Publication

Altered Functional Subnetwork During Emotional Face Processing: A Potential Intermediate Phenotype for Schizophrenia

IMPORTANCE: Although deficits in emotional processing are prominent in schizophrenia, it has been difficult to identify neural mechanisms related to the genetic risk for this highly heritable illness. Prior studies have not found consistent regional activation or connectivity alterations in first-degree relatives compared with healthy controls, suggesting that a more comprehensive search for connectomic biomarkers is warranted. OBJECTIVES: To identify a potential systems-level intermediate phenotype linked to emotion processing in schizophrenia and to examine the psychological association, task specificity, test-retest reliability, and clinical validity of the identified phenotype. DESIGN, SETTING, AND PARTICIPATIONS: The study was performed in university research hospitals from June 1, 2008, through December 31, 2013. We examined 58 unaffected first-degree relatives of patients with schizophrenia and 94 healthy controls with an emotional face-matching functional magnetic resonance imaging paradigm. Test-retest reliability was analyzed with an independent sample of 26 healthy participants. A clinical association study was performed in 31 patients with schizophrenia and 45 healthy controls. Data analysis was performed from January 1 to September 30, 2014. MAIN OUTCOMES AND MEASURES: Conventional amygdala activity and seeded connectivity measures, graph-based global and local network connectivity measures, Spearman rank correlation, intraclass correlation, and gray matter volumes. RESULTS: Among the 152 volunteers included in the relative-control sample, 58 were unaffected first-degree relatives of patients with schizophrenia (mean [SD] age, 33.29 [12.56]; 38 were women), and 94 were healthy controls without a first-degree relative with mental illness (mean [SD] age, 32.69 [10.09] years; 55 were women). A

graph-theoretical connectivity approach identified significantly decreased connectivity in a subnetwork that primarily included the limbic cortex, visual cortex, and subcortex during emotional face processing (cluster-level P corrected for familywise error = .006) in relatives compared with controls. The connectivity of the same subnetwork was significantly decreased in patients with schizophrenia (F = 6.29, P = .01). Furthermore, we found that this subnetwork connectivity measure was negatively correlated with trait anxiety scores (P = .04), test-retest reliable (intraclass correlation coefficient = 0.57), specific to emotional face processing (F = 17.97, P > .001), and independent of gray matter volumes of the identified brain areas (F = 1.84, P = .18). Replicating previous results, no significant group differences were found in face-related amygdala activation and amygdala-anterior cingulate cortex connectivity (P corrected for familywise error =.37 and .11, respectively). CONCLUSIONS AND RELEVANCE: Our results indicate that altered connectivity in a visual-limbic subnetwork during emotional face processing may be a functional connectomic intermediate phenotype for schizophrenia. The phenotype is reliable, task specific, related to trait anxiety, and associated with manifest illness. These data encourage the further investigation of this phenotype in clinical and pharmacologic studies.