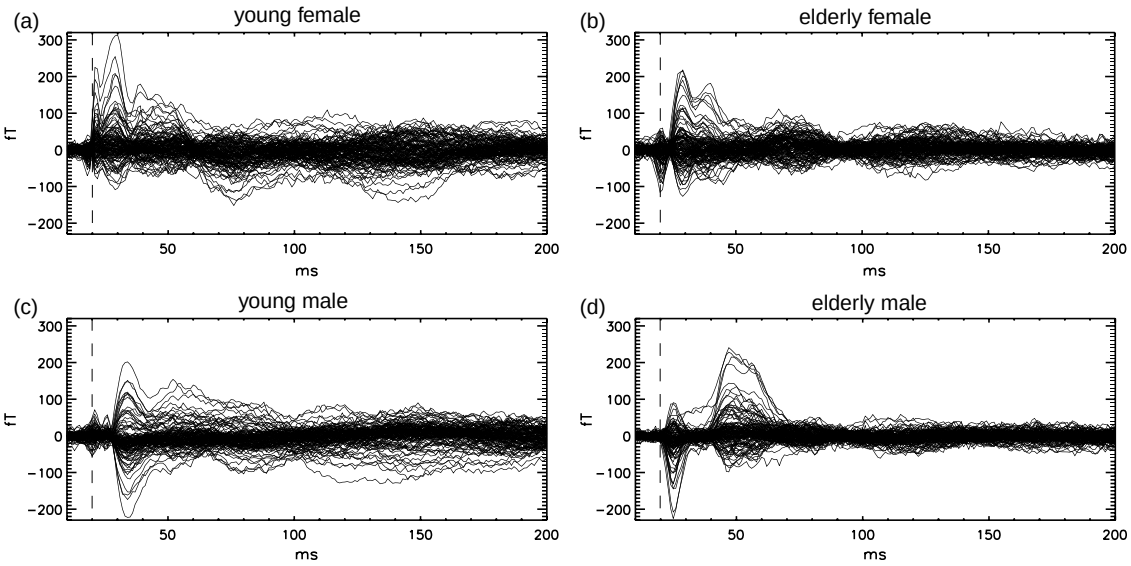

Fig. 2. Representative waveforms for four different subjects. The different tracings in each plot correspond to the different sensors. The 122 sensors (minus bad channels) are overlaid to provide a closer view of the overall response. The dashed line is located at 20 ms to guide the eye to the slightly different timing of the initial response seen in these four subjects. Although there was some variability in the overall structure of the waveforms, the modeled timecourses revealed very similar peaks across subjects for each cortical location modeled.

jitter across subjects in the peak latency of the first and second peak made it appear as a bump on the rising edge of the second peak in the averaged timecourse. An individual initial peak can be seen in the waveform example of the young female in Fig. 2. In addition, peak 2 (~32 ms) showed an age effect for the amplitude and duration, with the young showing larger amplitude responses than the elderly ($P=0.02$, $F=5.7$, df=46) and longer duration responses than the elderly ($P=0.0003$, $F=15.3$, df=46). The averaged responses for the elderly males also do not show a clear peak around 32 ms. This, again, is likely due to differences in latency across subjects as the individual waveforms and timecourses showed a peak prior to the 45 ms peak evident in the averaged timecourse (e.g. Fig. 2(b)). There was no significant difference in peak latency of peak 2. No significant results were found for later peaks in the S1 timecourse.

3.2. SEM results

In order to determine if the age effect identified as an amplitude difference in peak 1 was in part due to differential variability in the responses, we also present the averaged maximum SEM waveforms (see Fig. 6). Although there were consistent differences in the amplitude of the SEM across groups, we did not find greater variability in the young subjects during the peak 1 interval of time when the young had lower amplitude averaged responses. There was an age effect in the latency of the first peak ($P<0.0001$, $F=19.7$, df=56). Although the elderly females showed a larger amplitude standard error for the first peak than the young females, there were no significant differences in amplitude for the first peak. The amplitude of the second peak has a significant age effect with the younger subjects showing increased variability (~31 ms) relative to the elderly subjects ($P=0.021$, $F=5.6$, df=56). Therefore, there was greater variability for the young during the time interval that the young showed larger amplitude responses than the elderly. There were no significant differences in the peak amplitude for peak 3 (~47 ms). These results show that the variability of the averaged responses is an additional factor to consider when looking at aging and gender effects. However, it does not explain the difference in amplitude identified in the S1 timecourses.

3.3. Higher-order source results

The averaged timecourses for the pre-central gyrus and cS2 are presented in Fig. 7. Despite the close proximity of the pre-central gyrus source to S1, the timecourse results

Table 1
Prevalence of sources identified in best models

	S1	PCG	Contra S2	Ipsi S2	Parietal
Young ($N=22$)	40	22	25	28	15
Elderly ($N=11$)	21	14	18	14	11

S1, primary somatosensory cortex; PCG, pre-central gyrus; Contra S2, contralateral secondary somatosensory cortex; Ipsi S2, ipsilateral secondary somatosensory cortex; Parietal, posterior parietal cortex.

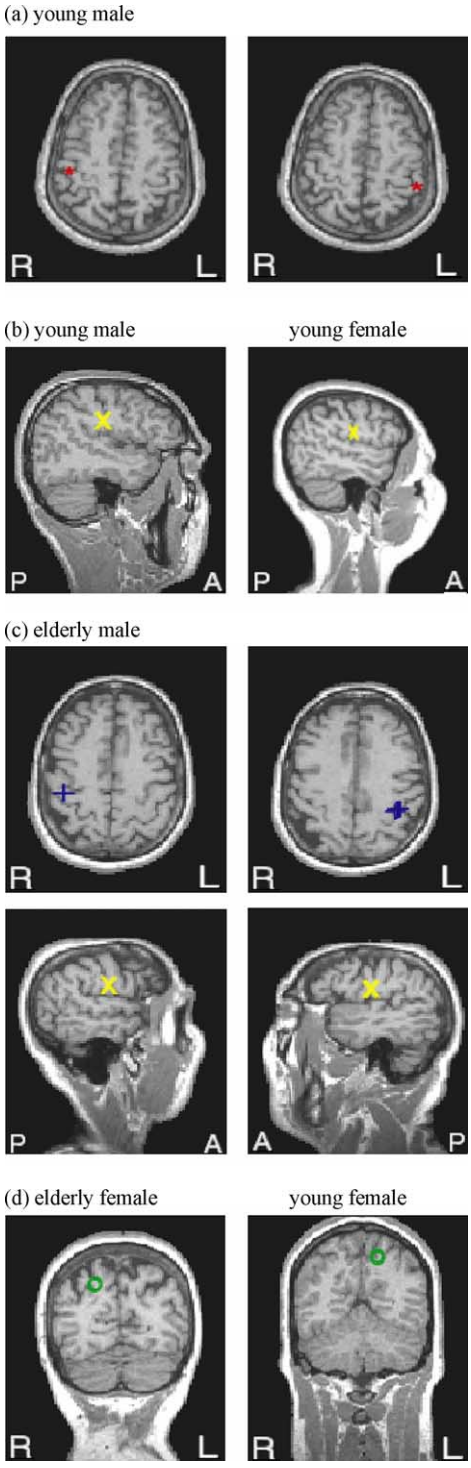

Fig. 3. Representative source locations for the five sources that were reliably identified in the modeling of the somatosensory responses. (a) shows S1 (red *) source locations in one young male for left and right median nerve stimulation. S1 was reliably localized to the post-central gyrus in all subjects. (b) shows contralateral S2 (yellow ×) source locations for two young subjects evoked by left median nerve stimulation. (c) shows pre-central gyrus sources (blue +) and contralateral S2 (yellow ×) sources from one elderly male for left and right median nerve stimulation, respectively. (d) shows posterior parietal sources (green o) for elderly and young females.

show considerably different patterns than that seen in S1. There was a significant age effect for peak 1 (~22 ms) with the elderly showing larger amplitude and longer duration responses than the young (amp: $P=0.026$, $F=5.8$, df = 19; duration: $P=0.047$, $F=4.5$, df = 19). Peak 2 (~31 ms) did not show a significant age effect for amplitude as seen in peak 1 of the S1 timecourse. Peak 3 (~48 ms) showed only a difference in duration with age with the young having significantly longer duration for this peak than the elderly ($P=0.04$, $F=4.7$, df = 21). As suggested in the cS2 source timecourse, the amplitudes for the first and second peaks (~28 and 51 ms) were significantly greater for the females than the males (peak 1: $P=0.04$, $F=4.6$, df = 32; peak 2: $P=0.028$, $F=5.5$, df = 24). There was no significant difference in age between genders in either of the two age categories. The third peak (~90 ms) was significantly stronger for the young than for the elderly ($P=0.047$, $F=4.2$, df = 37). There was no significant difference in latency with age in the S2 source, contrary to the original hypothesis. Although the averaged timecourses for iS2 and posterior parietal cortex suggested some interesting differences, the increased variability in the timecourses seen across subjects and the decreased number of timecourses in the averages did not provide any significant age or gender effects for these two sources.

4. Discussion

This study in part confirms previous findings in the aging SEP literature. We found a similar increase in amplitude and latency of the initial peak for the S1 source with age. In addition, we identified a larger amplitude response in the young for the second peak of the S1 timecourse. Although we identified differences in the variability of the responses as a function of age, it was shown that variability is not the cause of the decreased amplitude of the initial peak in the young. In addition, peak 2 of the S1 timecourse showed a significant age-related difference with the young showing a larger amplitude response than the elderly. Previously unreported gender- and age-related differences were also identified in the contralateral S2 and pre-central gyrus sources. Contrary to the hypothesis, there were no latency differences identified in the S2 sources associated with age. Together, these results suggest a surprising level of sensitivity to age- and gender-related differences in the simple median nerve somatosensory response using MEG methods.

4.1. Comparisons with previous somatosensory results

The S1 results agree well with the results for the N20 peak reported by Huttunen et al. (1999). Our results on latency and left/right differences of the N20 response are also consistent with previous findings. That is, there are only

Table 2
Averaged source locations across subjects in head-centered Cartesian coordinates (mm)

Source	Right stimulation			Left stimulation		
	x	*y*	*z*	*x*	*y*	*z*
Single dipole S1	−38.5 (0.8)	−4.1 (1.5)	84.7 (1.5)	39.7 (1.7)	3.3 (3.1)	82.7 (2.8)
Multi-dipole S1	−35.4 (0.9)	−4.3 (1.6)	83.1 (1.2)	36.5 (1.1)	−3.5 (1.6)	84.8 (1.5)
cS2	−37.5 (1.5)	3.6 (2.1)	61.6 (1.7)	39.4 (1.9)	7.3 (2.8)	60.7 (1.9)
iS2	33.8 (1.2)	7.5 (1.6)	62.1 (2.2)	−32.0 (1.8)	0.6 (2.5)	63.7 (2.4)
Pre-central gyrus	−27.5 (1.4)	−2.4 (1.7)	85.8 (1.6)	29.7 (1.3)	−1.2 (3.0)	85.8 (2.3)
Posterior parietal	−8.6 (5.0)	−19.1 (1.7)	83.2 (3.2)	12.5 (3.7)	−18.4 (2.4)	80.5 (3.2)

slight increases in latency of the initial primary somatosensory response associated with increasing age (Dorfman and Bosley, 1979; Kazis et al., 1983; Shaw, 1992; Simpson and Erwin, 1983; Strenge and Hedderich, 1982; Tanosaki et al., 1999). The remaining analyzed peaks of the S1 response did not show consistent differences in latency with age. There were no consistent differences between left and right median nerve stimulation (Huisman et al., 1985; Kazis et al., 1983; Simpson and Erwin, 1983).

Our results deviate from the previously published results, however, for the second peak of the S1 response. Previous SEP reports have found either consistently larger amplitude responses in the elderly in the later components (Desmedt and Cheron, 1980, 1981; Ferri et al., 1996; Kakigi and Shibasaki, 1991; Lüders, 1970; Touge et al., 1997) or no reported age-related effect (Hume et al., 1982; Kazis et al., 1983; Liberson, 1976). In addition, Huttunen et al. (1999) did not find age-related effects for any components later than the N20 peak. The most likely explanation for this discrepancy with previous results is the modeling approach employed by the current study. As described briefly in Section 1, the multi-dipole spatio-temporal modeling approach allows one to fully characterize the active sources for the time interval analyzed. The SEP studies focused on waveforms at one electrode rather than source timecourses. This information can and most likely does include responses from multiple sources. Depending on the locations of the multiple sources the combined waveform is likely to appear different from the individual timecourses associated with the active sources. Huttunen et al. (1999) used inverse modeling procedures; however, they sequentially modeled the peaks in the waveform with a single dipole model. Based on previously published MEG results and animal literature, it is clear that there is more than one source active after the initial N20 peak. Therefore, we suggest that the larger amplitude second peak identified in the S1 timecourses of the young is a new result. Although the explanation for the larger amplitude response in the young is unclear, it could be related to a general change in the pattern of the S1 response with age. In intracortical recordings in monkeys, Arezzo et al. (1981) confirmed long duration S1 responses and determined that this was largely due to feedback from

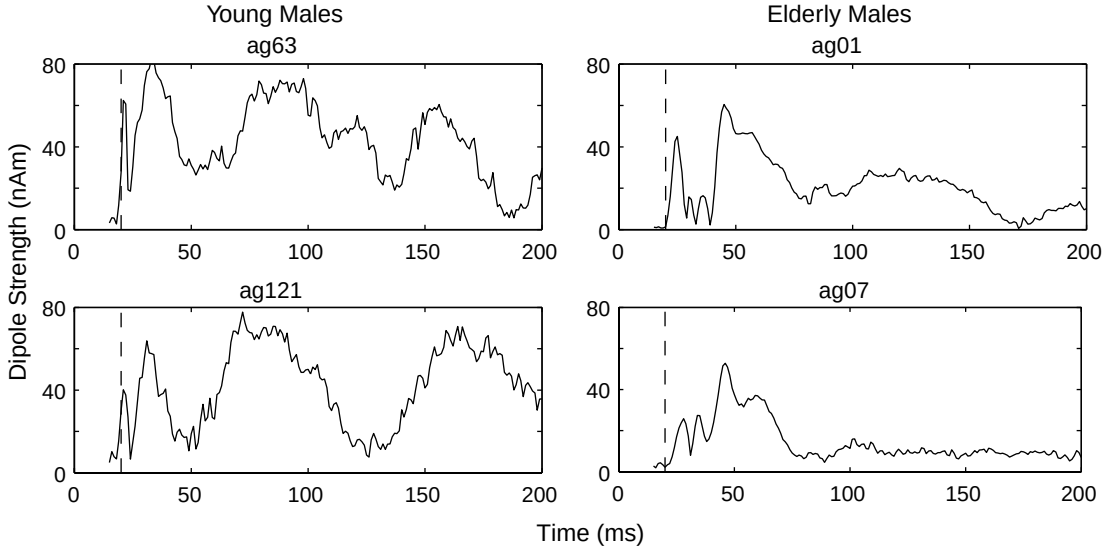

Fig. 4. Representative S1 timecourses from two young and two elderly males. The dashed line at 20 ms post-stimulus allows for direct comparison between the onset times in the young versus elderly male subjects. This result was consistent although less dramatic in the females as can be seen in the averaged timecourses in Fig. 5. One can also see that the timecourses for the elderly in this figure showed lower amplitude responses in the later time intervals.

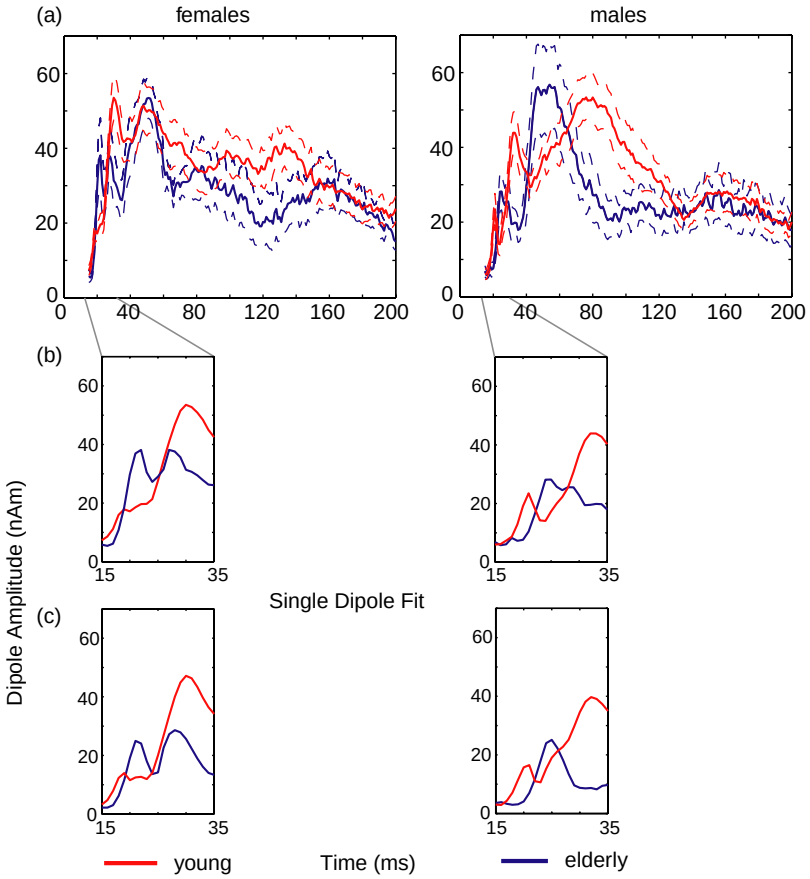

Fig. 5. (a) The averaged S1 timecourses for the young and elderly females and males. The dashed lines denote the standard error associated with the averaged timecourses. One can see that the standard error increased with latency. Therefore, the significant results were found in the first 100 ms post-stimulus. See the text for details of these significant differences. (b) Shows an enlarged version of the 15–35 ms time window. One can see clear delays in the elderly relative to the young for the initial peak as well as larger amplitude responses for the elderly for the initial peak. (c) Shows the results of a single dipole fit for this same time interval. Very similar responses are seen for single dipole and multi-dipole fits during a time interval where primarily S1 activity is expected. The statistical results are consistent across the multi-dipole and single-dipole models.

higher order areas. Their results also suggest a good correspondence between monkey and human responses to median nerve stimulation. Therefore, the aging related differences may be related to different feedback patterns from the other cortical areas feeding into the later portion of the S1 response. Although most of the age-related sensory changes reported by the elderly can be attributed to peripheral changes, including slower responses and reduced sensitivity (Craig and Rollman, 1999; Baloh et al., 2003), they may also be related to cortical changes such as those identified in this study.

The secondary somatosensory response has been described and investigated by a number of groups (Aine et al., 2000; Forss and Silen, 2001; Hari and Ilmoniemi, 1986; Jousmaki, 2000; Korvenoja et al., 1999; Torquati et al., 2002). These previous results showed the initial onset of the cS2 source occurring at 45–60 ms. However, our results agree with the earlier onset times found by Aine et al. (2005), Inui et al. (2004), and Korvenoja et al. (1999). As mentioned by Frot and Mauguiere (1999), the close vicinity of area S2 to primary somatosensory cortex, as well as the close proximity and direct connections to thalamus, bring into question the longer initial onset time previously reported for S2.

Contrary to the hypothesis, S2 latencies were not longer in the elderly. Previous SEP results have suggested increases in central conduction time with age (Adler and Nacimiento, 1988; Desmedt and Cheron, 1980; Dorfman and Bosley, 1979; Drechsler, 1978; Shaw, 1992; Strenge and Hedderich, 1982; Tanosaki et al., 1999). Although these results are consistent in finding increased conduction time with age, the increase is small, e.g. 2 ms between N20 and N27 peaks (Adler and Nacimiento, 1988). These results and the close proximity of S1 and S2 suggest that one cannot measure significant timing differences with the current number of subjects.

Previous results have been mixed in terms of the presence of an early pre-central gyrus source. Based on intracortical surface recordings, Allison et al. (1991) argued that there were only two separate sources in the post-central gyrus and not an additional source on the pre-central gyrus. However, Arezzo et al.'s (1981) results from intracortical

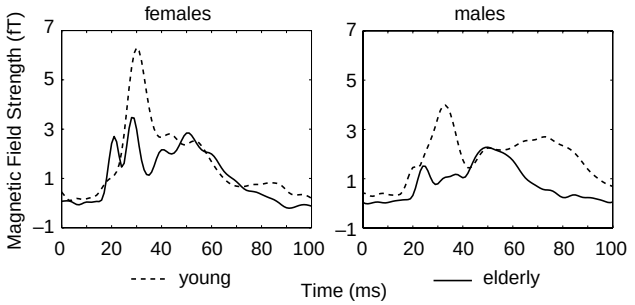

Fig. 6. The standard error waveforms (similar to that shown in Fig. 1(b)) averaged across subjects. The dashed line corresponds to the young and the solid line corresponds to the elderly. Unlike the timecourse averages, where each timecourse was associated with a particular source and averaged across subjects, the averages in this figure were of the SEM waveforms. One channel was chosen for each subject and condition (left and right) to include in the average. The channel chosen for the waveform average was the channel with the largest amplitude standard error in the time interval 15–25 ms post-stimulus. This allowed a direct comparison of the results obtained in Fig. 5 and permitted us to evaluate the possible influence of variability on the amplitudes identified in peak 1. In general it appears that larger amplitude responses in Fig. 5 corresponded to larger standard error seen in this figure.

depth electrodes in monkeys show the presence of a pre-central gyrus source. Three previous MEG results have also reported a pre-central gyrus source (Huang et al., 2000; Inui et al., 2004; Kawamura et al., 1996). Although this source is relatively close to S1, the two sources were not oriented in parallel (Huang et al., 2000), which greatly increases the resolvability of sources using MEG. Although additional sources will generally improve the overall fit using percent of variance as a measure, previous results (Supek and Aine, 1993) have found that using reduced χ^2 as a measure of goodness-of-fit does not improve significantly once the correct model order has been reached since this approach takes the number of parameters into consideration. Also, the correspondence between this source and the motor source identified during a finger lift motor task in the Huang et al. study, suggests that the localization of this source is correct. Finally, the difference in the timecourse results between the S1 source and pre-central gyrus source suggests that the two sources are distinct. Since this source has not been reported in previous aging studies and task manipulations were not performed in the current study, it is difficult to determine the meaning of this result. The aging effect found in the initial peak is likely related to a decrease in inhibition similar to the interpretation for S1.

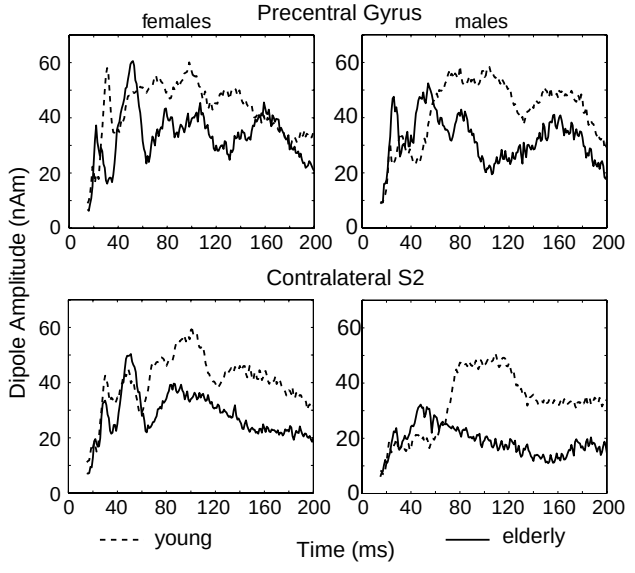

Fig. 7. The averaged timecourses for the remaining sources that were reliably identified in response to median nerve stimulation. Only the pre-central sulcus and contralateral S2 responses showed significant differences based on either age or gender. The remaining two sources had more variable responses across subjects and were not modeled as reliably as the previously discussed sources.

4.2. Age-related amplitude differences

As mentioned in Section 1, previous SEP and MEG studies on the age-related responses to median nerve stimulation have shown increased amplitude in the elderly age-group. The common explanation for this increase in amplitude is that there is decreased inhibition in the elderly (Drechsler, 1978; Dustman et al., 1985, 1996; McDowd and Oseas-Kreger, 1991). Evidence from animal studies on the neuronal makeup of the somatosensory cortex adds credence to this explanation. For example, Brunso-Bechtold et al. (2000) did not find a decrease in neuronal number in the aging somatosensory cortex of the rat. They only found a decrease in the number of inhibitory synapses as a function of age. Our auditory studies show a similar large amplitude response in the elderly for the initial 40–50 ms response in the superior temporal gyrus (Aine et al., 2005; Kovacevic et al., 2005) presenting a consistent picture for the initial response across sensory systems. Therefore, our results are consistent with the theory that increased amplitude in the elderly is associated with decreased inhibition.

An additional explanation for decreased amplitudes of peaks in EEG and MEG studies is poorly synchronized responses. Due to fast neuronal responses, only well synchronized responses provide the opportunity for significant summation. As mentioned in Section 1 large numbers of active neurons are needed to generate a measurable MEG or EEG response; the synchronicity of the response has considerable impact on the measured amplitude. If these responses were not well synchronized, one would see increased variability of the response relative to the background noise of the sensors around the time of the evoked response. Although there was increased variability in all subjects during the time interval associated with the evoked response (15–200 ms), increased variability was not associated with decreased amplitude in the young. Therefore, poor synchronization cannot be the explanation for the reduced amplitude of the initial peak in the young.

Interestingly, the larger amplitude response in peak 2 for the young was associated with larger variability in the young. Measuring the variance of the response cannot by itself identify whether the variability is related to jitter in the time domain or jitter in the amplitude of the response. Since jitter in the time domain will lead to decreased amplitude of the averaged response, this suggests larger variability in the amplitude of the second peak in the young. Therefore, although the variability does not explain the reduced amplitude of the initial peak in the young, variability does seem to play a role in the normal evoked response. Although signal averaging is currently necessary to obtain a measurable signal in MEG, these results on the variability of the evoked response suggest attempts at performing single-trial analysis should be continued. New approaches to account for trial-to-trial variability (Truccolo et al., 2002) may also provide a means to address this aspect of MEG data.

4.3. Gender differences

The gender differences noted in the first two peaks in contralateral S2 are also interesting. Many of the previous studies did not address the question of gender differences (Adler and Nacimiento, 1988; Desmedt and Cheron, 1981; Drechsler, 1978; Ferri et al., 1996; Kazis et al., 1983). In the cases where gender was investigated, a number of SEP studies reported no gender differences (Chu, 1986; Dustman et al., 1985; Kakigi and Shibasaki, 1991; Zumsteg and Wieser, 2002). The only report of larger amplitude signal in females was by Kakigi and Shibasaki (1992) in their study of tibial nerve responses; they did not find gender-related differences in their median nerve study (Kakigi and Shibasaki, 1991). Huttunen et al. (1999) did not identify any gender differences either, although they limited the scope of their study to S1. The SEP studies generally analyzed the electrode with the largest amplitude response, which is likely dominated by S1 activity. This dominance of S1 activity may explain why many SEP studies did not find any gender differences. Therefore, the current results are generally consistent with previous results in that no gender differences were found in the S1 timecourses. The studies that characterized the SEP responses across the decades agreed that, in general, there is a U-shaped amplitude response of the N20 peak with age (Hume et al., 1982; Lüders, 1970). That is, during childhood the amplitude is large, it decreases with increasing age and increases again after subjects reach middle-age. Perhaps the U-shaped amplitude response of males and females is offset relative to age, leading to gender differences of age-matched categories. The few studies that examined neurophysiological gender differences (Anokhin et al., 2000; Grachev and Apkarian, 2000) have noted some gender differences but they did not address specific differences related to somatosensory cortex. Therefore, it is possible that S2 responds differently in males and females based on fundamental differences in the brains of males and females, or possibly, different maturation rates lead to differences in age-matched gender categories. There is not sufficient evidence to rule out one explanation over the other at this time.

4.4. Conclusions

In sum, spatio-temporal multi-source modeling provided good differentiation of subjects' median nerve responses based on age and gender categorizations. The results are consistent with the premise that the elderly have decreased inhibition relative to the young. The gender differences may be related to basic gender differences or differential maturation rates of the human brain. Additional studies using this simple sensory paradigm may help provide more insight on how age-related sensory changes affect cognitive and behavioral changes reported in the elderly.

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