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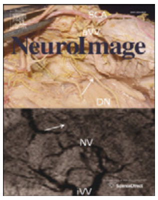

How anatomical asymmetry of human auditory cortex can lead to a rightward bias in auditory evoked fields

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ABSTRACT

Auditory evoked fields and potentials, such as the N_1 or the 40-Hz steady state response, are often stronger in the right compared to the left auditory cortex. Here we investigated whether a greater degree of cortical folding in left auditory cortex could result in increased MEG signal cancelation and a subsequent bias in MEG auditory signals toward the right hemisphere. Signal cancelation, due to non-uniformity of the orientations of underlying neural currents, affects MEG and EEG signals generated by any neuronal activity of reasonable spatial extent. We simulated MEG signals in patches of auditory cortex in seventeen subjects, and measured the relationships between underlying activity distribution, cortical non-uniformity, signal cancelation and resulting (fitted) dipole strength and position.

Our results suggest that the cancelation of MEG signals from auditory cortex is asymmetric, due to underlying anatomy, and this asymmetry may result in a rightward bias in measurable dipole amplitudes. The effect was significant across all auditory areas tested, with the exception of *planum temporale*. Importantly, we also show how the rightward bias could be partially or completely offset by increased cortical area, and therefore increased cortical activity, on the left side. We suggest that auditory researchers are aware of the impact of cancelation and its resulting rightward bias in signal strength from auditory cortex. These findings are important for studies seeking functional hemispheric specialization in the auditory cortex with MEG as well as for integration of MEG with other imaging modalities.

Introduction

Structural and functional asymmetries are an important theme in a large body of work investigating auditory processing in human. It has been consistently shown, for example, that the auditory evoked N_1m response is larger in the right compared to the left auditory cortex. First, amplitude differences were demonstrated directly with diotic stimulation (Howard and Poeppel, 2009; Ross et al., 2005). Second, it has been demonstrated with monaural or lateralized binaural setups that left-sided stimuli produce less lateralization towards the contralateral right auditory cortex than vice-versa (Gutschalk et al., 2012; Hine and Debener, 2007; Johnson and Hautus, 2010; Kanno et al., 1996; Mäkelä et al., 1993; Palomäki et al., 2005). Rightward lateralization of auditory evoked fields is not limited to the N_1m, but has also been observed for the 40-Hz steady-state response and sustained fields (Gutschalk et al., 2012; Ross et al., 2005). As work in this field develops, though, researchers need to consider the fact that uneven signal cancelation effects can arise due to underlying brain anatomy, leading to a bias in auditory evoked fields. Below, we outline how this effect can occur.

The human auditory cortex is well known to be asymmetric on average across the population (Galaburda et al., 1978a). The *planum temporale*, for example, has been shown to be larger, in general, on the left (Geschwind and Levitsky, 1968; Steinmetz, 1996), with left-deeper-than-right perisylvian asymmetry (Hill et al., 2010). Increased folding of left auditory cortex is thought to be related to a left-hemisphere dominance for speech (Galaburda et al., 1978b). While speech specificity is thought to start beyond the auditory core and belt areas, the higher volume of left hemisphere speech areas might still produce a higher convolution of the left auditory cortex in the absence of any functional significance. Alternatively, a larger volume of cortical connecting fibers (connecting, for example, to larger left *planum temporale*) has been hypothesized to be related to a preferential role for left primary auditory cortex (PAC) in processing temporal aspects of auditory stimuli (Penhune et al., 1996). As for PAC, which is associated with the medial part of Heschl's gyrus (Braak, 1978; Hackett et al., 2001; Morosan et al., 2001), asymmetry measurements have been less clear. Using MR scans, Penhune et al. (1996), found a significant left > right asymmetry and larger volumes of white, but not gray matter in left

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Heschl's gyrus. However, Rademacher et al. (2001) used histological methods and found left > right PAC volume only in men, and almost symmetric PAC volume in women.

Functional lateralization of auditory cortex has also been extensively studied (Schirmer et al., 2012). One suggestion is that the left hemisphere is more sensitive to temporal sound features, whereas the right hemisphere is more sensitive to spectral sound features (Zatorre and Belin, 2001). Left and right auditory cortices may also have distinct temporal integration windows (Boemio et al., 2005). Finally, the lateral right auditory cortex appears to be specialized for spatial sound processing (Zatorre and Penhune, 2001). A number of studies have probed functional lateralization of the auditory cortex by use of EEG and MEG (Eulitz et al., 1995; Luo and Poeppel, 2012; Okamoto et al., 2009). For the interpretation of these studies, anatomical confounds may be critical. While an anatomical source for the right-wards lateralized N_1m has been previously discussed (Hine and Debener, 2007; Howard and Poeppel, 2009), no attempts have yet been made to test this hypothesis.

In the current work, we investigated whether the *structure* of the human auditory cortex could result in uneven signal cancelation such that MEG and EEG auditory signals are *biased* towards the right hemisphere. Specifically, we sought to test whether there was increased cortical folding in the left auditory cortices of our subjects and whether this increased folding could result in a greater degree of MEG signal cancelation. We measured signal detection from left and right auditory regions, to test whether cancelation effects could lead to apparent functional asymmetries. Although MEG and EEG have been used clinically and in research for many decades, the exact investigation of MEG/EEG cancelation effects has only recently been enabled, largely due to advances in automated MRI-based geometrical modeling of the cortical surfaces (Dale et al., 1999; Fischl et al., 2001) as well as by improvements in forward modeling techniques and computer hardware to enable accurate MEG and EEG field calculations for hundreds of thousands of sources on the cortex.

Cancelation occurs because MEG and EEG signals are generated largely by pyramidal neurons oriented normally to the cortex (Hämäläinen et al., 1993) and, as the human cerebral cortex is highly convoluted, sources within an extended area of activation will typically generate magnetic fields with varying polarity that superpose or cancel, depending on the local geometry of the cortex. It is well known that, especially in the sulci, this cancelation effect can result in a significantly reduced net field. In fact, this cancelation effect is present in both MEG and EEG signals generated by any neuronal activity of reasonable spatial extent. Using simulations, Ahlfors et al. (2010), investigated the relationship between source extent and MEG signal cancelation and showed, for example, that MEG signal was reduced by 50% on average for a patch of activity with a 10 mm radius. For a patch with radius 50 mm this cancelation effect was up to 90%. Ahlfors et al. (2010) also pointed out, in an earlier study, that individual variations in cortical folding may cause asymmetric degree of cancelation between the hemispheres in the extracranial magnetic field (Ahlfors et al., 1999).

For the current study, we used high-resolution MRI-based geometrical modeling of the cortical surfaces of 17 real subjects, and we simulated MEG signals arising from patches of auditory cortex and fitted dipoles to these data. We estimated cancelation effects and cortical non-uniformity, using indices defined in the recent study by Ahlfors et al. (2010). Additionally, we evaluated response lateralization based on dipoles fitted to the simulated data, following methods typically chosen by studies reporting lateralization in the auditory cortex. We expected anatomical asymmetry of auditory cortex to impact signal cancelation in two competing ways. First, larger left auditory cortex should result in stronger MEG signals on the left, if underlying activity is uniform. On the other hand, increased cortical folding on the left is expected to result in greater signal cancelation in the left auditory cortex. Based on the finding of right-lateralized auditory evoked fields summarized above, we hypothesize that the higher degree of cancelation on the left will balance, or maybe even supersede, the increase of signals due to larger activated area in the left hemisphere.

Materials and methods

Simulations

Simulated evoked response MEG data were created using MNE software (http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php). The simulations were based on real MEG and MRI data acquired from two previous studies for which we had written informed consent from subjects for further usage (subject and experiment details are given below). The real MRI data were used to provide an accurate model of the cortical surface for each of our subjects, and the real MEG data were used to extract realistic parameters for head positions relative to MEG sensors.

For cortical surface reconstruction, we used the Freesurfer software (http://surfer.nmr.mgh.harvard.edu/) and high-resolution structural MRI data (Dale et al., 1999; Fischl et al., 2001). In addition, we also extracted the inner skull surface using the watershed algorithm from the FreeSurfer software package (Sègonne et al., 2004). This surface was used as input to the single-compartment boundary-element model (BEM) used to compute the MEG signals (Hämäläinen and Sarvas, 1989). We also used real MEG data (corresponding to the same subjects) to extract the head-position relative to sensor location information for our MEG simulations.

We created two simulation scenarios: one where activated source areas were equal in size and magnitude on the left and right side, and one where activated source regions reflected macroscopically defined auditory cortex regions as defined by an anatomical atlas (unequal sizes). We incorporated different-sized as well as both asymmetric and symmetric ROIs, as would be expected in real experiments, depending on the anatomical area and cortical response of interest, which may be either focal or widespread.

Equal-sized simulation

We created two approximately circular ROIs with 469 dipoles each, placed approximately 1 mm apart at the vertices of the accurate triangulation of the cortical surface of an average subject (fsaverage) provided by FreeSurfer and centered on Heschl's gyrus in the left and right hemisphere. These “standard” ROIs were then transformed back to each subject's anatomical space. Due to anatomical differences across subjects, transformed ROIs were no longer equal-sized across subjects and hemispheres. Therefore, we adjusted the transformed ROIs by removing dipoles furthest away from the center-of-mass, such that left vs. right ROI extent was constant within subject. The mean Talairach coordinates of these equal-sized ROIs in Heschl's gyrus (denoted HG-eq) are given in Table 1. We employed a total dipole amplitude of 50 nAm for each ROI.

Atlas-based simulation

Simulated source areas were four different ROIs on the left and right hemispheres of seventeen subjects. The ROIs were automatically generated using FreeSurfer software based on the Destrieux atlas, a subject-specific parcellation of the brain based on gyral and sulcal regions, where the borders are given by curvature values of the surface (Fischl et al., 2004). As shown in Fig. 1, three of the ROIs corresponded to subcomponents of the AC. The fourth ROI corresponded to these three subcomponents combined, was referred to as the auditory cortex (AC) ROI. The mean center of mass of each label in Talairach coordinates is given in Table 1.

In the simulations, current dipoles oriented perpendicular to the cortex were situated at every vertex of a 1-mm grid covering each of the ROIs. Using the same software (MNE and Freesurfer) we measured the number of dipole sources within each ROI (n), as well as the