A recent study from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) investigated the genetics of the auditory event-related potential, a putative psychosis biomarker.

Genetic studies of psychotic disorders suggest the presence of many risk genes, each with small effect sizes. However, the risk associated with combinations of genes may be significant because they are likely to affect multiple points in key neural systems.

The auditory oddball event-related potential is a noninvasive electrical brain response elicited by an external auditory stimulus, and P300 is a major event-related potential subcomponent. P300 abnormalities have been reported in multiple studies of schizophrenia and psychotic bipolar disorder, which suggests this event-related potential subcomponent is a putative psychosis biomarker.1-3 Furthermore, previous studies have found that known schizophrenia risk genes (eg, DISC1, NRG1, COMT) are associated with P300 abnormalities.4-6

The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study was performed to investigate intermediate phenotypes from multiple modalities and their genetic underpinnings in psychosis. Using data from the B-SNIP trial, Narayanan and colleagues7 examined the effects of simultaneous coupling of multiple genes on event-related potential subcomponents, which had not previously been studied. From a cohort of about 2600 patients, they looked at 449 individuals for whom both genotyping (genomic DNA from a peripheral blood sample) and event-related potential (based on electroencephalographic data while performing the auditory oddball task) were available.

The study sample included 144 patients with schizophrenia (diagnosis of either schizophrenia or schizoaffective disorder, depressed type); 210 patients with psychotic bipolar disorder (diagnosis of either schizoaffective disorder, bipolar type, or bipolar I disorder with psychotic features); and 95 healthy controls, aged 15 to 65 years. Out of approximately 1 million genes, genetic data were reduced to about 20,000 significant single nucleotide polymorphisms. Parallel independent component analysis was used, which links event-related potential activity with synergistic gene clusters.

The authors found that 4 of 8 independent event-related potential components (designated E1, E2, E3, and E6) were significantly connected to 3 of the 11 genetic components (designated G1, G4, and G9). More specifically, E6 was negatively correlated with G1, and E1 was positively correlated with G9; G4 was negatively correlated with E2 and positively correlated with E3. Genetic component G1 was enriched with genes associated with process networks, including neurogenesis-axon guidance and cell adhesion, and metabolic networks, including lysophosphatidylserine and sphingomyelin pathways. G4 was enriched with genes associated with process networks, including cell adhesion and synaptogenesis, and multiple metabolic networks, including lysophosphatidylserine and ceramide pathways. G9 was enriched with genes associated with immune response genes (complement pathways) and G-protein signaling, as well as process networks, including cell adhesion and the inflammation-complement system.

The strengths of the study included the use of high-density spatial event-related potential data in a large, multisite study of patients with psychosis. Primary limitations included the lack of matching groups by age, sex, and sample size (although these were controlled for in the analyses), as well as
potential medication effects. The authors identified both novel and known psychosis risk genes, whose interaction mediates event-related potential abnormalities in patients across the spectrum of psychotic disorders. They found evidence of a strong, multifactorial genetic component to these abnormalities, which comprise genes involved in the control of neuronal circuits and neurodevelopmental processes. In particular, cell adhesion is the prominent network process driving the event-related potential abnormalities in the psychoses.

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Disclosures:
Dr Miller is Associate Professor in the Department of Psychiatry and Health Behavior at Georgia Regents University and Schizophrenia Section Editor for Psychiatric Times. [Full bio]. He reports no conflicts of interest concerning the subject matter of this article.

References:


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