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

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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.

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

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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% 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 min, 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 0.1-200 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 >2500 fT for MEG data and >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