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## High Potential of Facial Biomarkers to Diagnose Psychotic Disorders

Neus Martínez-Abadías, Noemí Hostalet, Laura Mariscal-Uceda, Rubèn González, Alejandro González, Belén Canals-Borrell, Xavier Sevillano, Erick Canales-Rodríguez, Pilar Salgado-Pineda, ... [See all authors](#) ✓

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### Abstract

Schizophrenia (SCZ) and Bipolar Disorder (BP) are severe psychiatric disorders (PD) that affect more than 3% of the world's population and are among the leading causes of disability worldwide. Current diagnostic systems represent these PD as independent categorical entities. However, recent studies propose that both disorders would be two different manifestations of the same psychotic spectrum continuum. Differential diagnosis is mainly based on their clinical presentation, and reliable biomarkers remain an unmet clinical need. Since the brain and the face are derived from the same ectodermal origins and their development is intimately integrated through common genetic signaling, facial biomarkers emerge as one of the most promising biological risk factors for PD. Here, we assessed the potential of facial anatomy in predicting the diagnosis of SCZ and BP. Analyses were performed in a sample of 180 adults distributed in three groups of BP patients (n=46), SCZ patients (n=67), and CNT (n=67) matched by age and premorbid IQ. Faces were manually annotated from reconstructions of magnetic resonance scans. Facial shape correctly discriminated patients with BP and SCZ, even when facial differences between patients and CNT were so subtle that are not recognizable to the untrained eye or by exploratory multivariate statistical techniques. After cross-validation, 62-65% of patients were correctly diagnosed based on face shape. This percentage is similar to the discriminatory power of other genetic and brain biomarkers. Using Artificial Neural Networks, we tested a machine learning algorithm based on facial morphology to diagnose SCZ. The overall accuracy in diagnostic classification was greater than 90%, whereas the precision ranged between 70-95%

depending on the model. We also trained a Support Vector Machine classification algorithm to diagnose BP. Results showed that BP is harder to diagnose from facial biomarkers than SCZ, achieving a 72% accuracy. Euclidean Distance Matrix Analysis (EDMA) detected local facial differences involving the eyes, nose and mouth, and the relative separation/position between them. Facial anomalies were more abundant in SCZ patients, with 43-48% distances across the whole face significantly different from control subjects. In BP, the percentage of facial anomalies was lower, 24-32%, especially in women. Some facial differences were common to SCZ and BP, although the sense of change could be different among disorders. Remarkably, EDMA showed facial patterns that are disorder and gender-specific. These results demonstrate that an analysis of the spectrum of psychotic disorders under a gender perspective is crucial to further understand these disorders and to identify reliable biomarkers that can lead to early PD diagnosis.



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