second experiment, we examined event-related potentials (ERPs) recorded during the same contour perception task in PSZ, HCs, as well as people with bipolar affective disorder (PBP) and first-degree biological relatives of PSZ (RelPSZ), which allowed us to examine the diagnostic specificity of perceptual abnormalities.

***Results:*** Source signals revealed PSZ to exhibit diminished delta and theta frequency responses in visual cortex. HCs showed theta responses to the contour within visual areas V1 and V3 that were lateralized (contralateral to the visual field where the contour appeared), while PSZ failed to show such lateralization. HCs also had theta responses to the contour that were modulated by the perceptual context created by surrounding stimuli, while this theta modulation was absent in PSZ. Interestingly, PSZ who had stronger contextual modulation of theta in V1 tended to better discern the contours, and PSZ who more strongly modulated theta in V3 reported more unusual perceptual experiences in their daily lives. In the second experiment, contextual modulation of brain responses was absent in the early brain responses (P1 and N1 ERPs prior to 200 msec) for all groups. The P2 ERP response (240 msec), recorded over lateral occipital regions, was significantly modulated by perceptual context, but this modulation was weaker for both PSZ and RelPSZ. These similar aberrations suggest that genetic liability for schizophrenia is associated with diminished suppressive functions in visual cortex involved in visual context processing.

***Conclusions:*** In sum, multimodal imaging and electrophysiological data provide evidence that initial registration of visual stimuli is specifically aberrant in schizophrenia. Diminished effects of perceptual context during contour detection may reflect genetic liability for schizophrenia and is apparent in biological relatives of individuals with this disorder. Additionally, low-frequency oscillations within visual cortex may reflect the pathophysiology of abnormal visual perception in schizophrenia.

## 16.3 ARE VISUAL MOTION PERCEPTION AND DETECTION OF ANIMACY CRITICAL TO HIGHER-ORDER SOCIAL COGNITIVE FUNCTION IN SCHIZOPHRENIA?

Jason Johannesen*[,1], Paul Lysaker[2], Alison James[3], Joshua Kenney[1], Morris Bell[1]

*[1]Yale University School of Medicine; [2]Roudebush VA Medical Center, Indiana University School of Medicine; [3]Kaiser Permanente*

***Background:*** The observation that individuals with schizophrenia tend to misinterpret subtle social cues is often attributed to deficit in Theory of Mind (ToM). While ToM is commonly assessed using videos portraying interaction between actors, recent work in vision science shows that stimuli with no innate animate features can also convey similar social information through motion alone. These simplified stimuli are advantageous for experimental purposes and may provide further insights into perceptual mechanisms supporting social cognitive function. The Social Attribution Task-Multiple Choice (SAT-MC), based on the classic Hieder and Simmel (1944) stimuli, tells a story using three geometric shapes moving about a centrally fixed figure, followed by questions about what the viewer observed. Although there are no explicit social cues, viewers typically detect actions suggestive of relationships between objects, their intentions, and emotions. This talk will present findings from three studies examining psychometric, functional, and neurophysiological aspects on SAT -MC performance in schizophrenia.

***Methods:*** Study 1 examined psychometric properties of two forms of the SAT-MC in comparison to video-based social cognitive tests using human actors in 32 schizophrenia (SZ) and 30 substance use disorder (SUD) participants. Study 2 examined functional relationships of the SAT-MC and affect recognition (BLERT) performance across neurocognitive, metacognitive, ToM, and symptom domains in 72 adults with SZ. Study 3 is an in-progress investigation of neurophysiological mechanisms of social cognition using test versions adapted for EEG recording. Chronic SZ, clinical high-risk (CHR), and healthy age-matched community samples are being collected.

***Results:*** SZ scored significantly lower than SUD on two versions of the SAT-MC, each classifying ~60% of SZ as impaired, compared with ~30% of SUD. The two SAT-MC forms demonstrated good test-retest and parallel form reliability, minimal practice effect, high internal consistency, similar patterns of correlation with social cognitive test performance, and compared favorably to social cognitive tests across psychometric features. When examining functional correlates of SAT -MC performance, impairment is found to co-occur with deficits in affect recognition in the majority of cases but relates uniquely to reductions in verbal memory and emotional intelligence measures. Finally, a preliminary analysis (n=8 SZ, n=2 CHR) of EEG collected during SAT-MC video presentation finds significant correlations (r=.66-.72) between occipito-parietal gamma desynchronization and task performance. Additional analyses find task-related EEG during SAT to be predictive of affect recognition (BLERT) and ToM (TASIT) performance, with correlates including alpha desynchronization in frontal, occipital, and temporal regions, and synchronization of temporal theta and occipital gamma (all r > .5).

***Conclusions:*** SAT-MC performance is found to be reliable using different stimuli, related to affect recognition and ToM in three independent samples, and shows high diagnostic specificity in classifying SZ against a SUD sample. Functional correlates also involve encoding and emotional intelligence abilities tested outside the visual modality. Analysis of neural oscillatory activity related SAT-MC performance to visual and attention processes, as well as engagement of a broader social cognitive network applied to affect recognition and ToM tasks. Impairment in visual motion processing appears integral to schizophrenia pathophysiology and a critical factor influencing social cognitive abilities attributed to higher-order ToM ability.

## 16.4 VISUAL DISTURBANCES UNDERLIE ABNORMAL EYE GAZE PERCEPTION IN PSYCHOSIS: PSYCHOPHYSICAL AND EFFECTIVE CONNECTIVITY EVIDENCE

Ivy Tso*[,1], Mike Angstadt[2], Timothy Johnson[2], Vaibhav Diwadkar[3], Stephan Taylor[1]

*[1]University of Michigan Medical School; [2]University of Michigan; [3]Wayne State University*

***Background:*** Deficits in social cognition are pervasive in schizophrenia (SZ) and strong predictors of poor functional outcomes. Understanding of the mechanisms underlying critical social cognitive dysfunctions in SZ will advance our understanding of the disorder and help design targeted treatment. In this presentation, we examine a basic building block of social cognition—eye gaze perception—in SZ and bipolar psychosis (BP). Given the frequent documentations of visual perceptual anomaly in SZ, we specifically evaluate the role of visual disturbances in altered gaze processing in psychosis. We used psychophysics to isolate distinctive cognitive processes involved in gaze perception (Study 1) and applied dynamic causal modeling (DCM) to fMRI data to illuminate aberrant brain dynamics responsible for altered gaze processing (Study 2).

***Methods:*** In Study 1, 157 participants (47 SZ; 55 BP; and 55 healthy controls, HC) viewed faces with varying gaze directions and made two-forced choice eye contact judgments ("yes" or "no"). In each individual, eye contact endorsement was examined as a logistic function of gaze direction. The slope and absolute threshold of this perception curve were used to index, respectively, visual perceptual sensitivity and self-referential bias. Individual measures and group differences were estimated using hierarchical Bayesian modeling. Markov Chain Monte Carlo (MCMC) implemented in WinBUGS was used to sample from the joint posterior distribution to estimate posterior probabilities of the parameters. In Study 2, 27 SZ participants and 22 HC completed a gaze perception task during BOLD fMRI. They viewed faces with varying gaze directions and made two-forced choice

judgments of eye contact or gender (control task). Time series from the V2 visual cortex (V2), posterior superior temporal sulcus (pSTS), inferior parietal lobule (IPL), and posterior medial prefrontal cortex (pMPFC) were extracted and subject to DCM analysis. Initial model family comparison showed that models with gaze modulations on both bottom-up connections from V2 and top-down connections from pMFC had the highest evidence compared with models with gaze modulations on either bottom-up or top-down connections. Models from this model family were then subject to post-hoc Bayesian model selection to select the best model for each individual. Parameter estimates of the winning model were taken to group-level analyses using t-tests.

***Results:*** In Study 1, both clinical groups showed high posterior probabilities of reduced perceptual sensitivity (SZ: 99.96%; BP: 98.7%) and increased self-referential bias (SZ: 98.7%; BP: 93.71%) when compared with HC during gaze perception. Although BP generally positioned in between SZ and HC, it was not statistically distinguishable from SZ. In Study 2, DCM revealed that, as expected, attending to gaze (vs. gender) strengthened bottom-up connections from V2 to IPL (t= 3.50, p = .001) and to pSTS (t= 2.53, p = .015) across participants. Compared with HC, SZ showed weakened sensory input to V2 (t = -2.12, p = .042) and reduced feedforward connectivity from V2 to IPL (t = -2.09, p = .045). When processing gaze (vs. gender), HC relaxed pMFC suppression of V2, perhaps to allow more data-driven processes; conversely, SZ increased pMFC inhibition of V2 (t = -3.22, p = .002), presumably to compensate for impaired bottom-up processes by relying more on higher-level cognition to determine the self-referential nature of gaze.

***Conclusions:*** These findings suggest that gaze perception in psychosis, regardless of diagnostic category, is characterized by altered cognitive processes at both the perceptual and interpretation levels. However, effective connectivity analyses suggest that abnormal gaze processing may originate from dysfunctions of the visual cortex, and that aberrant top-down processes may be a compensatory mechanism. We are currently working on replicating these fMRI findings and will be launching an experimental study using transcranial magnetic stimulation to confirm the causal role of visual cortical dysfunction in altered gaze processing in psychosis.

## 17. THE OPTIMISE STUDY: AMISULPRIDE AND OLANZAPINE FOLLOWED BY OPEN-LABEL TREATMENT WITH CLOZAPINE IN FIRST-EPISODE SCHIZOPHRENIA

Celso Arango
*Hospital General Universitario Gregorio Marañon*

No accepted treatment algorithm exists for patients with first episode schizophrenia. Whether switching antipsychotics, how long to wait for a response, or if early use of clozapine improves out-come in first-episode schizophrenia is unknown. The OPTiMISE study assessed 481 first episode schizophrenia patients using three phase switching study. Patients with a first episode of schizophrenia entered a four-week open treatment with amisulpride. Those patients who did not achieved remission entered a 6-week, randomized, double-blind study of either continuation of amisulpride or switching to olanzapine. Those patients who still not achieved remission were treated with clozapine for 12-weeks in an open study design. Levi et al will present data on predictors of relapse after the first psychotic episode. Multivariate analyses showed significant effects on relapse only for cannabis use (OR=2.011, 95% CI:1.024–4.087, p=0.021). Studies should investigate the effect of cannabis cessation programs on relapse rates.

Armida et al will present the prevalence of negative symptoms of moderate severity, unconfound-ed by depression and extrapyramidal symptoms at baseline (U-NEG), and their persistence over the three phases of the OPTIMISE trial (i.e., after 4, 10 and 22 weeks of treatment). The impact on re-mission and psychosocial functioning of persistent negative symptoms (PNS) was also assessed. U-NEG were observed in 263/446 subjects (59% of the whole cohort of first-episode, recent-onset subjects Unconfounded negative symptoms predicted poor psychosocial functioning. Persistent negative symptoms were associated with the worse psychosocial functioning at all phases and were the most resistant to antipsychotic treatment including clozapine. Baandrup et al evaluated the scalability of the PANSS negative symptom subscale using Rasch (or IRT) analysis. They found that the negative symptom subscale does not possess the necessary properties to be a valid rating scale. However, the individual negative symptom items possess better scalability and seem better suited for future research in negative symptoms.

Finally, Glaichenhaus et al will present data supporting that serum level of some cytokines combined with clinical subtypes (based on a hierarchical clustering approach using the
PANSS) predict remission. The predictive value of this model was 73%,

## 17.1 PREDICTORS OF RELAPSE IN FIRST EPISODE PSYCHOSIS PATIENTS IN REMISSION

Mark Weiser*[,1], Linda Levi[1], Stefan Leucht[2], Inge Winter-van Rossum[3], Renè Kahn[4]
*[1]Sheba Medical Center; [2]Technische Universität München; [3]UMC Utrecht; [4]Icahn School of Medicine at Mount Sinai*

***Background:*** Patients in their first psychotic episode often respond to antipsychotic medications, with rates of response up to 80%. The OPTIMISE project was a large three-phase multicenter study, which included 446 patients in their first psychotic episode, who received open-label amisulpride, and/or double-blind amisulpride or olanzapine for 10 weeks. Of the patients recruited, 63% went into remission, as defined by the Andreasen criteria. This present study attempted to identify predictors of later relapse in these initial remitters during a follow-up period of up to a year and a half.

***Methods:*** Relapse was defined by changes of PANSS scores compared to time of remission at any time during the follow-up period using one of two different criteria: (1) ≥ 20% increase in total PANSS score from the time of remission, or (2) no longer meeting one or more of the Andreasen criteria. Potential predictors tested in the analyses were age, sex, duration of untreated psychosis, cannabis use, baseline PANSS scores, and insight, as measured by the drug attitude inventory (DAI) scale and the Knowledge of Psychotic Illness (KPI) Questionnaire. Univariate analyses examining the effect of each of these potential predictors on risk for relapse were performed. Those variables who were significant in the univariate analyses were included in a multivariate logistic regression.

***Results:*** When using the 20% increase of PANSS criterion for relapse, a total of 67 out of 446 patients (15%) were included in the analyses, using the criterion of no longer meeting Andreasen criteria identified 101 out of 446 (23%) patients. When using the relapse criterion of 20% increase in PANSS, univariate analyses showed a significant effect on relapse, with lower baseline score increasing risk of relapse: for baseline positive PANSS score (OR=0.918, 95% CI: 0.868–0.971, p=0.003), baseline negative PANSS score (OR=0.926, 95% CI: 0.883–0.972, p=0.002), baseline general psychopathology PANSS score (OR=0.943, 95% CI: 0.911–0.976, p=0.001), and cannabis use (OR=2.284, 95% CI: 1.116–4.678, p=0.024). Multivariate analyses showed significant effects on relapse only for cannabis use (OR=2.011, 95% CI:1.024–4.087, p=0.021). Both univariate and multivariate analyses were not significant when using the relapse criterion of not meeting one or more Andreasen criteria.

***Conclusions:*** Cannabis use was the only significant clinical factor that increased risk for relapse. These findings are similar to previous studies which showed a strong correlation between cannabis use and earlier and more frequent relapses. Patients and family members should be made aware of this finding and future studies should investigate the effect of cannabis cessation programs on relapse rates.