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Neural predictors of substance use disorders in Young adulthood

Jessica W. O'Brien[a,b], Shirley Y. Hill[a,b,*]

[a] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[b] Department of Psychology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

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ABSTRACT

Offspring from multiplex, alcohol-dependent families are at heightened risk for substance use disorders (SUDs) in adolescence and young adulthood. These high-risk offspring have also been shown to have atypical structure and function of brain regions implicated in emotion regulation, social cognition, and reward processing. This study assessed the relationship between amygdala and orbitofrontal cortex (OFC) volumes obtained in adolescence and SUD outcomes in young adulthood among high-risk offspring and low-risk controls. A total of 78 participants (40 high-risk; 38 low-risk) from a longitudinal family study, ages 8–19, underwent magnetic resonance imaging; volumes of the amygdala and OFC were obtained with manual tracing. SUD outcomes were assessed at approximately yearly intervals. Cox regression survival analyses were used to assess the effect of regional brain volumes on SUD outcomes. The ratio of OFC to amygdala volume significantly predicted SUD survival time across the sample; reduction in survival time was seen in those with smaller ratios for both high-risk and low-risk groups. Morphology of prefrontal relative to limbic regions in adolescence prospectively predicts age of onset for substance use disorders.

1. Introduction

Individuals with a family history of alcohol use disorders (AUDs) are at increased risk for developing substance use disorders (SUDs) (Cloninger et al., 1981; Verhulst et al., 2015), and offspring from multiplex, alcohol-dependent families are at especially high risk for early onset SUDs (Hill et al., 2008). Determining the specific genetic mechanisms of familial transmission has been challenging given the multiple clinical subtypes of SUD and variable expression across the lifespan (Hill, 2010). Accordingly, increased attention has been focused on finding biological variation associated with familial risk that predisposes individuals to increased risk for SUD. Longitudinal studies that follow individuals with a family history of AUD from childhood and adolescence into young adulthood may allow for identification of potential biomarkers that contribute to risk and resilience within at-risk populations (Hill and O'Brien, 2015).

High-risk offspring with a family history of AUD have been shown to demonstrate atypical structure and function of brain regions involved in executive control, affective regulation, decision making, and social cognition (Cservenka, 2016; Hill and O'Brien, 2015). Previous research indicates that compared to healthy controls from low-risk families, adolescent and young adult offspring with a family history of AUD show volumetric reductions in the right hemisphere of the orbitofrontal cortex (OFC) (Hill et al., 2010, 2009b) and the amygdala (Benegal et al., 2007; Dager et al., 2015; Hill et al., 2001, 2013). These results have been observed in samples where either the majority of cases had not yet developed a substance use disorder (Dager et al., 2015; Hill et al., 2001), were alcohol-naïve (Benegal et al., 2007), or the reduction in volume was seen even when cases with substance use disorder were removed (Hill et al., 2013, 2009b). Adults with AUD also show volumetric reductions of the OFC and amygdala compared to healthy controls (Durazzo et al., 2011; Makris et al., 2008), and atypical structure and function of these regions may be one biological mechanism that confers risk for SUDs.

Importantly, atypical morphologies of the orbitofrontal cortex and amygdala during childhood and adolescence have been shown to relate to established risk factors for substance use disorders. Longitudinal family studies, as well as cross-sectional research on healthy adults and children, have demonstrated that reductions in orbitofrontal cortex volume and cortical thickness are associated with higher rates of externalizing behaviors (Ameis et al., 2014), greater impulsivity (Hill et al., 2009b; Schilling et al., 2013) and impaired decision-making (Hill and O'Brien, 2015), deficits that are independently associated with increased risk for substance use, abuse, and dependence (Bechara et al., 2001; O'Brien et al., 2014; Verdejo-Garcia et al., 2008). Amygdala volume has been shown to be significantly correlated with P300 amplitude (Hill et al., 2001), a well-established endophenotype of risk for substance use and externalizing behavioral disorders (Hill et al., 2009a;

* Correspondence to: Department of Psychiatry, University of Pittsburgh Medical Center, 3811 O' Hara St., Pittsburgh, PA 15213, USA.
E-mail address: syh50@pitt.edu (S.Y. Hill).

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Iacono et al., 2002). In addition, the volume of both amygdala and OFC seen in adolescence have been associated with variation in the tendency to be behaviorally inhibited in early childhood (Hill et al., 2010). Importantly, other longitudinal studies have demonstrated that the degree of behavioral inhibition seen in early childhood is related to subsequent SUD outcomes (Caspi et al., 1996; Williams et al., 2010). These results suggest that atypical structure and function of the OFC and amygdala during adolescence, when alcohol and drug use behaviors first emerge, may confer particular risk for substance use disorders.

Adolescence is characterized by dynamic brain changes that occur in the context of major physiological, psychological, and social transitions. This developmental period is also associated with increased emotional reactivity, sensation seeking, and risky behavior, along with dramatic increases in rates of alcohol and drug use during the teenage years (Bava and Tapert, 2010; Casey et al., 2008). Developmental neuroimaging studies indicate that during adolescence, the brain undergoes regionally-specific trajectories of neurogenesis and pruning in subcortical, limbic brain regions, including the amygdala, reaching peak volume in early adolescence, whereas prefrontal regions, including the OFC, undergo a protracted period of development extending into adulthood (Giedd et al., 2015; Ostby et al., 2009). In fact, amygdala volume is inversely correlated with cortical thickness of prefrontal brain regions, including the OFC, in typically developing youth (Albaugh et al., 2013). Accordingly, the increased incidence of risk-taking and impulsive behavior that characterize adolescence likely relates to the unique imbalance of functionally mature limbic regions and immature prefrontal regions during this period of development (Casey et al., 2008; Galvan et al., 2007). Although adolescents, as a group, are more likely to engage in risky behaviors, some adolescents are more prone to engage in risky behaviors than others, putting these individuals at potentially greater risk for negative outcomes (Casey et al., 2008; Galvan et al., 2007). Individuals who demonstrate an exacerbated discrepancy in development of prefrontal versus limbic brain regions in adolescence may be at especially high risk for poor outcomes, including substance use disorders.

Converging evidence indicates that structural abnormalities in the OFC and amygdala may increase risk for SUDs. To the best of our knowledge, no studies to date have provided evidence for a direct association between premorbid volumetric reductions in the OFC and/or amygdala and subsequent substance use disorder outcomes. Accordingly, the current study sought to determine whether volumetric differences in the amygdala and OFC observed between high-risk adolescents and low-risk controls would relate to early-onset SUD outcomes in young adulthood. Utilizing a developmental perspective informed by neurobiological models of risk taking in adolescence (Casey et al., 2008), we hypothesized that volume of the OFC, relative to volume of the amygdala, would be a stronger predictor of SUD outcome than either regional volume considered independently.

2. Methods

2.1. Subjects

The present report is based on analysis of data for 78 third-generation offspring who are part of an ongoing family study that selected families through their parents' generation. The offspring were evaluated during childhood, adolescence, and young adulthood at approximately yearly intervals in childhood and biennially in young adulthood. A total of 40 high-risk (HR) offspring from paternal multiplex families were studied (17 females and 23 males) along with 38 low-risk (LR) offspring (19 females and 19 males). MRI data was collected when participants were between the ages of 8 and 19. Mean age at last follow-up for the present sub-sample is 20.6 years. This study has ongoing approval from the University of Pittsburgh Institutional Review Board. All participants provided consent at each visit. Children provided assent with parental consent.

High-risk offspring were drawn from families selected to be part of a larger family study of alcohol dependence in which the presence of two adult alcohol dependent (AD) brothers were required for entry into the study. These brothers are the fathers or uncles of the HR subjects in the present analyses. In-person structured interviews using the Diagnostic Interview Schedule (DIS) (Robins et al., 1981) had been performed for the majority of all living and available relatives of the proband by risk-status-blind interviewers, with two family history reports used for deceased or unavailable relatives. Families had not been included if primary, recurrent major depression, bipolar disorder, schizophrenia, or a primary SUD other than AD was present, for either the proband pair of AD brothers or their first-degree relatives.

Low-risk community control families consisting of two brothers and their parents were identified through an index case who responded to a newspaper advertisement requesting participants who were interested in a study of heritable aspects of personality. Families were chosen on the basis of having the same structural characteristics as the HR families (at least two adult brothers) and an absence of axis I psychopathology based on the outcome of a DIS interview that provided Diagnostic and Statistical Manual (DSM) and Feighner criteria for alcoholism (Feighner et al., 1972). Low-risk families were included if all first- and second-degree relatives of the index case were free of alcohol and other drug dependence.

2.2. Procedures

2.2.1. Substance use outcome data

SUD outcome was determined using age-appropriate clinical diagnoses obtained during childhood/adolescence (yearly before age 19) with the Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers et al., 1985) and with the Composite International Diagnostic Interview (CIDI) (Janca et al., 1992) and CIDI-Substance Abuse Module (CIDI-SAM) (Cottler et al., 1989) biennially during young adulthood.

2.2.2. Socioeconomic status

Socioeconomic status (SES) was assessed using the Hollingshead Four-Factor Index of Socioeconomic Status (Hollingshead, 1975) at each yearly visit. The SES status closest to the time of MRI acquisition was selected for use in analyses.

2.2.3. MRI structural acquisition methods

Subjects were scanned during childhood and adolescence using a GE 1.5 T scanner located at the University of Pittsburgh Medical Center Magnetic Resonance Research Center. After a localizer scan to ensure optimal head placement, T1 weighted axial images with a slice thickness of 1.5 mm were obtained using a 3 dimensional spoiled gradient recalled echo in the steady state (3D SPGR) (TE = 5 ms, TR = 24 ms, flip angle = 45 degrees, acquisition matrix = 192 × 256, NEX = 1, FOV = 24 cm). Slices were resliced in the coronal plane through the anterior commissures to provide a reproducible guide for image orientation. In addition, axial proton density and T2 weighted images were obtained covering the whole brain at a slice thickness of 5 mm, slice gap = 0 mm ([double spin echo, TE = 17 ms and 102 ms, TR = 3000 ms], acquisition matrix = 256 × 192, NEX = 1, FOV = 24 cm). All scans were reviewed by a neuroradiologist when suspected structural abnormalities were present.

2.2.4. Region of interest analysis

Region of interest (ROI) volumes were obtained by reliable raters using manual tracing techniques with BRAINS2 software (Magnotta et al., 2002). Semi-automated segmentation of grey, white, and cerebrospinal fluid volumes was completed by the raters using successive iterations to maximize the kappa value. After aligning T1, T2, and proton density images, two raters blind to group membership traced the volumes of the OFC, amygdala, and intracranial volume (ICV)