**Title**Auditory Steady State Response and its Age-Related Changes in Patients with Phelan McDermid Syndrome and Idiopathic Autism

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**Introduction**: Auditory steady-state response (ASSR) is a brain response that occurs when the brain stem and auditory cortical system perceive and entrain to rapid sounds presented at a constant frequency. ASSR provides a non-invasive way of assessing neural synchrony and reflects the functioning of excitatory and inhibitory inputs. Past studies have identified 40 Hz ASSR as a robust measure of altered neural synchrony in psychiatric disorders such as schizophrenia and bipolar, in which the excitatory/inhibitory input balance is disrupted. Age-related increases in the strength of the 40 Hz ASSR have been observed in typically developing (TD) adolescents, reflecting increasing neural synchrony as the brain matures. However, while emerging evidence show altered ASSR in autism, less is known about how this response develops with age in this population, or in other neurodevelopmental disorders (ND) associated with autism. The current study is focused on idiopathic autism spectrum disorder (iASD), as well as Phelan McDermid syndrome (PMS), a rare ND that shares symptomatology with iASD. Electroencephalography (EEG) was recorded from patients with PMS, iASD and TD controls from a large age range (2 to 31), to examine ASSR to auditory stimuli presented at two frequencies (beta, 20 Hz, and gamma 40 Hz). We hypothesized neural synchrony, as measured by inter-trial phase coherence (ITC) at the time of ASSR presentation, to be altered across different neurodevelopmental disorders, compared to TD individuals across ages. Further we expected to observe increasing neural synchrony, to some extent, in PMS and iASD groups and replicate this pattern in TD as found by past research.

**Method**: 50 iASD, 21 PMS and 42 TD participants (Mage= 12.77 +/- 7.80 years) completed an ASSR paradigm. The ASSR paradigm involved the presentation of 150 click trains, at 20 Hz and at 40 Hz in separate runs. Each stimulus was presented for 1100ms with an inter-trial interval of 700ms. Data were filtered, re-referenced to the average, and segmented to the event onset. We completed artifact detection, bad channel replacement, and baseline corrections before conducting time-frequency analyses and calculating inter-trial phase coherence (ITC) from the central (Cz) electrode. ITC measures the consistency of phases across multiple trials, and it is a value between 0 and 1, where 0 represents a random distribution of phase angles between the trials, which implies a-synchrony, and 1 reflects absolute neural synchrony. After excluding participants with less than 25 usable segments, we used a Kruskal-Wallis test to look for differences in ITC at 20 and 40Hz across the diagnosis and age groups and linear regression to model ITC at 20 and 40Hz as a function of age.

**Results**: When splitting the ND group into their respective diagnoses, there were no significant differences in the 20Hz (χ2 = 3.49, p = 0.17) and 40Hz (χ2 = 3.7, p = 0.16) ITC ASSR between PMS, iASD and TD participants. Across groups, 40 Hz (R2(77) = 0.32, p < 0.001), but not 20 Hz (R2(71) < 0.01, p = 0.84), ITC increased with age, and this pattern was also observed within each group (ASD: R2(30) = 0.20, p < 0.01; PMS: R2(12) = 0.41, p = 0.01; TD: R2(31) = 0.43, p < 0.001). However, the steepness of the increase in ITC with age for 40Hz ASSR was weaker in iASD compared to TD (t = -2.94, p < 0.01). The effect was not seen in PMS (t = -0.778, p = 0.44).

**Discussion:** When ages are pooled across, our findings revealed no group differences in ITC for either 20 Hz or 40 Hz ASSR. The lack of group differences in the ASSR ITC agrees with prior literature. Further, if age is not accounted for, ASSR may not be the most robust biomarker for ASD or PMS, vs TD. We did find that coherence strength increased with age at 40 Hz across groups, though more slowly so in iASD compared to TD. Since ASSR is an indication of the excitatory/inhibitory balance (E/I balance), our findings support that as participants get older, regardless of their diagnosis, auditory systems are maturing, resulting in stronger neural synchrony, and this development is delayed within the autism cohort. One limitation is we only had ASSR EEG collected from one adult diagnosed with PMS. Future directions can include collecting more adult PMS ASSR and exploring the ASSR development with age in PMS. Further, development may not be best represented linearly; adolescence is a critical period of brain maturation. Future research can explore if a non-linear model may be a better fit for changes in ASSR over time.

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