

patient's clinical features. However, data from recent research suggest that a number of different neuroimaging measures and peripheral biomarkers may be used to distinguish patients who present with similar symptoms but have quite distinct clinical outcomes. This approach appears to be particularly promising in relation to two key clinical issues: predicting the onset of illness onset in people at high risk for psychosis and predicting the response to antipsychotic treatment in patients who have developed psychosis. Key findings from studies in these 2 areas of research will be reviewed, and the challenges associated with translating them into clinical practice will be discussed.

Concurrent Oral Presentations

64. A COMPUTATIONAL ANALYSIS OF VERBAL FLUENCY IN SCHIZOPHRENIA

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Background: Verbal fluency tasks are widely used to assess language organization and executive functioning. Meta-analyses of verbal fluency performance in individuals with schizophrenia (SZ) indicate greater impairment on semantic (SF) than phonemic fluency (PF). Because SF depends more on efficient word retrieval within subcategories (clustering) and PF more on shifting between subcategories (switching), fluency impairment has been linked to clustering difficulties in SZ. However, most scoring methods rely on subjective judgments to determine clusters and switches, which reduces reliability. Here, we test a novel computational method to objectively capture clustering, switching, and overall retrieval organization from fluency performance in SZ and demographically matched healthy controls (HC).

Methods: PF and SF ("animals") tasks were administered to SZ and HC. Responses were transcribed from audio recordings into text files for computational analysis using VFClust (Ryan et al, 2013). VFClust utilizes latent semantic analysis (LSA) to quantify the semantic similarity of ordered word pairs as well as a combination of the Carnegie Mellon Phonemic Dictionary (CMUDict) with the Levenshtein distance method to determine phonemic similarity of ordered word pairs. Similarity thresholds were established and applied to these pairwise similarity scores (PSS) to determine cluster or chain inclusion. Clusters included words in which every word pair in that cluster had a PSS above threshold. Chains consisted of words in which PSS of adjacent words were above threshold. Switches were counted when PSS were below threshold, signifying a shift from one category to another. Output metrics for each individual included total words produced, mean size of chains and clusters, number of chains, clusters, and switches, and mean PSS across all ordered word pairs for SF and PF.

Results: SZ were impaired compared to HC on SF but not PF. SF deficit was driven by a lower number of chains and clusters produced by SZ compared with HC. Group differences in SF were not driven by any other measures. Negative symptoms were inversely correlated with the total number of words produced and the switch count in SF.

Conclusion: Objective, computationally derived fluency metrics captured group differences observed in SF in SZ. Interestingly, the lack of difference in cluster size questions SZ deficits in generating sizable clusters. Instead, limitations in the ability to retrieve a variety of semantically associated words (multiple clusters) seem to underlie performance deficits. Intact switching despite lower number of clusters and chains could indicate increased activation between (conventionally) unrelated words. While altered, semantic relatedness could cascade to thought disorder and abnormal interpersonal interactions, in this study, we only observed a significant negative association with negative symptoms.

65. EFFECTS OF NMDA RECEPTOR ANTAGONISM IN PATIENTS WITH SCHIZOPHRENIA: IMPROVEMENT IN MARKERS OF CORTICAL OSCILLATORY DYNAMICS

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Background: NMDA receptor-associated oscillations in the gamma frequency band (30–80 Hz) are thought to underlie a variety of cognitive processes known to be disrupted in patients with schizophrenia (SZ). NMDA receptor functioning can be assessed in subjects by measuring evoked power and phase synchronization of gamma frequency oscillations in response to auditory steady state stimulation (ASSR). Therefore, both evoked power and phase synchronization of gamma frequency have promising applications as translational biomarkers for procognitive therapeutics. In previous work, we reported the low-to-moderate affinity NMDA-receptor antagonist, memantine, enhanced prepulse inhibition of startle and mismatch negativity in SZ patients. Here, we report the effects of a single dose of memantine on evoked power and phase synchronization of ASSR obtained in our previous study.

Methods: SZ patients (n = 18; M:F=11:7; mean age = 37.7 years; range:21–48) and healthy comparison subjects (n = 14; M:F = 10:4; age = 26.6 years; range:19–36) completed 2 test days separated by 1 week. On each test day, subjects received either memantine 20mg (p.o.) or placebo in a double-blind, randomized, counterbalanced, within-subject, crossover design. The ASSR paradigm was used to measure evoked gamma power and phase locking in response to 40 Hz click trains.

Results: Patients with SZ had reduced evoked gamma power and phase locking, consistent with previous reports (main effect of group - Power: $F = 5.89$, $df = 1.30$, $P < .025$; Phase locking: $F = 12.47$, $df 1.30$, $P < .0015$). Memantine-enhanced evoked power and phase locking in both SZ and healthy comparison subjects (drug effect - Power: $F = 6.40$, $df 1.30$, $P < .02$; Phase locking: $F = 8.49$, $df 1.30$, $P < .007$). Memantine effects on both gamma power and phase locking were also significant when groups were matched for age ($P_s < .005$ and $.0008$, respectively). Memantine-associated enhancement of gamma power and phase locking in SZ patients correlated negatively with age ($P_s < .0015$ and $.005$, respectively). Significant relationships were also identified in patients between memantine effects on gamma power and phase locking ($r = .74$, $P < .0005$), gamma power and mismatch negativity ($r = .54$, $P < .025$), and phase locking and prepulse inhibition of startle ($r = -.59$, $P < .027$).

Conclusion: A single dose of memantine normalized biomarkers of cortical oscillatory dynamics associated with NMDA receptor dysfunction in SZ patients. Our ongoing studies will clarify whether these acute changes are associated with beneficial clinical and functional outcomes and whether they predict enduring pro-cognitive effects. These data suggest gamma band ASSR parameters can be used as translational endpoints in early-phase clinical trials and in procognitive drug discovery.

66. BROAD MONITORING DEFICITS IN SCHIZOPHRENIA: CONVERGING EVIDENCE FROM A RAT MODEL OF PRENATAL KYNURENIC ACID ELEVATION

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Background: Cognitive deficits in people with schizophrenia (PSZ) are manifold. Efforts to develop pharmacotherapy for these symptoms rely on their reduction to a finite number of underlying problems. In recent years,