ACNP Abstract

Title: **Developing and validating a combined virtual reality - electroencephalogram paradigm to assess biomarkers of procognitive treatment response in schizophrenia patients**

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Background: After decades of procognitive research in schizophrenia (SZ) with no FDA approved procognitive drug in sight, therapeutic development has pivoted towards identifying biomarkers that predict procognitive treatment sensitivity. Mismatch negativity (MMN) and auditory steady-state gamma band responses (ASSR), electroencephalogram (EEG)-based measures of early auditory information processing (EAIP) predict the clinical and cognitive benefits of targeted cognitive training (TCT) response in treatment-refractory SZ patients, albeit, with modest power. An important question is, can we enhance the ability of EAIP "biomarkers" to predict cognitive and functional gains from TCT in SZ patients? For instance, measures of MMN and ASSR utilize isolated sound fragments (tones, clicks), presented in the artificial context of a laboratory setting. It is possible that EEG measures generated using contextually relevant naturalistic sound stimuli might more accurately reflect the brain's capacity for EAIP, and thereby be more sensitive to both EAIP deficits and treatment sensitivity. However, EAIP measures require millisecond-level stimulus control within a structured test session and are thus not easily assessed in a naturalistic setting. Virtual reality (VR) technology provides both the naturalistic context and tight experimental control needed to generate and assess potentially more ecologically relevant measures of EAIP. Here we developed a VR-based EEG paradigm to measure EAIP evoked by naturalistic sound stimuli (e.g., footsteps, jack hammer) presented in familiar VR-delivered contexts (e.g. walking down the street, walking past a construction site) and assessed the sensitivity of these VR-based measures to one-hour of TCT session.

Methods: Two VR-EEG paradigms were developed to measure MMN and ASSR. Carefully screened, medically stable, psychiatrically healthy adults (HS) and SZ patients ages 18-45 yo with an intelligence quotient (IQ) above 80 measured using wide range achievement test-3 (WRAT-3) completed a screening visit followed by a test day. Eligible subjects completed a comprehensive neurocognitive (MATRICS Consensus Cognitive Battery (MCCB)) and functional (Brief UCSD Performance Based Skills Assessment (UPSA-B)) assessment during the screening visit and on test day completed both standard laboratory- and VR- based EEG measures before and after a one-hour "sound sweeps" TCT session in a randomized, order-balanced design. Pearson's correlation was used to determine the validity, reliability, and biomarker potential of VR-based MMN and gamma evoked power (γEP) in healthy subjects (HS) and SZ patients.

Results: 5 subjects have completed testing to date [N= 4(HS) and N=1(SZ)]. Participants were in their late twenties (28 ± 10 yrs), high school educated (14.4 ±2.3 yrs), women (60%) with a WRAT-3IQ of 111.7 ± 11.6, MCCB composite score of 14 (n=1 (SZ)) and 52.2 ± 7.3 (n=4 (HS)) and UPSA-B total score of 9 (n=1 (SZ)) and 18 ± 1.4 (n=4 (HS)). Participants registered a mild level of discomfort on the Simulator Sickness Questionnaire (SSQ) and high scores on the Presence Questionnaire (PQ) (80.5 (range: 58-120)) after the VR condition, the latter suggestive of higher sense of presence in the VR environment. Collectively, these findings indicate that the VR-based EEG paradigms were immersive and well tolerated. The average baseline auditory processing speed (APS) pre- TCT training = 65 millisecond vs. Post- TCT training APS =36 millisecond (n=4 (HS)) suggesting a 55% gain in APS. Overall participants completed an average of 15 (range 12-21) (n=4 (HS)) and 6 (n=1(SZ)) training blocks. Subject testing and analysis of VR-based neurophysiological (EEG) data are ongoing and results will be presented in full. However, a preliminary observation of the EEG data (N= 1 (HS) and N=1 (SZ)) showed VR-based MMN and γEP to be comparable to standard laboratory-based MMN and γEP, with VR-based measures in this one SZ patient reduced compared to one HS and exhibiting malleability after one hour of TCT.

Conclusions: Our preliminary findings and observation of the VR-based EEG data suggests that VR-based EEG paradigms are well tolerated, immersive, and can generate robust MMN and γEP in both HS and SZ patients. Testing is ongoing, and a complete comparison between VR-based EEG measures and TCT performance will be reported.