Examining the effects of low-dose ketamine on neural responses of children with ADNP syndrome

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BACKGROUND

• ADNP syndrome is caused by pathogenic variants in the activity dependent neuroprotective protein (ADNP) gene and is characterized by intellectual disability, autism spectrum disorder (ASD), speech and motor delays, and medical comorbidities.

• Ketamine is an NMDA antagonist which has been suggested to upregulate expression of ADNP and affects excitatory and inhibitory neural systems by blocking glutamatergic binding and inhibiting GABA release (Baumgarten et al., 2016; Brown et al., 2015; Jensen et al., 2005; Abdallah et al., 2015).

• The auditory steady-state response (ASSR) measured by electroencephalography (EEG) assesses neural synchrony and has been shown to index the balance of excitatory and inhibitory neural pathways, modulated by GABAergic and glutamatergic systems (Sivarao et al., 2016; Light et al., 2017; Tada et al., 2020).

METHOD

Participants:
• EEG was recorded from 10 children ages 5-12 years with ADNP syndrome; participants with unusable data were excluded from analyses.

<table>
<thead>
<tr>
<th>ADNP</th>
<th>N</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 Hz</td>
<td>8</td>
<td>9 (2.07)</td>
<td>3F, 5M</td>
</tr>
<tr>
<td>40 Hz</td>
<td>7</td>
<td>9 (2.00)</td>
<td>3F, 4M</td>
</tr>
</tbody>
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EEG:
• EEG data was recorded using a 128-channel net.
• In separate runs, participants heard 150 trials of 500ms click trains with a stimulation rate of 20Hz or 40Hz; inter-trial interval was 50ms.
• Data were cleaned before conducting time-frequency analysis to extract intertrial phase coherence (ITC) at 20 and 40Hz.
• ITC is a value between 0 and 1, where 0 reflects a random distribution of phase angles and 1 reflects absolute neural synchrony.
• Average ITC at each time point was calculated from the Cz central electrode.

RESULTS

Ketamine Infusion:
• Data were collected from all participants at Baseline (pre-drug administration) and Day 1, Week 1, Week 2, and Week 4 following a single ketamine intravenous infusion at 0.5 mg/kg over 40 minutes.

No significant differences were found between Baseline and Day 1, Week 1, or Week 2 (p > 0.1).

Conclusions:
• The increase in evoked gamma band oscillations at Week 1 suggests an effect of ketamine related to enhancing glutamatergic functioning in ADNP syndrome, likely caused by NMDA receptor modulation.
• Conversely, the decrease in beta ITC at Week 1 may be indicative of an inhibitory effect of ketamine causing decreased GABA concentrations.
• These findings may be important in the treatment of ADNP syndrome, as gamma and beta neural oscillations are implicated in several important cognitive processes and may relate to clinical symptoms.
• This study suggests the potential of ASSR as a biomarker of ketamine treatment response in ADNP syndrome.
• In the future, we plan to employ a placebo-controlled, double-blind, crossover design to examine the effects of ketamine on neural and behavioral outcomes in ADNP syndrome.
• We plan to investigate how ASSR can be used as a stratification biomarker to predict which individuals with idiopathic ASD have alterations in neural pathways overlapping with ADNP syndrome and are therefore likely to respond to ketamine.

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