HHS Public Access

Author manuscript

Int J Psychophysiol. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Int J Psychophysiol. 2017 April ; 114: 16–23. doi:10.1016/j.ijpsycho.2017.01.013.

MEG and EEG demonstrate similar test-retest reliability of the 40 Hz auditory steady-state response

Kristina T. Legget, Ph.D.[a,b,*], **Allison K. Hild, B.S.**[a,b], **Sarah E. Steinmetz, M.S.**[a,b], **Steven T. Simon, M.D.**[b], and **Donald C. Rojas, Ph.D.**[c]

[a]Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States

[b]Department of Medicine, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States

[c]Department of Psychology, Colorado State University, Fort Collins, CO, United States

Abstract

The auditory steady-state response (ASSR) is increasingly being used as a biomarker in neuropsychiatric disorders, but research investigating the test-retest reliability of this measure is needed. We previously reported ASSR reliability, measured by electroencephalography (EEG), to 40 Hz amplitude-modulated white noise and click train stimuli. The purpose of the current study was to (a) assess the reliability of the MEG-measured ASSR to 40 Hz amplitude-modulated white noise and click train stimuli, and (b) compare test-retest reliability between MEG and EEG measures of ASSR, which has not previously been investigated. Additionally, impact of stimulus parameter choice on reliability was assessed, by comparing responses to white noise and click train stimuli. Test-retest reliability, across sessions approximately one week apart, was assessed in 17 healthy adults. On each study day, participants completed two passive listening tasks (white noise and click train stimuli) during separate MEG and EEG recordings. Between-session correlations for evoked power and inter-trial phase coherence (ITPC) were assessed following source-space projection. Overall, the MEG-measured ASSR was significantly correlated between sessions ($p < 0.05$, FDR corrected), suggesting acceptable test-retest reliability. Results suggest greater response reproducibility for ITPC compared to evoked responses and for click train compared to white noise stimuli, although further study is warranted. No significant differences in reliability were observed between MEG and EEG measures, suggesting they are similarly reliable. This work supports use of the ASSR as a biomarker in clinical interventions with repeated measures.

[*]Corresponding author: Kristina T. Legget, Ph.D., Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, 13001 E. 17th Place, Mail Stop F546, Bldg. 500, Rm. E4315, Aurora, CO 80045, Phone: (303) 724-5809, Fax: (303) 724-6227, Kristina.Legget@ucdenver.edu.

Keywords

magnetoencephalography; electroencephalography; auditory evoked response; inter-trial phase coherence; auditory steady state response

1. Introduction

The 40 Hz auditory steady-state response (ASSR) is increasingly being used as a marker of brain function in various neuropsychiatric disorders. 40 Hz amplitude-modulated stimuli (e.g., amplitude-modulated tones, white noise, or click trains) can be used to entrain the ASSR, which peaks around 40 Hz in humans (Azzena et al., 1995; Hari et al., 1989) and can be measured using electroencephalography (EEG) or magnetoencephalography (MEG). ASSR abnormalities have been observed in autism spectrum disorders (Wilson et al., 2007), schizophrenia (Brenner et al. 2003; Hayrynen et al., 2016; Kwon et al., 1999; Light et al., 2006; O'Donnell et al., 2013; Roach et al., 2013; Spencer et al., 2008; Thune et al., 2016), and bipolar disorder (Isomura et al., 2016; Maharajh et al., 2007; O'Donnell et al., 2004; Oda et al., 2012; Rass et al., 2010). Heritability of these abnormalities has been suggested, as they have also been identified in first-degree relatives of individuals with autism (Rojas et al., 2011) and schizophrenia (Hong et al., 2004; Rass et al., 2012). The exact mechanism underlying ASSR abnormalities in these disorders is unclear. Much evidence suggests that ASSR abnormalities reflect dysfunctional gamma-aminobutyric acid (GABA) neurotransmission, leading to inefficiencies in brain inhibitory function (Brenner et al., 2009; Kwon et al., 1999; Lewis et al., 2005; O'Donnell et al., 2013; Vohs et al., 2010). However, there is also evidence suggesting that the ASSR involves glutamatergic dysfunction (Brenner et al., 2009; Kwon et al., 1999; Leishman et al., 2015; O'Donnell et al., 2013; Plourde et al., 1997; Sivarao et al., 2013; Sivarao, 2015; Sivarao et al., 2016; Vohs et al., 2012), particularly supported by emerging evidence that the 40 Hz ASSR may be more sensitive to *N*-methyl-D-aspartate (NMDA) receptor antagonism than to GABA-A receptor antagonism (Sullivan et al., 2015). With this growing body of evidence, the ASSR demonstrates strong potential as a biomarker in clinical studies of neuropsychiatric disorders (O'Donnell et al., 2013; Sivarao, 2015; Thune et al., 2016).

Given the increasing use of the ASSR in studies evaluating underlying neurophysiology of these disorders, it is important to determine the test-retest reliability of this response. This is also essential in establishing ASSR utility in clinical evaluations of novel therapeutic approaches for neuropsychiatric disorders. We recently reported the first assessment of EEG-measured ASSR test-retest reliability (McFadden et al., 2014). This study found the ASSR to be reliable between two sessions spaced approximately one week apart, to both 40 Hz amplitude-modulated white noise and click train stimuli. To date, only one study has assessed test-retest reliability of the MEG-measured ASSR (Tan et al., 2015). Tan et al. evaluated the MEG-measured ASSR across two sessions in response to both 5 Hz and 40 Hz amplitude-modulated tones. Overall, they found the ASSR to both tones to be reliable across sessions.

The purpose of the current study was to further assess the reliability of the MEG-measured ASSR and to compare the reliability of the MEG-measured ASSR to the EEG-measured ASSR, which has not previously been investigated. Although MEG-measured ASSR reliability has previously been investigated with tone stimuli, this has not been assessed for other stimuli commonly used to elicit the ASSR, such as white noise and click train stimuli. The consistency of the ASSR, to both 40 Hz amplitude-modulated white noise stimuli and click train stimuli, across two sessions spaced approximately one week apart, was measured using both MEG and EEG. The impact of stimulus parameters on reliability was determined by comparing reliability of the responses to white noise vs. click train stimuli. Based on previous findings, we hypothesized that overall, the ASSR would be significantly correlated between the two sessions. Furthermore, based on our previous EEG results (McFadden et al., 2014), we hypothesized that the MEG-measured ASSR to click train stimuli would be more reproducible than that to white noise stimuli. In our previous EEG findings (to white noise and click train stimuli) and Tan et al.'s MEG findings (to tone stimuli) (Tan et al., 2015), ITPC measures demonstrated potentially greater reliability than evoked power measures. As such, we hypothesized that the same would be observed for MEG responses to white noise and click train stimuli in the current study.

2. Methods

2.1. Participants

Nineteen adults completed the study. Data for two participants were excluded from analyses due to excessive noise (N = 1) and technical difficulties during recording for one of the conditions (N = 1). As such, data analyses were completed for 17 participants (9 male, 8 female, mean age = 30.4 +/− 9.1 years). Racial and ethnic identities were ascertained separately, with 5.9% identifying as African American/Black, 5.9% as Asian, and 88.2% as Caucasian; 23.5% of participants identified as Hispanic and 76.5% as non-Hispanic. Individuals were excluded from study participation if they had MEG-related contraindications (e.g., dental work causing data artifacts) or a personal history of current or past neurological or Axis I psychiatric disorder, as assessed by the SCID Screen Patient Questionnaire-Extended (First et al., 1991). All SCID assessments were administered by a trained masters-level research assistant. Participants were recruited via fliers and mass email postings. All study procedures were approved by the Colorado Multiple Institutional Review Board. Written, informed consent was obtained from all participants.

2.2. Stimuli and Paradigm

Participants completed two study days, separated by approximately one week (mean = 10.6, SD = 6.1 days apart, minimum of 5 days between sessions). On each study day, participants completed two passive listening tasks during both EEG and MEG recording. All participants reported having normal hearing. The ASSR was entrained by 40 Hz amplitude-modulated (100 percent depth) white noise stimuli in one task, and by 40 Hz amplitude-modulated click train stimuli in the other. Stimuli were presented binaurally through foam insert earphones (EEG: Compumedics Neuroscan, Charlotte, NC; MEG: E.A.R., Cabot Safety Co., Indianapolis, IN) at 75 dB SPL for 500 ms (inter-trial interval of 1000 ms), with a total of 200 trials of each type. For the click train stimulus, each click was 2 ms in duration delivered

every 25 ms for a total of 500 ms. Both tasks were presented for a total of 5 minutes, with breaks given between tasks.

2.3. MEG and EEG Data Acquisition

Continuous MEG data were acquired with a 4D Neuroimaging (San Diego, CA) Magnes WH3600 neuromagnetometer system with 248 axial first-order gradiometers in a custom-built magnetically-shielded room. Prior to MEG recording, the location and orientation of the MEG coils relative to each subject's head were determined by digitizing a set of fiducial reference points on the head using a magnetic digitizer (Polhemus 3SPACE). Left and right preauricular points and the nasion, as defined by the International 10–20 electrode system (Jasper, 1958), were digitized as reference points, and the shape of each participant's head was digitized for use in constructing a volume conductor model for source localizations. Data were collected at a sampling rate of 678.17 Hz. Recordings were made with participants supine with eyes open.

As described previously (McFadden et al., 2014), continuous EEG data were acquired with a 64-channel electrode cap (EASYCAP GmbH, Herrsching, Germany). Electrode placement used a standard 10–10-system (Nuwer et al., 1998) and impedances were below 10 kΩ at all sites. To assess horizontal and vertical eye movements, electrodes were placed on the outer canthi of both eyes and the supra-orbit of the right eye. An electrode in the middle of the forehead served as the ground. ERP recordings were amplified using Neuroscan SynAmps 2 amplifiers (Compumedics Neuroscan, Charlotte, NC), with a passband of .1–200 Hz and digitized at 1000 Hz. Recordings were average-referenced offline. Participants were asked to sit upright with their eyes open during recording.

2.4. MEG and EEG Data Preprocessing

Offline, MEG and EEG data were preprocessed using Brain Electrical Source Analysis (BESA) 6.0 software (BESA GmbH, Grafelfing, Germany). For both MEG and EEG data, 1000 ms epochs were created, starting 200 ms prior to stimulus onset and lasting for 800 ms post-stimulus onset. Data were baseline-corrected to the mean of the pre-stimulus period. Eye blink artifacts were removed after a pattern search following principal component analysis identification of typical blink topography from manual identification of a typical eye blink (Ille et al., 2002). Following eye blink correction, threshold-based artifact rejection was used to remove any epochs with activity greater than 2500 fT for MEG data and greater than 100 μV for EEG data. Data were then visually inspected and epochs with any additional movement or eye blink artifacts were removed from further analyses. For MEG data, out of the 200 recorded trials, an average of 185.6 (SD: 24.2) trials were accepted and used for further analyses for session 1 of the white noise task, with 185.9 (SD: 21.9) accepted for session 2. For the click train task, an average of 188.7 (SD: 15.0) trials were accepted for session 1, with 186.5 (SD: 21.4) accepted for session 2. For EEG data, an average of 183.1 (SD: 23.8) trials were used for further analyses for session 1 of the white noise task, with 183.1 (SD: 17.3) accepted for session 2. For the click train task, an average of 188.8 (SD: 31.6) trials were accepted for session 1, with 178.4 (SD: 20.7) accepted for session 2.

2.5. MEG and EEG Data Analysis

2.5.1. Source-Space Projection—Source-space projection (also called signal-space projection or lead field synthesis (Robinson, 1989; Teale et al., 2008)) was performed in BESA (Scherg, 1990; Scherg and Berg, 1996; Scherg and Von Cramon, 1986). For MEG data, following preprocessing, average evoked waveforms were computed for each participant for each task (white noise and click train stimuli) and each session (1 and 2). Source analysis was performed by fitting left and right hemisphere equivalent current dipoles to the 40 Hz ASSR in the band-pass filtered (30–50 Hz) averaged response between 200–500 ms (see Figure 1 for example waveforms). A spherical head model was used. Dipoles were approximately located in primary auditory cortex, and the mean dipole model residual variance was 15.7% (SD: 9.7). For EEG data, given that electrode locations were fixed across all participants, a grand average evoked waveform was computed across all participants, across both tasks and sessions. As with MEG data, source analysis was performed by fitting left and right hemisphere equivalent dipoles to the 40 Hz ASSR in the band-pass filtered (30–50 Hz) averaged response between 200–500 ms. A four-shell ellipsoidal head model was used for EEG source analysis. Residual variance was 8.8%. For both MEG and EEG data, source solutions were used to project the raw data for each participant (i.e., the original preprocessed data) into the source domain using a source montage in BESA (Scherg et al., 2002), resulting in a virtual electrode for each participant for left and right hemispheres (i.e., two data channels). The projection was done separately for each session (1 and 2) for each task (white noise and click train stimuli).

2.5.2. Time-Frequency Transformation—As previously described (McFadden et al., 2014), following source-space projection, time-frequency transformation was performed by complex demodulation (Hoechstetter et al., 2004; Papp and Ktonas, 1977) in BESA. This was done for both MEG and EEG data. Within BESA, the time and frequency space was sampled in 2.5 Hz and 20 ms bins for further analyses. Time-frequency representations for both evoked activity, normalized to the pre-stimulus baseline, and inter-trial phase coherence (ITPC) were both derived from BESA (Hoechstetter et al., 2004; Scherg, 1990; Scherg and Berg, 1996; Scherg and Von Cramon, 1986) and then imported into Matlab (R2012a; MathWorks, Inc., Natick, MA) using FieldTrip routines (Oostenveld et al., 2011). ITPC is a measure of event-related phase locking across trials (inter-trial consistency), sometimes referred to as phase-locking factor (PLF), which ranges from 0 (purely non-phase-locked) to 1 (strictly phase-locked) (Roach and Mathalon, 2008; Tallon-Baudry et al., 1996).

2.5.3. Auditory Steady-State Response (ASSR) Comparison—A comparison of the ASSR between white noise and click train stimuli for EEG data has been reported previously (McFadden et al., 2014). The current paper reports the same comparison for MEG data. Dependent-samples t-tests were run using FieldTrip routines (ft_freqstatistics.m) to compare the ASSR (collapsed across sessions) for the white noise task to that for the click train task. A false discovery rate (FDR; Genovese et al., 2002) of $q = 0.05$ was used to correct for multiple comparisons. This was performed for both the evoked response and ITPC, for both left and right hemispheres. Additionally, a comparison of the ASSR between EEG and MEG data was performed, also using dependent-samples t-tests with FieldTrip

routines and FDR for multiple comparison correction ($q = 0.05$). This was performed for both types of stimuli (white noise and click train) and both hemispheres.

2.5.4. Reliability: Between-Session Correlation—For both tasks (white noise and click train stimuli), correlation routines in Matlab (using the Statistical Toolbox function, corcoeff.m) were used to determine between-session reliability for evoked activity and ITPC. This was calculated separately for EEG and MEG data. For each virtual electrode (right and left hemisphere), each individual time-frequency bin for session 1 was compared to the corresponding time-frequency bin for session 2 across all participants (for both the evoked response and ITPC). This was performed separately for right and left hemispheres. FDR, as described in Benjamini and Hochberg (Benjamini et al., 2001), of $q = 0.05$ was used to correct for multiple comparisons across channels and time-frequency bins. In addition to examining reliability in this manner, we also collapsed results across time and frequency, examining the average correlations at 40 Hz across 200–500 ms. Comparisons between correlation coefficients (alpha of 0.05) were made using r to p conversion for between-sessions comparisons and using the Fisher r-to-z transformation for comparisons between stimulus type (white noise vs. click train), hemisphere (left vs. right), measures (evoked power and ITPC), and data type (MEG vs. EEG).

3. Results

3.1. ASSR Comparison

Figure 2 shows time-frequency plots of the grand-averaged evoked power and ITPC for MEG data for both types of stimuli (white noise and click train), for both left and right hemispheres. Data are collapsed across sessions. Between-task differences, with clicks producing greater ASSRs compared to white noise stimuli, only survived multiple comparison correction ($p < .05$, FDR-corrected) for left hemisphere ITPC (between 30–40 Hz, between 200–280 ms). There were no significant differences between stimulus types for evoked power in either hemisphere or for right hemisphere ITPC.

Figure 3 shows an example of the comparison of MEG to EEG data in response to both white noise and click train stimuli, for right hemisphere ITPC. Data analyses were collapsed across session, but for visualization of response reliability, data are displayed separately for sessions 1 and 2. When comparing MEG data to EEG data, a greater ASSR for MEG ITPC data in response to white noise stimuli (both hemispheres) only survived multiple comparison correction ($p < 0.05$, FDR-corrected) in a small number of voxels. Differences between the MEG and EEG ASSR (ITPC) in response to click train stimuli did not survive multiple comparison correction. A similar pattern was observed for evoked power, but there were no significant MEG vs. EEG differences.

3.2. Between-Session Reliability

The MEG-measured ASSR was significantly correlated ($p < 0.05$, FDR corrected) in the right hemisphere between sessions 1 and 2 across the majority of voxels between 30–50 Hz and 200–500 ms for ITPC and evoked power for click train stimuli and for ITPC for white noise stimuli (Figure 4). This correlation was only significant for a small number of voxels

for the evoked power response to white noise stimuli, and was not observed throughout the ASSR window. A similar pattern was observed for left hemisphere reliability (data not illustrated). For left hemisphere, the correlation across the ASSR window (30–50 Hz, 200–500 ms) was significant for click train stimuli (both ITPC and evoked power, $p < 0.05$, FDR corrected), but not for white noise stimuli. No voxels survived multiple comparison correction in the between-session correlation of the evoked power response to white noise stimuli; only a small number of voxels were significant in this range in ITPC to white noise stimuli.

Means and ranges of correlation coefficients collapsed across the ASSR (40 Hz, 200–500 ms) for each hemisphere are detailed in Table 1 for each stimulus type (white noise stimuli and click stimuli) for evoked power and ITPC, for both EEG and MEG data. Effects observed when collapsing across the ASSR window demonstrate similar findings to those above. The mean ASSR (40 Hz, 200–500 ms) between sessions 1 and 2 was significantly correlated for all click train measures (evoked power and ITPC, left and right hemispheres, EEG and MEG data; see Table 1). For white noise stimuli, mean ASSR correlations between sessions were significant for all ITPC measures (left and right hemispheres, EEG and MEG data), but were only significant for one measure of evoked power (left hemisphere, EEG). The correlation between sessions 1 and 2 for white noise stimuli did not reach significance for left or right hemisphere evoked power for MEG ($p > 0.05$), or for right hemisphere evoked power for EEG ($p = 0.062$). When the mean ASSR reliability (40 Hz between 200–500 ms) was compared between task-type, however, click train response reliability was only significantly greater than white noise response reliability for left hemisphere evoked power, $p = 0.003$.

Significant between-session correlations were observed for the mean ASSR (40 Hz, 200–500 ms) for all ITPC measures (both stimuli, both hemispheres, both MEG and EEG), as shown in Table 1. Between-session correlations were significant for evoked power responses to click train stimuli (for both hemispheres and both MEG and EEG), but the evoked power response to white noise stimuli was only significantly correlated between sessions for left hemisphere EEG measures. Although there was a trend towards a significant difference between ITPC and evoked power reliability for the response to white noise stimuli in the right hemisphere ($p = 0.089$), no differences in mean reliability between ITPC and evoked power reached statistical significance.

Reliability of the EEG-measured ASSR for this study has previously been reported (McFadden et al., 2014), but means and ranges of correlation coefficients for EEG data are also reported in Table 1. Although EEG data for all 19 subjects were reported in our previous manuscript (McFadden et al., 2014), we are only presenting EEG data here for the same 17 subjects for which we have complete MEG data. No significant differences in mean ASSR reliability (40 Hz between 200–500 ms) between EEG and MEG data were observed for either stimulus type (white noise, click train), measure (evoked power, ITPC) or hemisphere (right, left), $p > 0.05$. Additionally, there were no significant differences in mean reliability at 40 Hz between left and right hemispheres for either stimulus type or measure ($p > 0.05$).

4. Discussion

Overall, the current study provides further support for test-retest reliability of the ASSR. This is an important finding, given the increasing use of the ASSR as a biomarker in investigations of neuropsychiatric disorders (O'Donnell et al., 2013; Sivarao et al., 2016; Thune et al., 2016). Consistent with our previous findings with EEG data (McFadden et al., 2014), we found the ASSR to be reliable across two sessions, spaced approximately one week apart. These findings are also consistent with those of Tan and colleagues, who recently demonstrated reliability of the MEG-measured ASSR to 40 Hz amplitude-modulated tone stimuli (Tan et al., 2015). Furthermore, this is the first study to compare ASSR reliability between MEG and EEG data. We found no differences in reliability between the EEG-measured ASSR and the MEG-measured ASSR, assessed in the same group of participants across two sessions. This supports the use of the ASSR as a potential biomarker of brain function, for both MEG and EEG.

The current study used source-space projected data to assess response reliability. One reason for this is that source space projection can improve signal-to-noise ratio in MEG ASSR data, above that of analyses in sensor space (e.g., see Tan et al., 2015). Although it is more common to measure in sensor space in the EEG literature, certain ERP measures also appear to benefit from source-analysis related improvement in signal-to-noise ratio and test-retest reliability (e.g., see Segalowitz et al., 2010). As much of the literature involving the use of the ASSR as a biomarker in studies of neuropsychiatric disorders uses source-space projected data, at least when the imaging technique is MEG (e.g., see meta-analysis of EEG and MEG ASSR from Thune et al., 2016), we felt it would be more applicable to assess reliability of this measure.

For MEG data, the ASSR was significantly correlated between sessions for both types of stimuli (white noise and click train). Reliability of ITPC, however, appeared to be more robust than that of evoked power, in that it was significantly reliable for all measures (both hemispheres, both stimuli, both MEG and EEG data), while the evoked response was significantly reliable in response to click train stimuli, but less consistently so in response to white noise stimuli (i.e., the mean response was not significantly reliable for MEG left or right hemisphere response or EEG right hemisphere response to white noise stimuli). This interpretation does warrant caution, however, because although the results suggest the ITPC to be more consistently reliable than the evoked power response, this difference did not reach statistical significance when comparing mean correlation coefficients at 40 Hz between 200–500 ms. While we did observe a trend towards the ITPC correlation being greater than that for evoked power for the right hemisphere response to white noise stimuli, additional studies are necessary before this conclusion can be reached. The potentially greater ITPC compared to evoked power reliability could be due to the ITPC being amplitude-independent, which is not the case for evoked power. These results are consistent with our findings in EEG data, in which results also suggested ITPC may be more reliable between sessions than evoked power (McFadden et al., 2014). These findings also support those of Tan et al., who observed higher correlation values for ITPC compared to evoked power (Tan et al., 2015).

While the current findings and those of Tan and colleagues (Tan et al., 2015) suggest reliability of the MEG response across multiple types of stimuli (40 Hz amplitude-modulated white noise, click train, and tone stimuli), our results suggest that the ASSR to click train stimuli may be more reliable than that to white noise stimuli. This conclusion should also be interpreted with caution, however, given that differences between response reliability to click train and white noise stimuli only reached statistical significance for one measure (left hemisphere evoked power). However, all measures in response to click train stimuli were significantly reliable across sessions, but measures in response to white noise stimuli were not consistently reliable (i.e., the mean response to white noise was not significantly reliable for evoked power in MEG left or right hemisphere or EEG right hemisphere), supporting the potential for greater response reliability to click train stimuli. We also found that the click train stimuli appeared to produce a greater ASSR, although this only survived multiple comparison correction for left hemisphere ITPC. Given this, the reliability of the response elicited by various stimulus types could be an important consideration during study design, particularly for clinical studies in which repeated measures are used. As our study did not include tone stimuli and Tan et al. found 40 Hz amplitude-modulated tone stimuli to produce a reliable ASSR, future studies should directly compare tone to click train stimuli to determine which stimulus is likely to produce the most reliable response.

Of note, there were a number of differences between our assessment of ASSR reliability and that of Tan et al. (Tan et al., 2015). The current study included approximately double the number of trials per condition (mean of 186.67 trials) compared to that in the Tan et al. study (mean of 91.65 trials). The length of stimulus presentation also differed; each stimulus in the current study lasted 500 ms, while those in the Tan et al. study lasted 2000 ms. Accordingly, our study focused on the 200–500 ms post-stimulus time window, while Tan et al. investigated the 500–2000 ms post-stimulus time window. The method of assessing reliability also differed between the two studies; while we used Pearson's correlations, Tan et al. used intraclass correlations. That both studies found the ASSR to be reliable across sessions, despite differences in study design, trial numbers, and analysis methods, suggests that regardless of variation in these factors across studies, the ASSR appears to be reliable. This consistency in response reliability bodes well for the use of the ASSR in clinical investigations, given that differences such as these are common between studies.

Although no differences in test-retest reliability were observed between MEG and EEG data, the current study did observe a greater ASSR to white noise stimuli for MEG compared to EEG data in both right and left hemisphere ITPC. The same pattern was observed for click train stimuli and for the evoked power response to both types of stimuli, but those differences did not survive multiple comparison correction, suggesting that further study is needed to support this conclusion. This difference between MEG and EEG measurements could be due to variations in signal orientation; EEG is more sensitive to radial sources, while MEG is more sensitive to tangential sources, which predominate given the auditory cortical location within the superior temporal plane (Ahlfors et al., 2010; Hamalainen et al., 1993). Variations in measurement due to depth preferences of EEG and MEG may also contribute to these differences, along with potential influences of the skull and scalp on EEG-measured signals (Hamalainen et al., 1993).

The current study assessed test-retest reliability of the ASSR across sessions spaced approximately one week apart and Tan et al. investigated ASSR reliability across sessions spaced 1–11 days apart (Tan et al., 2015). As such, it is as of yet unclear if this response is reliable beyond a week, so future studies should assess test-retest reliability of the response across longer time periods to increase applicability for longitudinal clinical investigations. Additionally, this study only included participants without any psychiatric disorders. Future studies should address test-retest reliability of the ASSR in clinical populations of interest, such as autism and schizophrenia.

In conclusion, this study assessed the reliability of the MEG-measured ASSR in response to both amplitude-modulated white noise and click train stimuli, which has not previously been reported. Our observation of a reliable ASSR between sessions supports the findings of the only previous investigation of MEG-measured ASSR reliability, which assessed reliability of the response to tone stimuli (Tan et al., 2015). Our study is also the first to compare test-retest reliability of the ASSR between MEG and EEG data. That we observed a similarly reliable response in both MEG and EEG data suggests that either method can be reliably employed in studies of the ASSR. This work, and our previously reported findings of EEG-measured ASSR reliability (McFadden et al., 2014), further supports the use of the ASSR as a biomarker in clinical interventions with repeated measures. While conclusions based on differences between stimuli should be interpreted with caution, as further investigation is warranted with this only reaching statistical significance for left hemisphere evoked response, our current recommendation based on the existing evidence would be to assess the ASSR using click train stimuli rather than white noise stimuli. The current study also suggests that the ITPC may be more consistently reliable across sessions compared to evoked power, but this will also require further study before a conclusion can be reached.

Acknowledgments

The authors thank Alissa Wallace for her contribution to data collection and Adam Carroll for his contribution to data preprocessing. This work was supported by the National Institutes of Health [T32 MH015442 (KTL); K01 DK100445 (KTL), R01 MH081920 (DCR), and R01 MH082820 (DCR)]; and a National Alliance for Research On Schizophrenia and Depression (NARSAD) Independent Investigator Award (DCR).

References

Ahlfors SP, Han J, Belliveau JW, Hamalainen MS. Sensitivity of MEG and EEG to source orientation. Brain Topogr. 2010; 23:227–232. [PubMed: 20640882]

Azzena GB, Conti G, Santarelli R, Ottaviani F, Paludetti G, Maurizi M. Generation of human auditory steady-state responses (SSRs). I: Stimulus rate effects. Hear Res. 1995; 83:1–8. [PubMed: 7607975]

Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. Behav Brain Res. 2001; 125:279–284. [PubMed: 11682119]

Brenner CA, Sporns O, Lysaker PH, O'Donnell BF. EEG synchronization to modulated auditory tones in schizophrenia, schizoaffective disorder, and schizotypal personality disorder. Am J Psychiatry. 2003; 160:2238–2240. [PubMed: 14638599]

Brenner CA, Krishnan GP, Vohs JL, Ahn WY, Hetrick WP, Morzorati SL, O'Donnell BF. Steady-state responses: electrophysiological assessement of sensory function in schizophrenia. Schizophr Bull. 2009; 35:1065–1077. [PubMed: 19726534]

First, MB., Gibbon, M., Spitzer, RL., Williams, JBW., Benjamin, LS. Structured Clinical Interview for DSM-IV Screen Patient Questionnaire-Extended. Multi-Health Systems; Toronto, ON: 1991.

Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 2002; 15:870–878. [PubMed: 11906227]

Hamalainen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV. Magnetoencephalography: theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys. 1993; 65:413–497.

Hari R, Hamalainen M, Joutsiniemi SL. Neuromagnetic steady-state responses to auditory stimuli. J Acoust Soc Am. 1989; 86:1033–1039. [PubMed: 2794240]

Hayrynen LK, Hamm JP, Sponheim SR, Clementz BA. Frequency-specific disruptions of neuronal oscillations reveal aberrant auditory processing in schizophrenia. Psychophysiology. 2016; 53:786–795. [PubMed: 26933842]

Hoechstetter K, Bornfleth H, Weckesser D, Ille N, Berg P, Scherg M. BESA source coherence: a new method to study cortical oscillatory coupling. Brain Topogr. 2004; 16:233–238. [PubMed: 15379219]

Hong LE, Summerfelt A, McMahon R, Adami H, Francis G, Elliott A, Buchanan RW, Thaker GK. Evoked gamma band synchronization and the liability for schizophrenia. Schizophr Res. 2004; 70:293–302. [PubMed: 15329305]

Ille N, Berg P, Scherg M. Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. J Clin Neurophysiol. 2002; 19:113–124. [PubMed: 11997722]

Isomura S, Onitsuka T, Tsuchimoto R, Nakamura I, Hirano S, Oda Y, Oribe N, Hirano Y, Ueno T, Kanba S. Differentiation between major depressive disorder and bipolar disorder by auditory steady-state responses. J Affect Disord. 2016; 190:800–806. [PubMed: 26625092]

Jasper HH. The ten-twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol. 1958; 10:371–375.

Kwon JS, O'Donnell BF, Wallenstein GV, Greene RW, Hirayasu Y, Nestor PG, Hasselmo ME, Potts GF, Shenton ME, McCarley RW. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. Arch Gen Psychiatry. 1999; 56:1001–1005. [PubMed: 10565499]

Leishman E, O'Donnell BF, Millward JB, Vohs JL, Rass O, Krishnan GP, Bolbecker AR, Morzorati SL. Phencyclidine disrupts the auditory steady state response in rats. PLoS One. 2015; 10:e0134979. [PubMed: 26258486]

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005; 6:312–324. [PubMed: 15803162]

Light GA, Hsu JL, Hsieh MH, Meyer-Gomes K, Sprock J, Swerdlow NR, Braff DL. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. Biol Psychiatry. 2006; 60:1231–1240. [PubMed: 16893524]

Maharajh K, Abrams D, Rojas DC, Teale P, Reite ML. Auditory steady state and transient gamma band activity in bipolar disorder. Int Cong Ser. 2007; 1300:707–710.

McFadden KL, Steinmetz SE, Carroll AM, Simon ST, Wallace A, Rojas DC. Test-retest reliability of the 40 Hz EEG auditory steady-state response. PLoS One. 2014; 9:e85748. [PubMed: 24465679]

Nuwer MR, Comi G, Emerson R, Fuglsang-Frederiksen A, Guerit JM, Hinrichs H, Ikeda A, Luccas FJ, Rappelsburger P. IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol. 1998; 106:259–261. [PubMed: 9743285]

O'Donnell BF, Hetrick WP, Vohs JL, Krishnan GP, Carroll CA, Shekhar A. Neural synchronization deficits to auditory stimulation in bipolar disorder. Neuroreport. 2004; 15:1369–1372. [PubMed: 15167568]

O'Donnell BF, Vohs JL, Krishnan GP, Rass O, Hetrick WP, Morzorati SL. The auditory steady-state response (ASSR): a translational biomarker for schizophrenia. Suppl Clin Neurophysiol. 2013; 62:101–112. [PubMed: 24053034]

Oda Y, Onitsuka T, Tsuchimoto R, Hirano S, Oribe N, Ueno T, Hirano Y, Nakamura I, Miura T, Kanba S. Gamma band neural synchronization deficits for auditory steady state responses in bipolar disorder patients. PLoS One. 2012; 7:e39955. [PubMed: 22792199]

Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci. 2011; 2011:156869. [PubMed: 21253357]

Papp N, Ktonas P. Critical evaluation of complex demodulation techniques for the quantification of bioelectrical activity. Biomed Sci Instrum. 1977; 13:135–145. [PubMed: 871500]

Plourde G, Baribeau J, Bonhomme V. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. Br J Anaesth. 1997; 78:524–529. [PubMed: 9175966]

Rass O, Forsyth JK, Krishnan GP, Hetrick WP, Klaunig MJ, Breier A, O'Donnell BF, Brenner CA. Auditory steady state response in the schizophrenia, first-degree relatives, and schizotypal personality disorder. Schizophr Res. 2012; 136:143–149. [PubMed: 22285558]

Rass O, Krishnan G, Brenner CA, Hetrick WP, Merrill CC, Shekhar A, O'Donnell BF. Auditory steady state response in bipolar disorder: relation to clinical state, cognitive performance, medication status, and substance disorders. Bipolar disorders. 2010; 12:793–803. [PubMed: 21176026]

Roach BJ, Mathalon DH. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr Bull. 2008; 34:907–926. [PubMed: 18684772]

Roach BJ, Fort JM, Hoffman RE, Mathalon DH. Converging evidence for gamma synchrony deficits in schizophrenia. Suppl Clin Neurophysiol. 2013; 62:163–180. [PubMed: 24053039]

Robinson, SE. Theory and properties of lead field synthesis analysis. In: Williamson, SJ.Hoke, M.Stroink, G., Kotani, M., editors. Advances in biomagnetism. Plenum Press; New York: 1989. p. 599-602.

Rojas DC, Teale PD, Maharajh K, Kronberg E, Youngpeter K, Wilson L, Wallace A, Hepburn S. Transient and steady-state auditory gamma-band responses in first-degree relatives of people with autism spectrum disorder. Mol Autism. 2011; 2:11. [PubMed: 21729257]

Scherg, M. Fundamentals of dipole source potential analysis. In: Grandori, F.Hoke, M., Romani, GL., editors. Auditory evoked magnetic fields and electrical potentials (advances in audiology). Vol. 6. Karger; Switzerland: 1990. p. 40-69.

Scherg M, Berg P. New concepts of brain source imaging and localization. Electroencephalogr Clin Neurophysiol Suppl. 1996; 46:127–137. [PubMed: 9059786]

Scherg M, Ille N, Bornfleth H, Berg P. Advanced tools for digital EEG review: virtual source montages, whole-head mapping, correlation, and phase analysis. J Clin Neurophysiol. 2002; 19:91–112. [PubMed: 11997721]

Scherg M, Von Cramon D. Evoked dipole source potentials of the human auditory cortex. Electroencephalogr Clin Neurophysiol. 1986; 65:344–360. [PubMed: 2427326]

Segalowitz SJ, Santesso D, Jetha MK. Electrophysiological changes during adoloscence: a review. Brain Cogn. 2010; 72:86–100. [PubMed: 19914761]

Sivarao DV, Frenkel M, Chen P, Healy FL, Lodge NJ, Zaczek R. MK-801 disrupts and nicotine augments 40 Hz auditory steady state responses in the auditory cortex of the urethane-anesthetized rat. Neuropharmacology. 2013; 73:1–9. [PubMed: 23688921]

Sivarao DV. The 40-Hz auditory steady-state response: a selective biomarker for cortical NMDA function. Ann NY Acad Sci. 2015; 1344:27–36. [PubMed: 25809615]

Sivarao DV, Chen P, Senapati A, Yang Y, Fernandes A, Benitex Y, Whiterock V, Li YW, Ahlijanian MK. 40 Hz auditory steady-state response is a pharmacodynamic biomarker for cortical NMDA receptors. Neuropsychopharmacology. 2016; 41:2232–2240. [PubMed: 26837462]

Spencer KM, Salisbury DF, Shenton ME, McCarley RW. Gamma-band auditory steady-state responses are impaired in first episode psychosis. Biol Psychiatry. 2008; 64:369–375. [PubMed: 18400208]

Sullivan EM, Timi P, Hong LE, O'Donnell P. Effects of NMDA and GABA-A receptor antagonism on auditory steady-state synchronization in awake behaving rats. Int J Neuropsychopharmacol. 2015; 18:pyu118. [PubMed: 25556198]

Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. J Neurosci. 1996; 16:4240–4249. [PubMed: 8753885]

Tan HR, Gross J, Uhlhaas PJ. MEG-measured auditory steady-state oscillations show high test-retest reliability: a sensor and source-space analysis. Neuroimage. 2015; 122:417–426. [PubMed: 26216274]

Teale P, Collins D, Maharajh K, Rojas DC, Kronberg E, Reite M. Cortical source estimates of gamma band amplitude and phase are different in schizophrenia. Neuroimage. 2008; 42:1481–1489. [PubMed: 18634887]

Thune H, Recasens M, Uhlhaas PJ. The 40-Hz auditory steady-state response in patients with schizophrenia: a meta-analysis. JAMA Psychiatry. 2016; 73:1145–1153. [PubMed: 27732692]

Vohs JL, Chambers RA, Krishnan GP, O'Donnell BF, Berg S, Morzorati SL. GABAergic modulation of the 40 Hz auditory steady-state resposne in a rat model of schizophrenia. Int J Neuropsychopharmacol. 2010; 13:487–497. [PubMed: 19627651]

Vohs JL, Chambers RA, O'Donnell BF, Krishnan GP, Morzorati SL. Auditory steady state responses in a schizophrenia rat model probed by excitatory/inhibitory receptor manipulation. Int J Psychophysiol. 2012; 86:136–142. [PubMed: 22504207]

Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. Biol Psychiatry. 2007; 62:192–197. [PubMed: 16950225]

Highlights

- The auditory steady-state response (ASSR) is a potential neuropsychiatric biomarker.
- Test-retest reliability of the MEG-measured ASSR to varied stimuli was assessed.
- Reliability was compared between the MEG-measured and EEG-measured ASSR.
- The ASSR was determined to have acceptable test-retest reliability.
- MEG and EEG measures of the ASSR were similarly reliable.

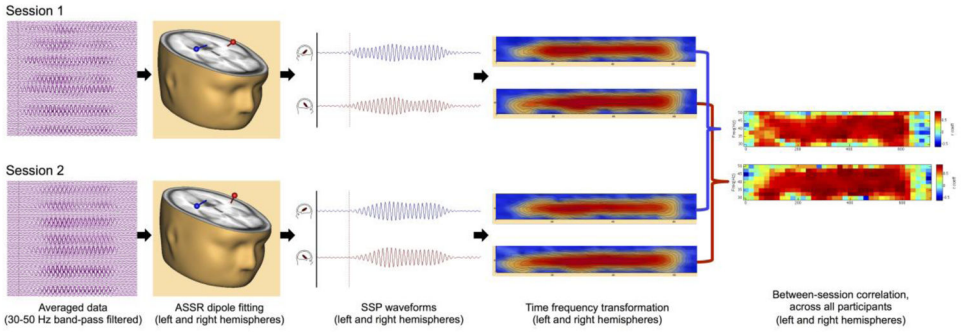

Fig. 1.

MEG raw, averaged, and source-space projected data. MEG data from a representative subject in response to white noise stimuli are presented for session 1 and session 2. From left to right, the raw band-pass filtered (30–50 Hz) data are shown for each session, followed by the grand average across all trials. The auditory steady state response (ASSR) dipole fit locations for each hemisphere (left and right) are then depicted, followed by the resulting source-space projected (SSP) averaged waveform resulting from each dipole.

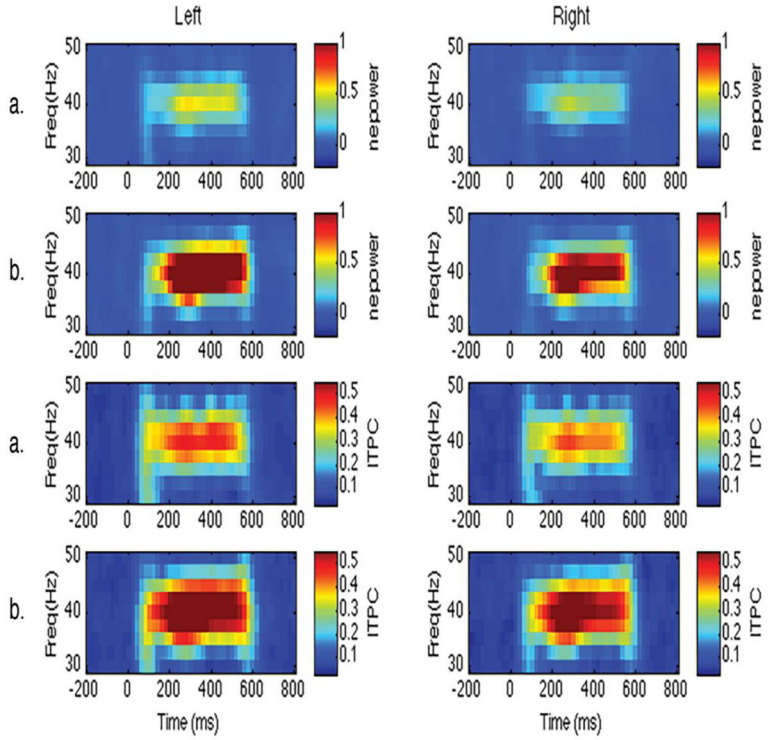

Fig. 2.

Grand averaged MEG data. Time-frequency representations of grand-averaged evoked activity (normalized to baseline) and inter-trial phase coherence (ITPC), collapsed across sessions, in response to white noise stimuli (a) and click train stimuli (b) in left and right hemispheres. nepower = normalized evoked power.

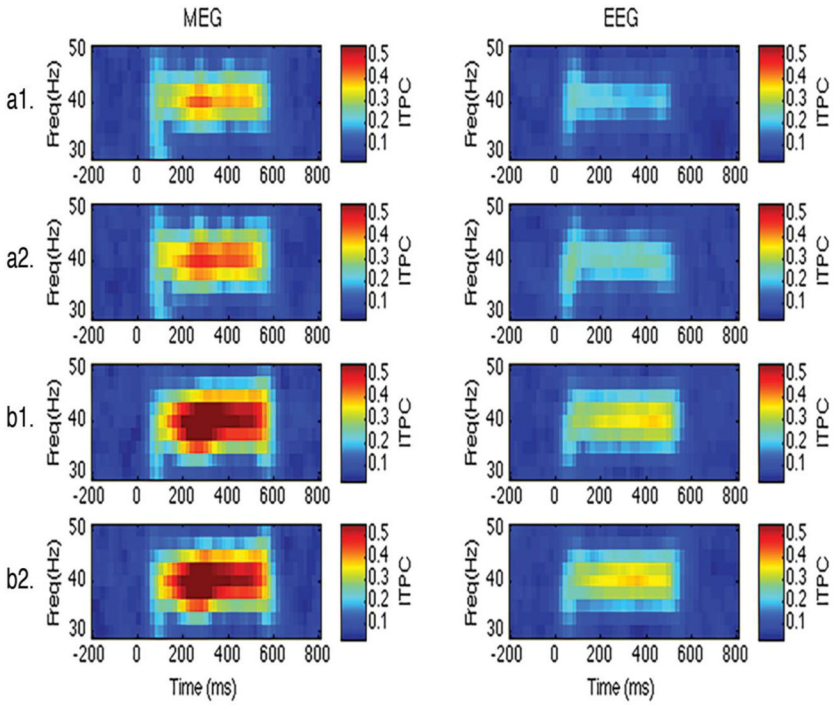

Fig. 3.

MEG and EEG grand averaged inter-trial phase coherence (ITPC). Time-frequency representation of right hemisphere grand-averaged ITPC in response to white noise stimuli (a1 = white noise session 1, a2 = white noise session 2) and click train stimuli (b1 = click train session 1, b2 = click train session 2), separately for MEG and EEG data.

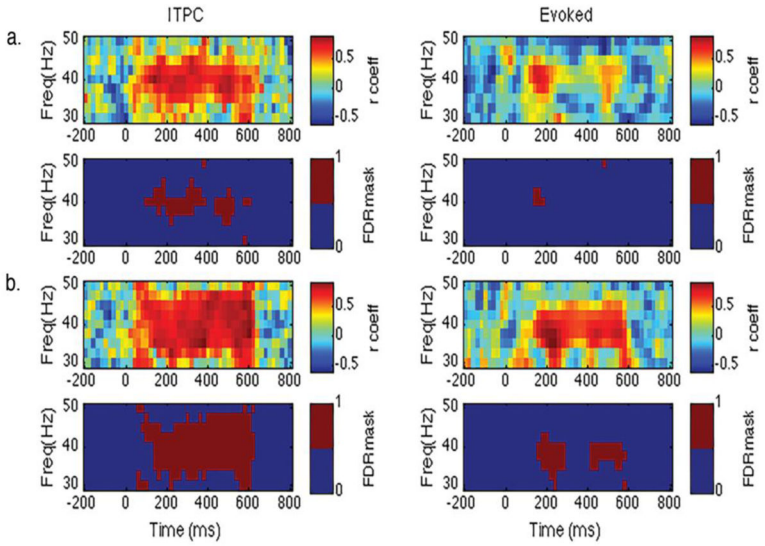

Fig. 4.

MEG data, between-session correlation results. Correlation results between sessions 1 and 2 for inter-trial phase coherence (ITPC) and evoked activity for right hemisphere white noise stimuli (a) and click train stimuli (b). In each plot, the first row shows the correlation coefficient (rcoeff) and the second row shows correlations that were significant following multiple comparison correction (FDR, $q = .05$; 0/blue = not significant, 1/red = significant). Left hemisphere results not illustrated to reduce redundancy.

Table 1

Correlation values (Pearson's r) between sessions 1 and 2 for the auditory steady-state response (40 Hz; 200–500 ms) as measured by MEG and EEG: time-frequency analyses.

			Click Train				White Noise				CT vs. WN
Data	**Chan**	**Measure**	**r**	**SD**	**Range**	**r^2**	**r**	**SD**	**Range**	**r^2**	**p**
MEG	Left	Evoked Power	.87[a]	.04	.76 – .91	.76	.20	.12	.06 – .39	.04	**
	Right	Evoked Power	.69[b]	.06	.60 – .81	.48	.32	.15	.15 – .65	.10	ns
	Left	ITPC	.78[a]	.02	.75 – .82	.61	.66[b]	.04	.60 – .74	.44	ns
	Right	ITPC	.77[a]	.04	.69 – .82	.59	.75[a]	.04	.68 – .81	.56	ns
EEG	Left	Evoked Power	.70[b]	.04	.62 – .75	.49	.56[c]	.09	.41 – .68	.31	ns
	Right	Evoked Power	.54[c]	.05	.44 – .63	.29	.45	.11	.26 – .62	.20	ns
	Left	ITPC	.90[a]	.02	.85 – .93	.81	.75[a]	.05	.67 – .86	.56	ns
	Right	ITPC	.81[a]	.05	.73 – .87	.66	.73[a]	.07	.57 – .84	.53	ns

CT = click train; WN = white noise; MEG = magnetoencephalography; EEG = electroencephalography; SD = standard deviation; ITPC = inter-trial phase coherence.

[a] $p < 0.001$;

[b] $p < 0.01$;

[c] $p < 0.05$ (r to p conversion)

** $p = 0.003$