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By our bootstraps: comparing methods for measuring auditory 40 Hz steady-state neural activity

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Abstract

Although the 40Hz auditory steady-state response (ASSR) is of clinical interest, the construct validity of EEG and MEG measures of 40Hz ASSR cortical microcircuits is unclear. This study sought to evaluate several MEG and EEG metrics by leveraging findings of (1) an association between the superior temporal gyrus 40Hz ASSR and age in the left but not right hemisphere, and (2) right- > left-hemisphere differences in the strength of the 40Hz ASSR. The present contention is that, if an analysis method does not demonstrate a left 40Hz ASSR and age relationship or hemisphere differences, then the obtained measures likely have low validity. Fifty-three adults were presented 500Hz sinusoidal stimuli modulated at 40Hz while MEG and EEG were collected. 40Hz ASSR activity was examined as a function of phase similarity (inter-trial-coherence, ITC) and percent change from baseline (total power, TP). A variety of head models (spherical and realistic) and a variety of dipole source modeling strategies (dipole source localization and dipoles manually fixed to Heschl's Gyrus) were compared. Several sensor analysis strategies were also tested. EEG sensor measures failed to detect left 40Hz ASSR and age associations or hemisphere differences. A comparison of MEG and EEG head-source models showed similarity in the 40Hz ASSR measures and in estimating age and left 40Hz ASSR associations, indicating good construct validity across models. Given a goal of measuring the 40Hz ASSR cortical microcircuits, a source-

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Declaration of Interest

The authors have no conflicts of interest to report.

modeling approach was shown to be superior in measuring this construct versus methods that rely on EEG sensor measures.

Keywords

superior temporal gyrus; 40 Hz auditory steady-state response; magnetoencephalography; electroencephalography

Brain neural activity is noninvasively assessed using electroencephalography (EEG) or magnetoencephalography (MEG). EEG and MEG activity is typically examined in frequencies ranging from delta (1 to 4 Hz) to gamma (~30 to 80 Hz). Gamma-band abnormalities (~30 to 80 Hz) are hypothesized to contribute to brain dysfunction and clinical symptoms in psychiatric disorders such as schizophrenia (Gandal, Edgar, Klook, & Siegel, 2012), autism spectrum disorder (Gandal, et al., 2010; Rojas & Wilson, 2014), post-traumatic stress disorder (Huang, et al., 2014), and attention-deficit hyperactivity disorder (Wilson, Wetzel, White, & Knott, 2012). Researchers speculate that treatments normalizing gamma rhythms will lead to clinical improvement, with some support for this claim provided by behavioral (Popov, Rockstroh, Weisz, Elbert, & Miller, 2012) and pharmacological studies (Heinrichs-Graham, et al., 2014; Wilson, Wetzel, White, & Knott, 2012).

In the auditory system, assessment of gamma cortical microcircuits is often accomplished using auditory 40 Hz steady-state stimuli: 40 Hz click trains or 40 Hz amplitude-modulated tones. Several different strategies have been used to measure activity from the cortical microcircuits generating the 40 Hz auditory steady-state response (ASSR). Given that left and right primary/secondary auditory cortex are the primary generators of the 40 Hz ASSR (e.g., (Gutschalk, et al., 1999; Hari, Aittoniemi, Jarvinen, Katila, & Varpula, 1980; Herdman, et al., 2003; Pantev, et al., 1993; Ross, Herdman, & Pantev, 2005; Ross, Picton, & Pantev, 2002)), several EEG (e.g., (Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009)) and most MEG studies (Edgar, et al., 2014; Teale, et al., 2008; Tsuchimoto, et al., 2011) have examined the 40 Hz ASSR in source space (i.e., left and right STG). In many studies examining patient populations, however, the 40 Hz ASSR is examined at the sensor level, often at EEG electrodes Cz or Fz (Brenner, Sporns, Lysaker, & O'Donnell, 2003; Galambos, Makeig, & Talmachoff, 1981; Kwon, et al., 1999; Light, et al., 2006; Rass, et al., 2012; Roach & Mathalon, 2008) or measuring the 40 Hz ASSR from the 1st component obtained after applying principal component analysis (PCA) to high-density EEG (Hamm, Gilmore, & Clementz, 2012).

Although the 40 Hz ASSR is of clinical interest, the construct validity of measures of EEG and MEG 40 Hz ASSR is unclear. In Messick's Unified Theory of Construct Validity (Messick, 1995), for a measurement method to measure what it claims to measure (Cronbach, 1955), it should have convergent, discriminant, and predictive qualities, providing external validity. As with other unobservables (Kozak, 1982), establishment of construct validity for the 40 Hz ASSR (and concomitantly the establishment of best practices) is impeded by the lack of a gold standard; specifically, there is no noninvasive

method (and perhaps also no invasive method) for determining the construct validity of EEG or MEG 40 Hz ASSR measures.

There is empirical evidence, however, to suggest that some methods to analyze the 40 Hz ASSR are better than others. For example, analysis strategies that fail to separately examine left and right hemisphere STG 40 Hz ASSR are potentially of concern as studies have shown lateralized gamma-band abnormalities in individuals with neurodevelopmental disorders such as schizophrenia (Edgar, et al., 2014; Gallinat, Winterer, Herrmann, & Senkowski, 2004; Haig, et al., 2000; Hall, et al., 2011; Spencer, et al., 2003; Tsuchimoto, et al., 2011). Hemisphere differences in the maturation of the STG 40 Hz ASSR (Edgar, et al., 2014; Edgar, et al., 2016), as well as right > left hemisphere differences in the strength of the 40 Hz ASSR (Edgar, et al., 2014; Edgar, et al., 2016; Ross, Herdman, & Pantev, 2005; Tsuchimoto, et al., 2011) raise additional concerns. Methods that do not separately examine left and right STG 40 HZ steady-state activity are potentially problematic as the 40 HZ ASSR measures obtained via analysis strategies that combine 40 Hz ASSR activity from multiple brain generators may lack discriminant and predictive qualities. Such suboptimal analysis strategies likely hinder our ability to develop inferences and thus guide future studies.

The present study sought to make progress on this issue by leveraging findings of (1) an association in adults between the STG 40 Hz ASSR and age in the left but not right hemisphere (Edgar, et al., 2014), and (2) the above noted right > left hemisphere differences in the strength of the 40 Hz ASSR. The present contention is that, if a 40 Hz ASSR analysis method does not allow a left STG 40 Hz ASSR and age relationship or hemisphere differences to be observed, then the obtained 40 Hz ASSR measures likely have low validity and thus that the analysis method is not optimal. To identify an optimal analysis strategy, a variety of head models in the forward calculation (spherical and realistic head models) and a variety of dipole source analysis strategies (dipole source localization (i.e., dipoles allowed to move throughout source space) and dipoles manually fixed to the midpoint of each Heschl's Gyrus (see details below)) were compared. We refer to this as different head-source models. Several sensor analysis strategies were also examined.

Because the left and right STG 40 Hz ASSR neural generators generally have a more optimal orientation for MEG (magnetic source and sink fields distinct over left and right hemisphere and thus distinct field patterns for left and right STG activity) than for EEG (electric source and sink fields for left and right STG superimposed at midline EEG electrodes), it was hypothesized that that MEG would provide superior estimates of the STG 40 Hz ASSR. Because left and right STG activity is difficult to separately distinguish at the EEG sensor level, it was also hypothesized that standard EEG sensor-level analysis strategies would not show associations with age and would thus not provide valid estimates of the 40 Hz ASSR. Finally, given a previous finding that estimates of left and right STG auditory activity were similar for source localized STG dipoles and anatomically constrained STG dipoles (Zvyagintsev, Thonnessen, Dammers, Boers, & Mathiak, 2008), no difference between these methods was anticipated.

Method

2.1 Subjects

Fifty-three healthy controls (35 males; mean age 39.6 ± 12.1 years) were recruited. Selection criteria were: (1) no history of axis I psychiatric dysfunction determined by Structured Clinical interview for DSM-IV Axis I disorders (SCID-I) (2), no history of substance dependence in the last 3 years, (3) no history of alcohol or other substance abuse in the last 3 months, (4) no history of head injury with loss of consciousness for more than 5 minutes or other neurological disease, and (5) no family history of a psychotic disorder in first-degree relatives by self-report. Before the study, the nature of the study was explained to all subjects and signatures were obtained on the consent forms approved by the Human Subjects Institutional Review Boards at the Raymond G. Murphy Veterans Affairs (VA) Medical Center and the Human Research Review Committee (HRRC) at the University of New Mexico School of Medicine.

2.2 Steady-state Task

The amplitude of a 500 Hz stimulus was modulated at 40 Hz, the modulation depth 100%. Stimuli of 1s duration were binaurally presented with a 4s offset-to-onset ISI (± 2 s) and delivered using a sound pressure transducer through conduction tubing to the ear canal via ear-tip inserts (ER3A; Etymotic Research, Elk Grove Village, Ill., USA). Prior to data acquisition, 500-Hz tones of 300 ms duration and 12.5 ms rise time were used to obtain auditory thresholds for each ear. Auditory thresholds were initially estimated via stepwise amplitude reduction until participants stopped verbally identifying the presence of the tone. For fine tuning, tone loudness was then adjusted within ± 10 dB of the preliminary threshold until a final threshold was confirmed (approx. 50% accuracy). For the 40-Hz steady-state task, for each ear, the peak intensity of the steady-state stimuli was presented 35 dB above each participant's hearing threshold.

Participants were asked to refrain from smoking for at least 1 h before the recording session. To ensure compliance, they were asked to report to the facility an hour before recording commenced, during which time participants were familiarized with equipment and procedures. Participants were administered the steady-state task following a paired-click task (not reported here). The number of steady-state stimuli presented depended on the MEG recording time available, although most participants were able to complete the full steady-state task. During the task the participants rested with their eyes focused on a crosshair on a screen approximately 2 feet from the participant. MEG data were examined only from participants with 50+ trials. The mean number of trials presented was 88 (SD = 18).

2.3 Structural magnetic resonance imaging (sMRI)

T1-weighted MPRAGE structural MR images were collected on a Siemens 3T TIM Trio scanner at the Mind Research Network. Images were collected with a field-of-view = 256×256 mm, 192 sagittal slices, and $1 \times 1 \times 1$ mm spatial resolution. This was a five-echo sequence with echo times of 1.64, 3.5, 5.36, 7.22, and 9.08 ms, a repetition time = 2530 ms, a gray-white matter contrast enhancement inversion recovery time of 1200ms, and 7° flip angle.

2.4 MEG, EEG, and sMRI Data Acquisition and Coregistration

MEG data were recorded in a magnetically shielded room (Vacuumschmelze, Germany) using all channels of a 306-channel Vector-View MEG system (Elekta-Neuromag, Helsinki, Finland). After a band-pass filter (0.1 – 330 Hz), MEG signals were digitized at 1000 Hz. EEG data were collected with Ag/AgCl electrodes from 60 equidistant sites (Falk Minow Customized Easy Cap®). EEG data were collected simultaneously with MEG, using the Elekta EEG amplifiers. The left mastoid served as the EEG reference at data collection. Electro-oculogram (EOG) (vertical EOG on the upper and lower left sides – bipolar channels) and electrocardiogram (ECG) (bipolar channels at the collarbone) were also obtained. During the MEG recording, the subject's head position was monitored using four HPI coils attached to the scalp.

To coregister MEG/EEG and sMRI data, three anatomical landmarks (nasion and right and left preauriculars) as well as an additional 200+ points on the scalp and face were digitized for each subject using the Probe Position Identification (PPI) System (Polhemus, Colchester, VT). To co-register the MEG/EEG and sMRI for each subject, the three fiducials were identified in the subject's sMRI, and a transformation matrix that involved rotation and translation between the MEG/EEG and sMRI coordinate systems was obtained by matching the 200+ points from the PPI measurements to the surface of the scalp and face from the structural MRI using BESA MRI 2.0.

2.5 Magnetic Source Analysis

MEG raw signals were first processed with Signal Space Separation (SSS; (Taulu, Kajola, & Simola, 2004)) using Maxfilter (Elekta MaxfilterTM; Elekta Oy). SSS separates neuronal magnetic signals arising from inside the MEG sensor array from external magnetic signals arising from the surrounding environment to reduce environmental noise and artifacts. Following SSS, eye-blink activity was corrected using the methods outlined in Berg & Scherg (Berg & Scherg, 1994). Using BESA 6.0, epochs –1000ms prestimulus to 1500 poststimulus onset were identified, and within this interval artifacts other than blinks were rejected by amplitude and gradient criteria (amplitude > 1200fT/cm, gradient > 800fT/cm/sample). Epochs (trials) without artifact were then averaged from –1000ms prestimulus to 1500ms poststimulus onset, and then the BESA 6.0 bandpass filter was applied with a center frequency of 40 Hz and a 20 Hz width (a bandpass filter superior to using separate low- and high-pass filters for extracting MEG/EEG activity in narrow frequency bands) with 100% of the activity passed at 40 Hz and 50% amplitude cutoffs at 30 Hz and 50Hz. This filtered artifact-free average was used for all source analyses below.

MEG data were analyzed only in source space. To investigate the effects of head model and source model on source localization as well as source timecourse measures (thus the calculation of total power and phase locking), for each participant a spherical head model and a realistic four-layer finite element method (FEM) head model were created. For the spherical and the FEM head model, source models with localized sources or with sources manually fixed to each participant's left and right Heschl's Gyrus were created. For each source model, both regional sources (i.e., a source with three (EEG) or two (MEG) single dipoles at the same location but with orthogonal orientations) and single dipole models were

created (Scherg & Ebersole, 1993). For MEG, the spherical head model of Sarvas (Sarvas, 1987) was used. Individual head models were also computed using the FEM, which allows the inverse solution to become more precise (Haueisen, Ramon, Eiselt, Brauer, & Nowak, 1997; Vanrumste, et al., 2002). In particular, the BESA MRI 2.0 software module was used to obtain FEM head models using each participant's T1-weighted MRI, creating four-layer FEM models that differentiate between the scalp, skull, CSF and brain, and thus which allow arbitrarily complex geometries. As shown in Figure 1, for MEG, a total of 8 source models were created.

For EEG, eye-blink correction, removal of artifacts, and creation of artifact-free epochs were obtained using the same procedures outlined for MEG. All EEG data were analyzed using an average reference. For EEG source analyses, a multi-shell spherical head model containing 4 homogeneous shells (brain, CSF, bone, and skin) was used, with the shells distorted into an ellipsoid that best fit the participant's EEG electrode cloud (EEG coordinates digitized using Polhemus), and with the center of the sphere determined from the EEG electrode locations (Berg & Scherg, 1994). For each participant, a four-layer FEM head model was also computed. For the Sphere and FEM EEG head models, the BESA default conductivity values were used: 0.33 S/m for scalp and brain tissue, 0.0042 S/m for skull tissue, and 1.79 S/m for cerebral spinal fluid. As with MEG, for EEG regional and single dipole source solutions were examined. Given that initial analyses showed that EEG source localization tended to localize the left and right sources to the midline, only EEG source models with regional and single-dipole sources manually fixed to the midpoint of left and right Heschl's Gyrus were examined. Thus, as shown in Figure 1, for EEG, a total of 4 source models were created.

The following text details how each MEG and EEG source model was created.

FEM and Sphere MEG Head Models: Source Localized—For the models created using source localization, determination of the location of the 40 Hz steady-state generators in the left and right hemisphere was accomplished by fitting a regional source (i.e., two orthogonal dipoles) in each hemisphere using either a Sphere or a FEM head model. For modeling the 40 Hz ASSR, data 300 to 900ms poststimulus were selected. Left- and right-hemisphere responses were jointly localized using all MEG channels. Once localized, the primary orientation over the 300 to 900ms interval was determined (this primary orientation not likely to coincide with one of the axes of the original un-rotated regional source dipoles). A source model containing the left- and right-hemisphere regional source (i.e., two rotated orthogonal dipoles at each location) as well as a source model containing only the single primary left and right STG oriented dipole were both examined.

FEM and Sphere MEG Head Models: Anatomically Constrained—MEG source models were also created using anatomical constraints. As noted in the Introduction, as the primary generator of the 40 Hz ASSR is well-modeled by a source in left and right Heschl's gyrus and surrounding regions (Herdman, et al., 2003; Ross, Herdman, & Pantev, 2005; Ross, Picton, & Pantev, 2002), after co-registering the MEG and sMRI data, each participant's left and right Heschl's Gyrus was visually identified and a regional source fixed to the 'center' of Heschl's Gyrus at an anterior to posterior midpoint and laterally

approximately two thirds from the medial termination of Heschl's Gyrus. If two Heschl's Gyri were present, the regional source was placed between the two Heschl's gyri. After placing the left and right regional sources, the primary orientation over the 300 to 900ms interval was determined. Analogous to the Sphere MEG analyses, a source model containing the left and right Heschl's Gyrus regional sources (i.e., two orthogonal dipoles at each location) as well as a source model containing only the single primary oriented dipole at each location were both examined.

FEM and Sphere EEG Head Models: Anatomically Constrained—EEG data (average reference) were analyzed in source space as well as sensor space. For source-space analyses, the EEG 40 Hz ASSR was analyzed using individualized four-shell ellipsoid and four-layer FEM head models with regional sources (i.e., three dipoles) as well as a single optimally oriented dipole. As previously noted, in most participants EEG source-localization attempts were generally unsuccessful, and in most participants the left and right sources tended to localize to the center of the head. Thus, for EEG, only models with sources fixed to left and right Heschl's Gyrus were considered. Specifically, as shown in Figure 1, regional source and single-dipole four-shell ellipsoid head models with sources fixed to Heschl's Gyrus were created. Of note, the same left and right Heschl's Gyrus location was used for EEG and MEG.

In addition to the EEG source models, as shown in Figure 1, 40 Hz ASSR time-frequency sensor measures were obtained at EEG sensors Cz, Fz, as well as clusters of left- and right-hemisphere EEG temporal sensors (18 sensors per hemisphere). Using all EEG sensors, EEG 40 Hz ASSR measures were also obtained via applying principal component analysis (PCA) to the whole-head EEG data and then using the timecourse associated with the first component of the PCA (computed over the 300 to 900ms interval).

2.6 Time-frequency analysis

For all above source models and sensor data, transformation from the time domain to the time-frequency domain used complex demodulation procedures (Papp & Ktonas, 1977) implemented in BESA 6.0, using frequencies between 4 and 60 Hz, in steps of 2Hz. Continuous data were analyzed relative to tone onset every 25 ms (i.e., each 40 Hz cycle), utilizing ± 39.4 ms and ± 2.83 Hz (full width at half maximum parameters) of contiguous data at each 25 ms step.

To compare with previous studies, 40 Hz steady-state total power and phase-locking were both examined. Total power and phase-locking measures were extracted from the single-trial complex time-frequency matrix. Total power (TP) is calculated by averaging the time-frequency spectra of each MEG epoch, thus providing a measure of the magnitude/power of oscillatory activity. TP was computed as percent-change score: $((\text{poststimulus activity} - \text{prestimulus activity}) / \text{prestimulus activity})$. For TP calculations, the prestimulus period was -800 to -200 ms. A measure of phase-locking referred to as inter-trial coherence (ITC) was also computed. ITC is a normalized measure with $\text{ITC}=1$ reflecting no phase variability and $\text{ITC}=0$ reflecting maximal phase variability across trials. For the source space analyses, the calculation of single-trial phase and magnitude used procedures outlined in Hoechstetter et

al. (Hochstetter, et al., 2004) where in each subject the derived source model was applied to the raw unfiltered data.

For each participant, a single 40 Hz steady-state TP and ITC value was obtained, the average TP and ITC within a 500 to 1000 ms and 38 to 42 Hz region-of interest (ROI). In addition, for each participant, a single 40 Hz prestimulus power measure (no baseline subtraction) was obtained by time-frequency transforming each trial and averaging power within a –800 to –200 ms and 38 to 42 Hz ROI (i.e., a 40 Hz prestimulus total power measure).

Results

Acronyms for each MEG and EEG source model are shown in Figure 1. Source model localization results (i.e., model differences in ‘x’, ‘y’ and ‘z’ axis dipole positions) and dipole orientation findings are presented in the Online Supplement.

For all analyses below, subjects more than 2.5 standard deviations were excluded (typically 1 to 2 subjects per analysis). For all analyses below, unless specified, the interaction term was not significant. For all significant main effect and interaction tests, Bonferroni correction was applied to interpret the finding.

MEG 40 Hz ASSR Inter-Trial Coherence

Although the analyses below showed significant MEG 40 Hz ASSR ITC differences between head-source models, the 40 Hz ASSR ITC value across head-source models was similar. Across head-source models, right > left hemisphere ITC differences were observed, and across head-source models associations between 40 Hz ASSR ITC and age were very similar.

Examining the MEG FEM models, a Model X Hemisphere ANOVA on 40 Hz ASSR ITC showed a main effect of Hemisphere (right>left), $F(1,52) = 34.61$, $p < 0.001$. A main effect of Model, $F(3,50) = 42.16$, $p < 0.001$, indicated the following order: MEG Fem_Loc_Single (ITC = 0.45) > Fem_Hes_Single (ITC = 0.43) > Fem_Hes_Full (ITC = 0.27) = Fem_Loc_Full (ITC = 0.27) ($ps > 0.05$).

Examining the MEG Sphere models, an ANOVA on 40 Hz ASSR ITC showed a main effect of Hemisphere (right>left), $F(1,52) = 27.37$, $p < 0.001$. A main effect of Model, $F(3,50) = 7.78$, $p < 0.001$, indicated the following order: MEG Sphere_Loc_Full (ITC = 0.47) > Sphere_Hes_Full (ITC = 0.45) = Sphere_Loc_Single (ITC = 0.46) ($ps < 0.05$), and with no other model differences.

Given that the FEM models showed significantly greater ITC for the single-dipole than for the full models, comparisons between the MEG Sphere and FEM models were performed only for the four single-dipole models. A Model X Hemisphere ANOVA on 40 Hz ASSR ITC showed a main effect of Hemisphere (right>left), $F(1,52) = 26.24$, $p < 0.001$. A main effect of Model, $F(3,50) = 19.82$, $p < 0.001$, showed lower ITC in MEG Fem_Hes_Single versus the other models ($ps < 0.05$), with no other model differences.

Figure 2 shows for the FEM and Sphere MEG model associations with age for 40 Hz ASSR ITC (top two rows). In this and the following figures showing MEG and EEG STG age and 40 Hz ASSR associations, data are shown for participants with a model goodness-of-fit (GOF) greater than 65%. So that the same participants could be included across the MEG and EEG head-source models, the 65% GOF threshold was obtained from the MEG Sphere_Hes_Single model (for plotting the MEG FEM and Sphere findings) or the EEG Sphere_Hes_Single model (for plotting the EEG FEM and Sphere findings). The number of participants with GOF above 65% is noted in the upper left corner of each scatterplot. Differences in MEG and EEG with respect to GOF and thus number of participants is further examined in the ‘Discussion’ as well as the ‘Online Supplement’.

Although as reported above there were significant model differences in the ITC values, as shown by the R^2 values in the Figure 2 scatterplots, except for the FEM full models, associations with age and 40 Hz ASSR ITC were very similar across source models (left and right hemisphere). Interclass correlation (ICC) analyses (excluding the FEM Full models) also indicated very similar ITC values in the left (ICC = 0.95) and right (ICC = 0.92) hemispheres.

With the exception of the MEG FEM Full models, given very similar ITC values between MEG Sphere and FEM models, and given no differences between models regarding associations with age in the left hemisphere, for analyses comparing MEG and EEG ITC the MEG Sphere_Hes_Single model was selected as being the ‘simplest’ head-source model.

MEG 40 Hz ASSR Total Power

Although the analyses below showed significant 40 Hz MEG ASSR TP differences between head-source models, the 40 Hz ASSR TP value across head-source models was similar. Across head-source models, right > left hemisphere TP differences were observed, and across head-source models associations between 40 Hz ASSR TP and age were very similar.

Examining the MEG FEM head models, a Model X Hemisphere ANOVA on 40 Hz ASSR TP showed a Hemisphere X Model interaction, $F(3,47) = 4.43$, $p < 0.01$. Simple-effects analyses showed greater right than left TP for all models ($p < 0.001$) except for MEG FEM_Loc_Full. In left and right hemispheres, the following order was observed: MEG FEM_Loc_Single > FEM_Hes_Single > FEM_Loc_Full = FEM_Hes_Full ($ps > 0.05$).

Examining the MEG Sphere head models, an ANOVA on 40 Hz ASSR TP showed a Model X Hemisphere interaction, $F(3,49) = 5.56$, $p < 0.001$. Simple-effects analyses showed greater right than left TP for all models, although with a greater hemisphere asymmetry for MEG Sphere_Loc_Full versus Sphere_Hes_Full. In left and right hemispheres, the following order was observed: MEG Sphere_Loc_Full = Sphere_Loc_Single > Sphere_Hes_Single > Sphere_Hes_Full ($ps > 0.05$).

Given for the FEM models significantly greater TP for the single-dipole versus full model, comparisons between the Sphere and FEM models were performed only for single-dipole models. A Model X Hemisphere ANOVA on 40 Hz ASSR TP showed a main effect of Hemisphere (right>left), $F(1,49)=17.79$, $p<0.001$. A main effect of Model, $F(3,47)=13.10$,

$p < 0.001$, showed the following order: MEG Sphere_Loc_Single > Sphere_Hes_Single = FEM_Hes_Single > FEM_Loc_Single.

Figure 3 shows for the FEM and Sphere MEG source models associations with age for TP (top two rows). Although as detailed above there were significant model differences in the TP values (e.g., lowest TP values for MEG FEM_Hes_Full), as shown by the R^2 values in the Figure 3 scatterplots, except for the FEM_Loc_Full model, associations with age were very similar across head models (left and right hemispheres). Interclass correlation (ICC) analyses (excluding the FEM Full models) also indicated very similar TP values in the left (ICC = 0.95) and right STG (ICC = 0.93) hemispheres.

Given very similar TP values for MEG Sphere and FEM, and given no differences between models regarding associations with age in the left hemisphere (with the exception of the FEM_Loc_Full model), for analyses comparing MEG and EEG TP the MEG Sphere_Hes_Single model was selected as being the ‘simplest’ head-source model.

MEG 40 Hz ASSR Prestimulus Activity

To better understand the 40 Hz ASSR TP findings, prestimulus activity was examined, measured as activity from –800 to –200 ms and between 38 and 42 Hz.

Examining the MEG FEM models, a Model X Hemisphere ANOVA on 40 Hz prestimulus activity showed a Model X Hemisphere interaction, $F(3,48) = 6.27$, $p < 0.001$. Simple-effects analyses showed right > left for both FEM_Hes models versus left > right for Fem_Loc_Single (and with a similar trend for Fem_Loc_Full). In both hemispheres, the strongest prestimulus activity was observed for Fem_Loc_Full and the weakest for FEM_Hes_Single.

Examining the MEG Sphere models, an ANOVA on 40 Hz prestimulus activity showed a main effect of Model, $F(3,49) = 54.61$, $p < 0.001$, that indicated the following order: MEG Sphere_Hes_Single > Sphere_Loc_Full > Sphere_Loc_Single > Sphere_Hes_Full.

As with the ITC and TP analyses, comparisons between the MEG Sphere and FEM models were performed only for the four single-dipole models. A Model X Hemisphere ANOVA on 40 Hz prestimulus activity showed a Model X Hemisphere interaction, $F(3,47) = 8.65$, $p < 0.001$. Simple-effects analyses showed right > left prestimulus activity for FEM_Hes_Single, left > right prestimulus activity for Fem_Loc_Single and Sphere_Loc_Single, and no hemisphere differences for Sphere_Hes_Single.

Figure 4 shows for the FEM and Sphere MEG head-source models associations with age for prestimulus activity (top two rows). Examination of the R^2 values indicates associations for the models with sources fixed to Heschl’s Gyrus, especially in the left hemisphere.

EEG 40 Hz ASSR ITC

Examining the EEG FEM models, a Model X Hemisphere ANOVA on EEG 40 Hz ASSR ITC showed only a main effect of Hemisphere (left > right), $F(1,49) = 18.77$, $p < 0.001$.

Examining the EEG Sphere models, a Model X Hemisphere ANOVA on EEG 40 Hz ASSR ITC showed a main effect of Hemisphere (right>left), $F(1,51) = 6.25$, $p < 0.05$, as well as a main effect of Model, $F(1,51) = 5.10$, $p < 0.05$, with EEG Sphere_Hes_Single (ITC = 0.28) > Sphere_Hes_Full (ITC = 0.27) ($p < 0.05$).

As for the MEG analyses, comparisons between the EEG Sphere and FEM models were performed only for the two single-dipole models. A Model X Hemisphere ANOVA on 40 Hz ASSR ITC showed a Model X Hemisphere interaction, $F(1,49) = 13.08$, $p < 0.001$. Simple-effects analyses showed left > right ITC only for FEM_Hes_Single and no hemisphere differences for Sphere_Hes_Single. In addition, in the right hemisphere, 40 Hz ASSR ITC values were larger for Sphere_Hes_Single than FEM_Hes_Single.

Figure 2 shows for the FEM and Sphere EEG source models associations with age for ITC (bottom row). As shown by the Figure 2 scatterplots and R^2 values, associations with age and left 40 Hz ASSR ITC appeared stronger for the Sphere versus FEM models. Given this difference, the EEG Sphere_Hes_Single model was selected for comparison with MEG as being the ‘simplest’ source model.

EEG 40 Hz ASSR TP

Examining the EEG FEM models, a Model X Hemisphere ANOVA on EEG 40 Hz ASSR TP showed a only main effect of Hemisphere (left > right), $F(1,51) = 12.70$, $p < 0.001$.

Examining the EEG Sphere models, a Model X Hemisphere ANOVA on EEG 40 Hz ASSR TP showed a main effect of model, $F(1,51) = 7.96$, $p < 0.01$, with EEG Sphere_Hes_Single TP > Sphere_Hes_Full.

Comparisons between the EEG Sphere and FEM models were performed only for the two single-dipole models. A Model X Hemisphere ANOVA on 40 Hz ASSR TP showed a Model X Hemisphere interaction, $F(1,50) = 8.17$, $p < 0.001$. Simple-effects analyses showed higher right TP for Sphere_Hes_Single than FEM_Hes_Single as well as left > right TP for FEM_Hes_Single .

Figure 3 shows for the FEM and Sphere EEG source models associations with age for TP (bottom row). As shown by the Figure 3 scatterplots and R^2 values, associations with age and left 40 Hz ASSR TP appeared stronger for the Sphere versus FEM models. Given this difference, the EEG Sphere_Hes_Single model was selected for comparison with MEG as being the ‘simplest’ source model.

EEG 40 Hz ASSR Prestimulus Activity

Examining the EEG FEM models, an ANOVA on 40 Hz prestimulus activity showed a main effect of Model, $F(1,52) = 49.90$, $p < 0.001$, and indicated greater prestimulus activity in EEG FEM_Hes_Full versus FEM_Hes_Single. A main effect of Hemisphere, $F(1,52) = 12.02$, $p < 0.001$, indicated right > left prestimulus activity.

Examining the EEG Sphere models, an ANOVA on 40 Hz ASSR prestimulus activity showed a main effect of Model, $F(1,52) = 8.23$, $p < 0.01$, and indicated greater prestimulus activity in EEG Sphere_Hes_Full versus Sphere_Hes_Single.

For comparison with the ITC and TP analyses, comparisons between the EEG Sphere and FEM models were performed only for the two single-dipole models. A Model X Hemisphere ANOVA on 40 Hz pre-stimulus activity showed a Model X Hemisphere interaction, $F(1,52) = 11.45$, $p < 0.01$. Simple-effects analyses showed in the left hemisphere greater prestimulus activity for Sphere_Hes_Single versus Fem_Hes_Single. In addition, whereas for the FEM_Hes_Single model prestimulus activity was greater in the right than the left hemisphere, for Sphere_Hes_Single no prestimulus hemisphere differences were observed.

Figure 4 shows for the Sphere EEG source models associations with age for the 40 Hz prestimulus measure (bottom row). As shown by the R^2 values in the Figure 4 scatterplots, associations with age were very similar (and also nonsignificant) across source models within each hemisphere.

Comparing MEG and EEG 40 Hz ASSR ITC, TP, and prestimulus activity

Given the above results, to reduce the number of analyses, only the MEG and EEG Sphere_Hes models were compared. A paired t-test of the goodness of fit (GOF) showed higher GOF for EEG (mean = 83%, SD = 11) than MEG (mean = 74%; SD = 12), $t(52) = 6.05$, $p < 0.001$. Differences in MEG and EEG with respect to GOF is examined in the 'Discussion' as well as the 'Online Supplement'.

A Model X Hemisphere ANOVA on 40 Hz ASSR ITC showed a Hemisphere X Model interaction, $F(1,51) = 8.40$, $p < 0.01$. Simple-effects analyses showed greater left ($p < 0.001$, Cohen's $d = 1.16$) and marginally greater right ($p = 0.08$, Cohen's $d = 1.47$) ITC for MEG than EEG. A significant right > left ITC difference was also observed only for MEG. A Model X Hemisphere ANOVA on 40 Hz ASSR TP showed a Model X Hemisphere interaction, $F(1,50) = 13.11$, $p < 0.001$. Simple-effects analyses showed a significant right > left TP difference only for MEG Sphere_Hes_Single. In addition, MEG TP was greater than EEG TP in both the left (Cohen's $d = 0.89$) and right hemisphere (Cohen's $d = 1.23$). Finally, a Model X Hemisphere ANOVA on 40 Hz prestimulus activity (38 to 42 Hz) showed a main effect of Model, $F(1,52) = 328.68$, $p < 0.001$, and indicated greater prestimulus power for EEG than MEG (Cohen's $d = 2.76$).

Finally, to compare EEG and MEG with respect to the ability to record a stable 40 Hz ASSR, the T^2_{circ} procedure described in Victor and Mast (Victor & Mast, 1991) was used to determine whether a left and right STG 40 Hz ASSR was present in each participant, via a quantitative analysis of a steady-state response against a background of additive noise. The left and right STG evoked time-domain 40 Hz ASSR was used for T^2_{circ} analyses, using as input epochs of 125 ms (= 5 cycles of 40 Hz activity), starting at 300 ms, and thus obtaining 5 epochs over a 300 to 925 ms period for each evoked 40 Hz ASSR. The T^2_{circ} analyses indicated, on average, a significant left and right STG 40 Hz ASSR in all participants. Paired t-tests comparing EEG and MEG T^2_{circ} values, however, clearly indicated higher-quality

responses for MEG than for EEG ($p < 0.05$, left Cohen's $d = 0.41$, right Cohen's $d = 0.42$). Indeed, for MEG the T^2_{circ} analyses indicated a significant 40 Hz ASSR in all but 3 participants in the left STG and in all participants in the right STG. In contrast, for EEG, there were 10 nonsignificant left STG and 8 nonsignificant 40 Hz ASSR. Figure 5b shows left and right STG time-domain evoked responses, showing in one representative participant lower T^2_{circ} values in EEG than MEG. These EEG and MEG differences are further examined in the Discussion.

MEG and EEG: 40 Hz ASSR and Age Associations

Figure 5 shows associations with age for MEG (blue) and EEG (red) for ITC (top panels), TP (center panels), and prestimulus power (bottom panels) for the MEG and EEG Sphere head models with single dipole sources fixed to left and right Heschl's Gyrus. Comparison of MEG and EEG R^2 values show qualitatively higher R^2 ITC and TP values for EEG, although statistical comparison of the MEG and EEG R^2 values showed that the differences were not large enough to reach significance ($p > 0.05$). Prestimulus findings, however, showed significant associations with age only for MEG, with increased left- and right-hemisphere prestimulus activity in older versus younger participants (significant in left hemisphere, trending in right hemisphere).

EEG 40 Hz ASSR Sensor Measures

The left panel of Figure 6 shows associations with age and 40 Hz ASSR ITC, TP and prestimulus activity for the midline EEG sensors as well as for the first PCA component. For ITC and TP, EEG sensor and PCA R^2 values were, on average, two to threefold smaller than the EEG left STG source R^2 values. The right panel of Figure 6 shows correlations between 40 Hz ASSR and age for the clusters of left- and right-hemisphere EEG temporal sensors. Only the association between age and the left sensor cluster 40 Hz ASSR ITC was significant ($p < 0.05$).

Discussion

A comparison of MEG and EEG STG head and source models showed similarity in the 40 Hz ASSR ITC and TP measures, indicating that choice of head and source models is not a primary concern. In particular, although across models there were statically significant differences in the 40 Hz ASSR ITC and TP estimates, for most of the head and source models associations between left STG 40 Hz ASSR ITC and TP and age were very similar (and in the right STG, across models, no associations with age). General similarity between the Sphere and FEM head models was not surprising given that STG regions are generally described well by a spherical head model, with results thus indicating that the use of a MEG or EEG spherical head model with sources manually fixed to left and right Heschl's Gyrus is an effective and efficient method for measuring the left and right STG 40 Hz ASSR.

Present results very clearly showed an advantage of examining the 40 Hz ASSR in source versus sensor space, as EEG sensor measures tended to combine left and right STG 40 Hz ASSR activity and thus mostly failed to detect 40 Hz ASSR and age associations (as well as failing to show the expected hemisphere differences in ITC and TP). As EEG sensor-level

analyses poorly measured the intended construct (neural generators of the 40 Hz ASSR) and as the sensor-level estimates also did not have predictive (age) or discriminant (left versus right) qualities, present findings indicated that EEG sensor-level analysis methods have poor construct validity for 40 Hz ASSR. As an example, examination of Figure 7 shows low and nonsignificant 40 Hz ASSR and age associations when measuring the 40 Hz ASSR from EEG sensors Cz and Fz, and when using the 1st component of a PCA. Of note, using the EEG source-model GOF to identify and remove participants with a low EEG SNR did not improve the EEG 40 Hz ASSR Cz and Fz and age associations (analyses not shown), indicating that the loss of the left 40 Hz ASSR and age association at the midline sensor level was due to the superimposition of 40 Hz ASSR activity from multiple brain regions (at least left and right STG as well as perhaps other brain regions). Of course, examination of EEG midline electrodes precluded the ability to examine the right > left 40 Hz ASSR TP and ITC pattern (hemisphere differences discussed in more detailed in the following text).

EEG PCA results were similar to midline EEG sensor-level results. To the extent that left and right STG 40 Hz ASSR activity is moderately correlated, PCA analyses likely combine left and right STG 40 Hz ASSR activity into a single component. Present findings indicated that this is a problem, as using the 1st principal component no associations with age were observed. Present findings thus indicate that a PCA approach poorly measures the intended construct – STG 40 Hz ASSR neural generators.

Regarding left and right EEG sensor-cluster findings, a significant association between the left-hemisphere EEG cluster 40 Hz ASSR ITC measure and age was observed. The difference in the association, with a R^2 value of 0.20 for the EEG Sphere_Hes_Single versus a R^2 value of 0.09 for left-hemisphere EEG sensors is likely a result of including ‘noise’ in the EEG sensor measure, due to the fact that in most participants selection of EEG channels over the left and right hemisphere includes EEG sensors where there is a field reversal and thus with little or no 40 Hz ASSR signal. In contrast, as an EEG source-modeling strategy combines sensor data when estimating source strength, the field reversal across EEG channels within a hemisphere is ignored. The observation of a EEG left 40 Hz ASSR ITC and age but no EEG left 40 Hz ASSR TP and age association was surprising, as TP is better estimated than ITC, especially when there is low SNR (Edgar, 2016). At present, the failure to observe an association between age and TP for the left EEG sensor cluster remains an open question.

Present findings empirically showed that a failure to separately examine the left and right 40 Hz ASSR generators removes real effects (associations with age). Present findings thus suggest that control versus patient group differences will be difficult to observe in sensor or PCA space, especially given that group differences are often reported to be lateralized (see Introduction). Dipole orientation findings presented in the Online Supplement suggest additional problems with a sensor based analysis approach. Similar to the Edgar et al. (Edgar, et al., 2003) findings for the auditory M50 left and right STG dipole orientations, a wide range of orientations in the sagittal plane was observed for the left and right STG 40 Hz ASSR dipoles. In particular, as shown in Online Supplement Figure 2, the MEG and EEG one and two standard deviation lines show that in many participants the 40 Hz ASSR peak source/sink ‘hotspots’ are not at EEG Cz or Fz. Such findings again demonstrate the

advantage of obtaining 40 Hz ASSR measures in source space, a strategy that provides the ability to ignore differences in dipole orientation across participants.

Present findings contribute to the literature on methodological issues related to measuring gamma activity in patient populations. For example, regarding schizophrenia, a prior study noted that a lack of group differences in some papers may be due to suboptimal filtering of gamma activity (Roach & Mathalon, 2008). Another report noted that the lack of studies observing associations between gamma activity and clinical symptoms may be due to small samples, medication confounds, and state versus trait effects (Mathalon & Ford, 2012). Present findings add to the literature by indicating that a lack of gamma and clinical measure associations in some studies is likely due to a failure to optimally measure the intended gamma construct.

Present findings thus establish the use of MEG and EEG head and source modeling for measuring the 40 Hz ASSR STG neural generators, with findings suggesting the use of a Sphere head model and with left and right sources manually fixed to Heschl's Gyrus. Confidence in this 'best practice' proposal requires acceptance of a few assumptions. In particular, given no gold standard (i.e., we cannot know the 'true' 40 Hz ASSR ITC and TP measure), a known association between the left STG 40 Hz ASSR and age was leveraged to determine whether a given analysis method provided valid estimates of the 40 Hz ASSR. In areas of research where activity that cannot be directly observed, this use of coincidence is commonly used to support confidence in unobservable measures. In addition to leveraging the left 40 Hz ASSR and age association, the present MEG source-model results replicated studies showing right > left 40 Hz ASSR ITC and TP (Edgar, et al., 2014; Edgar, et al., 2016; Ross, Herdman, & Pantev, 2005) and thus bolsters confidence in the present proposal.

Regarding the 40 Hz ASSR analysis strategy proposed here, it is of note that previous studies have shown that the proposed method for measuring the left and right STG 40 Hz ASSR can be largely automated. For example, automated identification of left and right Heschl's Gyrus can be obtained via the use of probabilistic cytoarchitectonic maps (Dammers, et al., 2007). As detailed in Zvyagintsev et al. (Zvyagintsev, Thonnessen, Dammers, Boers, & Mathiak, 2008), given large samples, developing an automated analysis pipeline that includes an automated determination of primary auditory cortex as well as a pipeline that includes automated artifact correction (e.g., eye-blink) can increase the ease, speed, and reliability of such analyses. Of note, the present study used each participant's sMRI to identify Heschl's Gyrus. Given that in some studies sMRIs are not obtained, future studies are needed to determine whether age-matched sMRI templates provide adequate estimates of the left and right STG 40 Hz ASSR or if different head sizes and shapes compromise the 40 Hz ASSR source measures too much.

Comparing Findings for the EEG and MEG Head Models

Contrary to the study hypotheses, age and left STG 40 Hz ASSR TP and ITC correlation values were similar for the EEG and MEG source models. Although EEG and MEG findings were generally similar, with such findings thus indicating the use of either whole-head EEG or MEG for examining STG 40 Hz auditory steady-state activity, several lines of evidence indicated a slight advantage of MEG over EEG for measuring the left and right STG 40 Hz

ASSR. First, T^2_{circ} values were significantly higher for MEG than EEG (see results for the Spherical Head Models with sources manually fixed to left and right Heschl's Gyrus), indicating a more stable and robust 40 Hz ASSR in MEG than in EEG. The finding of higher prestimulus activity for EEG than MEG (e.g., Figure 5 bottom row), and thus greater prestimulus 'noise' in EEG that is likely sustained throughout the poststimulus period, likely contributed to less significant T^2_{circ} values for EEG than MEG. Indeed exploratory posthoc analyses demonstrated that increased EEG prestimulus gamma activity was strongly associated with lower EEG T^2_{circ} values in the left STG ($R^2 = 0.19$, $p < 0.001$) and right STG ($R^2 = 0.16$, $p < 0.01$). MEG prestimulus gamma activity was not associated with MEG T^2_{circ} values, with such EEG and MEG differences again suggesting increased noise in the EEG recording. This was also observed in the time-domain evoked responses. As an example, Figure 7a shows left and right STG time-domain evoked responses, showing in one representative participant the higher prestimulus activity in EEG than in MEG as well as lower T^2_{circ} values for EEG than MEG.

Several factors may contribute to increased noise in the EEG than MEG recordings. First, there is evidence for a contribution of muscle artifact to EEG measures above 20 Hz (Whitham, et al., 2007). Second, given that EEG sensors detect superficial and deep brain activity, this may result in measuring prestimulus brain activity from STG and non-STG brain regions and thus erroneously obtaining higher prestimulus activity source model estimates in EEG versus MEG. It is also of note that for MEG, but not EEG, prestimulus activity was associated with age, thus suggesting that MEG is better at assessing 40 Hz steady-state neural generator prestimulus activity, perhaps due to greater sensitivity for MEG to activity only from the auditory 40 Hz STG steady-state generators¹ (Edgar, et al., 2003; Huang, et al., 2003).

The higher poststimulus 40 Hz steady-state ITC and TP values for MEG versus EEG (see top two rows of Figure 5) indicated another possible advantage of MEG over EEG, with these findings perhaps due to greater specificity of the MEG planar gradiometers to STG 40 Hz steady-state activity (i.e., detecting only 40 Hz steady-state activity and not also other deeper brain activity), and thus more accurate estimates of trial-to-trial phase and thus higher ITC for MEG versus EEG as well as better pre- to poststimulus estimates of the increase in auditory STG 40 Hz steady-state activity (i.e., TP) for MEG versus EEG. A additional difference between MEG and EEG source findings is of note; regarding hemisphere differences, the Sphere_Hes_Single source-model results showed the expected right > left TP findings only for MEG, with such findings again suggesting an advantage of MEG over EEG.

¹Given an age-related change in prestimulus power for MEG, the MEG TP measure may include a 'correction' for age, as older participants have increased MEG prestimulus activity, and thus in the computation of MEG TP more activity is removed from the poststimulus measure in older versus younger adults, and also the poststimulus numerator is scaled by a larger denominator in older versus younger adults. Regarding the age and prestimulus associations, it is also of note that these associations were observed only for the models with sources fixed to Heschl's Gyrus (FEM and Sphere). Given an effect of source depth on dipole source strength (i.e., dipoles localizing more medially necessarily stronger), the prestimulus and age associations observed in the FEM and Sphere models with sources fixed to Heschl's Gyrus are thought to be unbiased (thus unlike the source localization findings not effected by localization error due to SNR) and thus likely to show a true association. It is, however, unclear why similar associations were not observed for the EEG Sphere_Hes models. As ITC is not computed as a function of prestimulus activity, a prestimulus age-dependence likely does not affect the ITC measure (although ITC would be more difficult to correctly measure given poor SNR).

Although the finding of significantly higher GOF values for EEG than MEG might suggest an advantage of EEG over MEG, the Figure 7b EEG evoked sensor montage shows that whereas a 40 Hz ASSR is observed in almost all EEG sensors, a 40 Hz ASSR is observed only over left and right ‘temporal lobe’ MEG sensors (and almost no ASSR observed in frontal and occipital areas). Given such lower spatial sensitivity for EEG versus MEG, it is hypothesized that the EEG source model has less total variance to explain, and thus higher GOF values are obtained for EEG versus MEG.

Although the above evidence thus suggests better estimates of the STG 40 Hz ASSR for MEG than EEG, there is one exception: left STG 40 Hz ASSR and age associations were more robustly observed for EEG than MEG, especially if participants with low GOF were included. As shown in Online Supplement Figures 3 and 5, comparison of participants with higher versus lower MEG GOF values (far right bottom plots) showed that those with lower MEG GOF tended to have the lowest TP and ITC values, with these participants thus ‘removing’ left STG 40 Hz ASSR and age associations. In the present study, using a MEG GOF cutoff of 65%, approximately 20% of the participants were removed. Although the participants with low MEG GOF values did indeed tend to have lower MEG T^2_{circ} values (left STG $R^2 = 0.15$, right STG $R^2 = 0.09$), as previously indicated, the MEG T^2_{circ} analyses clearly showed that all but 3 participants had a statistically significant left and right 40 Hz ASSR, indicating that a low MEG GOF was not generally associated with a nonsignificant 40 Hz ASSR (as determined by T^2_{circ}). Present findings, however, suggest that for MEG the lower GOF and lower T^2_{circ} values identify a subset of participants with an identifiable but perhaps less well measured 40 Hz ASSR. Given a sensitivity profile of MEG planar gradiometers to more superficial cortical activity, perhaps in these participants the planar gradiometers may have ‘failed’ to fully detect the auditory 40 Hz ASSR. For example, perhaps in these participants the 40 Hz auditory steady-state generators were located very medial (and thus deep) in the superior temporal sulcus. MEG studies comparing auditory steady-state activity using planar and axial gradiometers are thus of interest.

Study Limitation and Future Directions

A limitation of the present study is that the source models focused only on the left and right STG 40 Hz steady-state generators. Previous studies have shown that other brain regions are involved in processing 40 Hz steady-state stimuli (Bish, Martin, Houck, Ilmoniemi, & Tesche, 2004). It is also noted that the present proposal for measuring the left and right STG 40 Hz ASSR via source modeling may not apply to other auditory measures such as the evoked gamma response or the 50 ms or 100 ms auditory evoked responses. Given that left and right STG regions are the primary contributors to these other auditory responses, however, findings similar to those obtained here for the 40 Hz ASSR are expected.

As previously noted, of interest are studies comparing the 40 Hz ASSR measured using planar versus axial gradiometer. Also of interest are studies combining the EEG and MEG data (Sharon, Hamalainen, Tootell, Halgren, & Belliveau, 2007), with such studies examining STG and non-STG 40 Hz auditory steady-state generators. Additional work is also needed to determine why an age-related association with the 40 Hz ASSR in adults is observed in the left but not right STG.

Finally, it is of note that the figures showing ITC results (e.g., Figure 2) suggest a floor effect for the ITC measure. Furthermore, as shown in Online Supplement Figures 3 and 4, in subjects with lower GOF, ITC values were found to cluster between 0.10 and 0.20 (with no ITC values below 0.10). Although ITC values range from 0 to 1.0, it is unlikely that in the case of no trial-to-trial phase synchrony the ITC estimate will in fact converge to zero. Simulations presented in the Online Supplement showed this to be true, with simulations showing that in the case of no trial-to-trial phase synchrony (i.e., $ITC = 0$), with ~100 trials, ITC values hover near 0.08.

Such limitations, inherent in the ITC signal processing procedure, will sometimes complicate interpretation of 40 Hz ASSR ITC findings, especially in studies examining patient populations with a weak 40 Hz ASSR. For example, in adult control versus patient studies, analyses showing group differences in gamma activity may be meaningful, indicating that a patient group does have decreased 40 Hz ASSR. However, given that for many of these patients (and some controls) their true 40 Hz ASSR ITC value exists within the noise floor, it may be difficult to determine associations with clinical measures or brain measures (e.g., gray matter). In younger populations, given that both control and patient groups will have a weak 40 Hz ASSR (Cho, et al., 2015; Edgar, et al., 2016; Rojas, et al., 2006), assessment of group 40 Hz ASSR differences in younger populations may not be possible. In any case, present findings indicate that the use of a source model with sources fixed to Heschl's Gyrus is the optimal way to assess 40 Hz ASSRs in these younger populations, with other studies noting the advantage of using prior knowledge in brain electromagnetic source analysis, especially in cases of identifying the correct source localization given poor SNR (Scherg & Berg, 1991).

Conclusions

As a measure of the 40 Hz ASSR cortical microcircuits, a source-modeling approach was shown to be superior to methods that rely directly on EEG sensor measures. The STG 40 Hz ASSR source measures provided predictive and discriminative capability and thus showed good construct validity. Obtaining measures of the STG 40 Hz ASSR via the proposed method - use of a Sphere head model and with left and right sources anatomically constrained to Heschl's Gyrus - is needed to facilitate inferences and guide future studies. Additional studies (likely multimodal brain imaging studies) are needed to determine why age and 40 Hz ASSR associations are observed only in the left hemisphere as well as why MEG is better than EEG at identifying the expected right > left hemisphere TP and ITC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 1 shows each MEG (left) and EEG (right) source models as well as methods used to measure the 40 Hz ASSR from EEG sensors. For MEG, eight head-source models were created: using a Sphere or FEM head model, using regional source or single dipole sources, and using sources localized based on individually optimized model fits or sources manually fixed to left and right Heschl's Gyrus. No MEG scalp models were tested (see main text). For EEG head-source modeling, only a Sphere head model was examined using the manually fixed Heschl's Gyrus sources. For EEG scalp measures, the 40 Hz ASSR was examined at EEG sensors Cz and Fz, using the 1st component of a PCA applied to all 64 EEG sensors, using clusters of 18 channels over the left hemisphere, and using clusters of 18 channels over the right hemisphere.

Figure 2.

Scatterplots showing correlations between left and right STG 40 Hz ASSR ITC and age for the MEG FEM (upper row), MEG Sphere (middle row), and EEG Sphere (bottom row) head models. Head-source model data are shown only for participants with a MEG or EEG Sphere_Hes_Single model GOF > 65%. Age is shown on the x axis and 40 Hz ASSR ITC on the y axis. R² values show the percent variance explained (* $p < 0.05$, ** $p < 0.05$). The number of participants with GOF > 65% is reported in the upper left corner of each scatterplot.

Figure 3.

Scatterplots showing correlations between left and right STG 40 Hz ASSR TP and age for the MEG FEM (upper row), MEG Sphere (middle row), and EEG Sphere (bottom row) head models. Source model data are shown only for participants with a MEG or EEG Sphere_Hes_Single model GOF > 65%. Age is shown on the x axis and 40 Hz ASSR ITC on the y axis. R^2 values show the percent variance explained (* $p < 0.05$, ** $p < 0.05$). The number of participants with GOF > 65% is reported in the upper left corner of each scatterplot.

Figure 4.

Scatterplots showing correlations between left and right STG 40 Hz prestimulus activity (averaging across 38 to 42 Hz from -800 to -200 prestimulus onset) and age for the MEG FEM (upper row), the MEG Sphere (middle row) and EEG Sphere (bottom row) head models. Source model data is shown only for participants with a MEG or EEG Sphere_Hes_Single model GOF $> 65\%$. Age is shown on the x axis and 40 Hz prestimulus power on the y axis. R^2 values show the percent variance explained ($*p < 0.05$, $**p < 0.05$). The number of participants with GOF $> 65\%$ is reported in the upper left corner of each scatterplot.

MEG and EEG Sphere Models Sources fixed to left and right Heschl's Gyrus

Figure 5.

Scatterplots directly comparing the 40 Hz ASSR age associations for the EEG and MEG Sphere_Hes_Single models for ITC (upper row), TP (middle row), and prestimulus activity (bottom row). Age is shown on the x axis and 40 Hz activity on the y axis. R² values show the percent variance explained (* $p < 0.05$, ** $p < 0.05$). The number of participants with GOF > 65% is reported in the upper left corner of each scatterplot.

EEG Sensor Measures 40 Hz ASSR and Age

Figure 6.

Left-panel scatterplots show correlations between 40 Hz ASSR and age for the EEG sensor measures (EEG Cz, Fz, and 1st component of a PCA). Associations are shown for ITC (upper row), TP (middle row), and 40 Hz prestimulus activity (bottom row). Right-panel scatterplots show correlations between 40 Hz ASSR and age for the clusters of left- and right-hemisphere EEG temporal sensors for ITC (upper row), TP (middle row), and prestimulus activity (bottom row). In all plots age is shown on the x axis and 40 Hz activity on the y axis. R^2 values show the percent variance explained (* $p < 0.05$, ** $p < 0.05$).

Figure 7.

Figure 7a shows left and right STG evoked time-domain source timecourses from a representative participant (MEG and EEG source timecourses similarly scaled). Examination of the prestimulus period shows less prestimulus activity in MEG versus EEG, with such prestimulus 'noise' differences likely extending to the poststimulus period and thus likely contributing to the lower T^2_{circ} value for EEG than MEG. Figure 7b shows MEG (left) and EEG (right) sensor plots, with focal a 40 Hz ASSR observed in the left and right 'temporal' sensors (and very little auditory activity in frontal and occipital regions) versus a very distributed 40 Hz ASSR observed in EEG sensors.