Dynamic Reasoning Patterns as Foundation for Biomarker Development in Schizophrenia

Tommy C. Blanchard[1], Jonathan Scott[1], Shaheen Lakhan[2] and Michael M. Halassa[1]

[1]Circuit Psychometrics, [2]Boricua Bio

Abstract:

Psychiatry lacks objective biomarkers for psychotic disorders, creating critical challenges in treatment selection, monitoring therapeutic responses, and clinical trial design. Among these is the ability to evaluate reasoning, critical for assessing delusional thinking, negative symptoms and overall functional capacity.
To address this challenge, we created PRISM: Psychiatric Reasoning Integrity Suite Monitor, a platform that collects behavioral choices, along with biometric data as subjects solve cognitively challenging scenarios. On the basis of behavioral choice alone, we achieve robust diagnostic discrimination and indication of promising treatment response tracking in real-world settings.

Methods: We assessed 41 participants: healthy controls (HC, n =15), schizophrenia patients during an acute psychotic decompensation (SCZ, n=20) and psychiatric controls without psychosis (PC, n =6). Participants completed 10 scenarios via interactive graphical interface (Fig. 1). Each scenrio presented three statements (S1, S2, S3) that sequentially clarified an ambiguous set of initial conditions. Participants were asked to rate the plausibility of multiple interpretations for each scenario at S1, and update their ratings as S2 and S3 were shown (Fig. 1). In addition to the ratings (12 measurements per scenario), we collected reaction times, biometrics including gaze, facial expression and voice (Fig. 2). We extracted features and applied unsupervised dimensionality reduction (principal component analysis; PCA) on nine features that showed discriminative potential and classification using extreme gradient boosting (XGBoost) with leave-one-out cross validation (LOOCV).

Results: We visualized the values of the first two principal components and compared SCZ vs. HC, which showed striking separation given that the PCA was performed on features extracted from rating data alone (Fig. 3A). The XGBoost confirmed this separation showing a classification accuracy of ~80% when comparing HC and SCZ (Fig. 3B). The specificity to illness class was further confirmed when evaluating patient controls without psychosis on this same classifier (Fig. 3C). The promise of PRISM in monitoring treatment response was evaluated by having repeated measurements across 3 patients who received xanomeline/trospium over a course of 2 -4 weeks (Fig. 3D).
To understand the contribution of scenario type to classification accuracy we examined behavioral feature loading on the top two principal components.
We found that scenarios with higher working memory load were primarily responsible for this result (Fig. 4). Lastly, we performed exploratory gaze data analysis and found that it is also likely to be discriminative (Fig. 5).

Figure 1

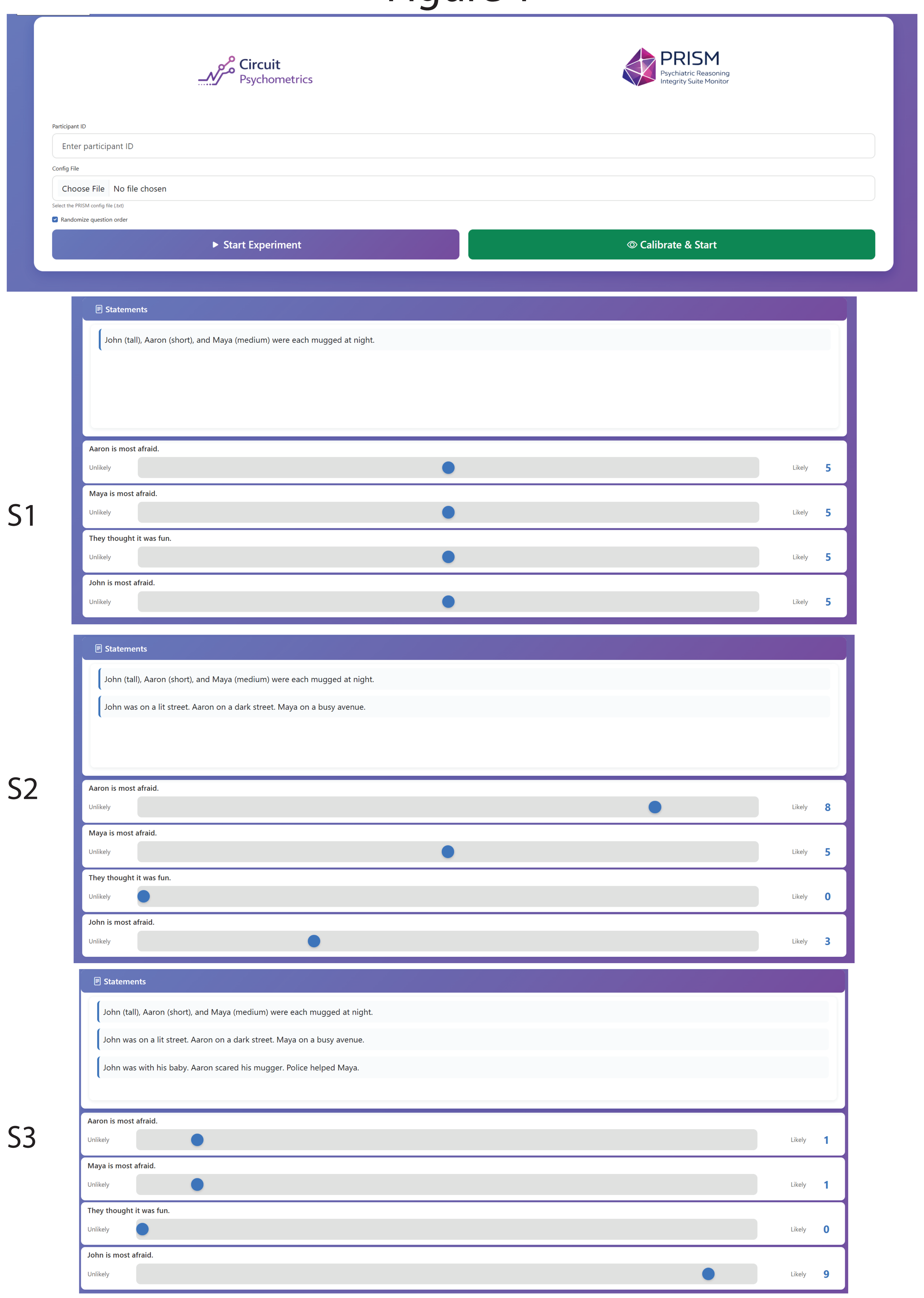


Figure 2

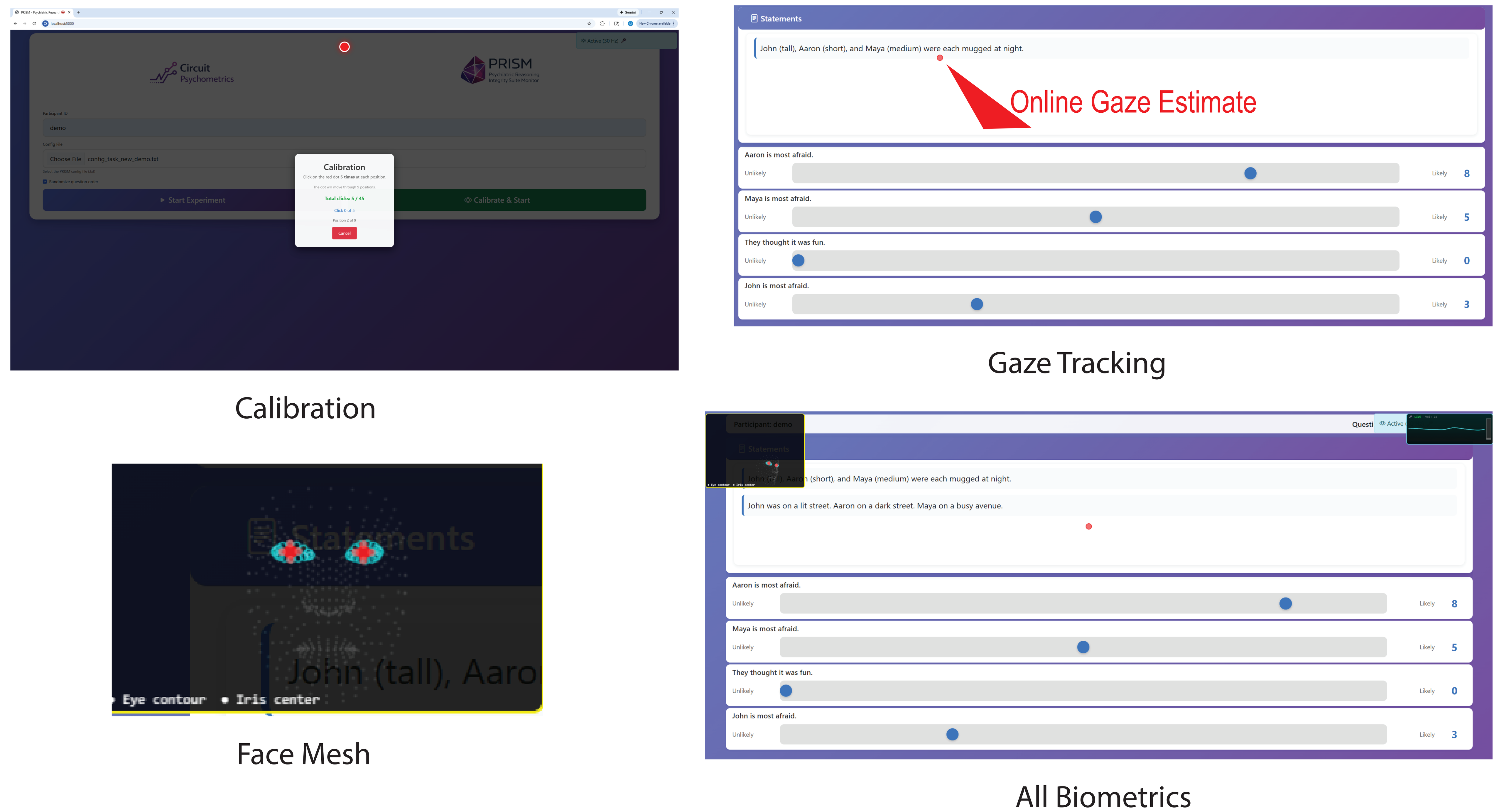


Figure 3

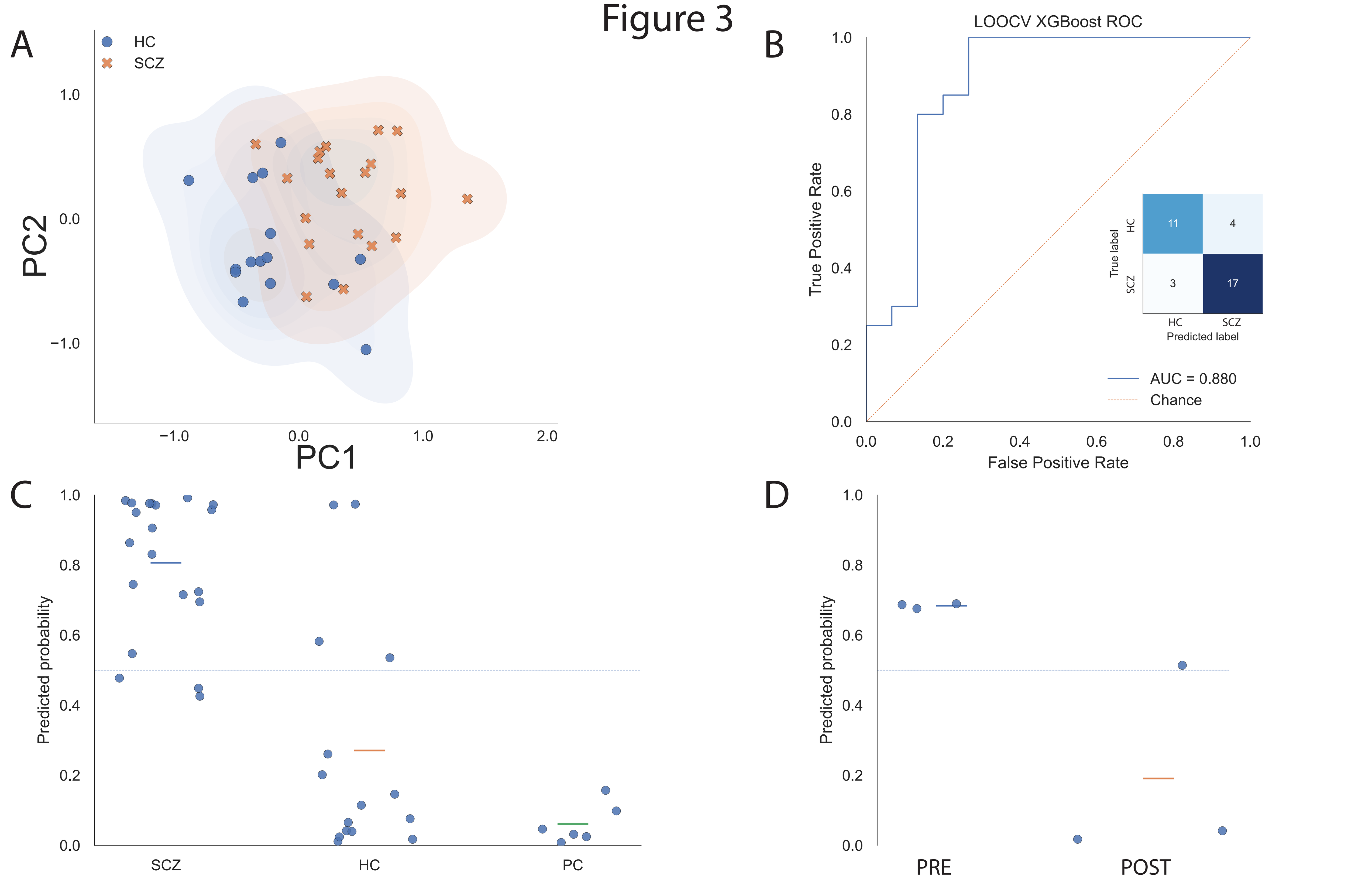


Figure 4

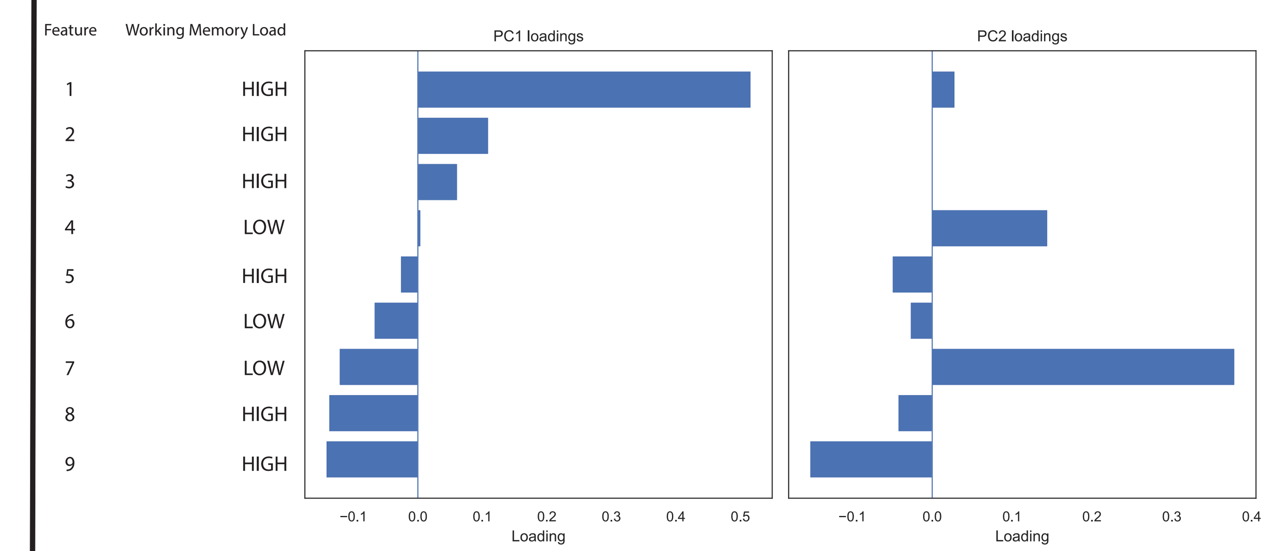
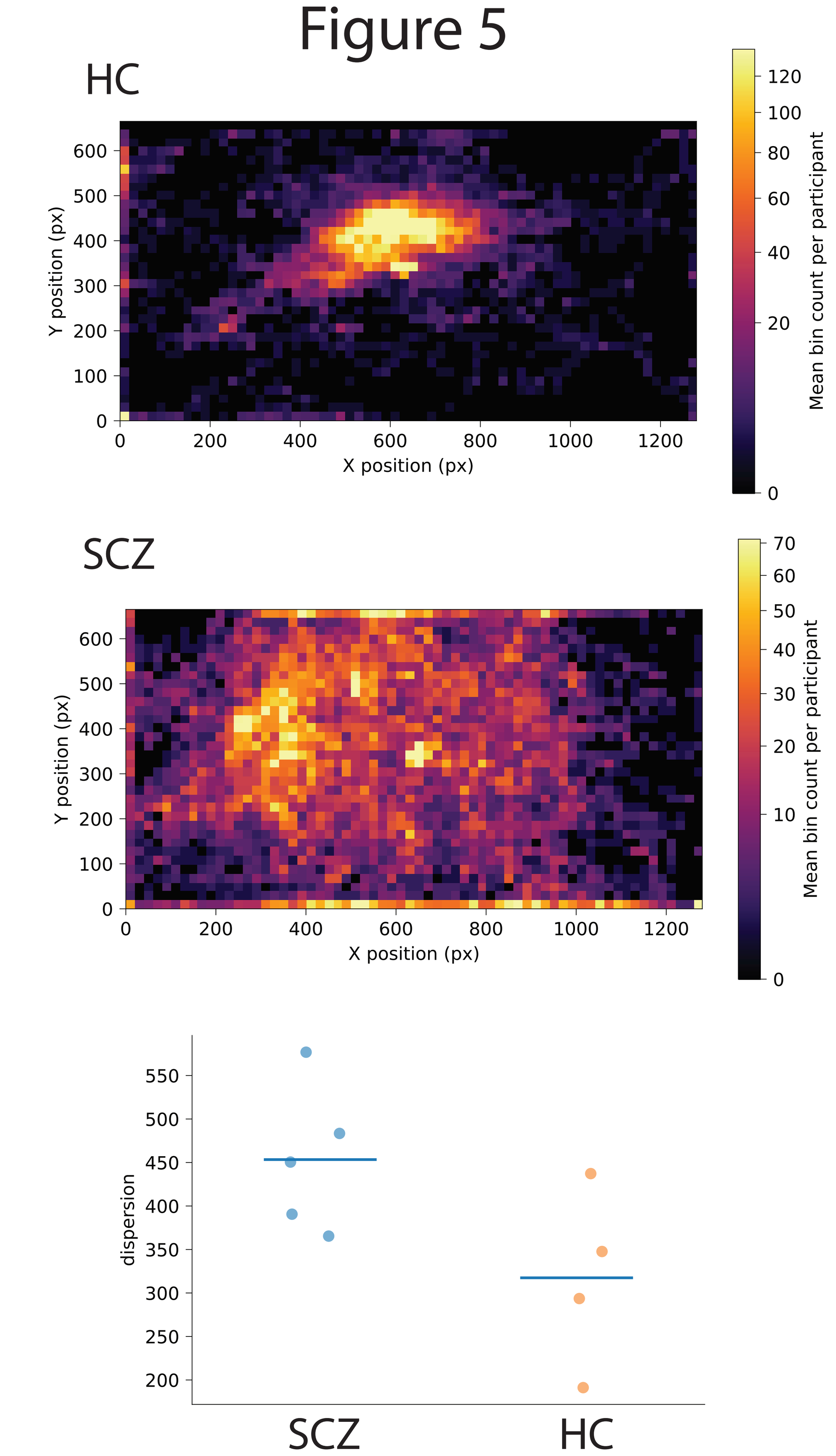


Figure 5



Conclusions:

PRISM provides objective, quantitative foundation for a cognitive-based biomarker in schizophrenia. Scenarios imposing higher working memory load reveal a path towards robust classification and, potentially, treatment monitoring. Biometrics including gaze provide additional data that will enrich phenotyping and stratification efforts. PRISM can readily be combined with qEEG and other neuroimaging methods to delineate neural correlates of reasoning deficits in schizophrenia and other psychiatric conditions.

*The authors declare no conflicts with respect to the work presented.

PRISM Psychiatric Reasoning Integrity Suite Monitor

Circuit Psychometrics