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# Disrupted resting brain graph measures in individuals at high risk for alcoholism

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ABSTRACT

Familial susceptibility to alcoholism is likely to be linked to the externalizing diathesis seen in high-risk offspring from high-density alcohol use disorder (AUD) families. The present study aimed at comparing resting brain functional connectivity and their association with externalizing symptoms and alcoholism familial density in 40 substance-naive high-risk (HR) male offspring from high-density AUD families and 30 matched healthy low-risk (LR) males without a family history of substance dependence using graph theory-based network analysis. The HR subjects from high-density AUD families compared with LR, showed significantly reduced clustering, small-worldness, and local network efficiency. The frontoparietal, cingulo-opercular, sensorimotor and cerebellar networks exhibited significantly reduced functional segregation. These disruptions exhibited independent incremental value in predicting the externalizing symptoms over and above the demographic variables. The reduction of functional segregation in HR subjects was significant across both the younger and older age groups and was proportional to the family loading of AUDs. Detection and estimation of these developmentally relevant disruptions in small-world architecture at critical brain regions sub-serving cognitive, affective, and sensorimotor processes are vital for understanding the familial risk for early onset alcoholism as well as for understanding the pathophysiological mechanism of externalizing behaviors.

## 1. Introduction

A family history of alcoholism constitutes a significant risk factor for the development of alcohol use disorders (AUDs) (Cotton, 1979). This risk is further elevated for individuals with a high family loading of early-onset AUD in multiple first- and second-degree relatives (Cloninger et al., 1986; Cotton, 1979; Schuckit, 1985). These individuals at high risk (HR) for AUDs can be reliably differentiated from persons at low risk (LR), even prior to their initiation of alcohol, on a variety of psychological and neurobiological predictors that are not confounded by alcohol (Cservenka, 2016; Hill and O'Brien, 2015). These include excessive externalizing behaviors (Hussong et al., 2008, 2007), atypical brain volumes (Benegal et al., 2007; Hill et al., 2013, 2011, 2009; Venkatasubramanian et al., 2007), atypical task-related functional brain activity (Acheson et al., 2009; Rangaswamy et al., 2004; Schweinsburg et al., 2004; Silveri et al., 2011) and connectivity (Cservenka et al., 2014; Herting et al., 2011; Spadoni et al., 2013; Wetherill et al., 2012). They also differ in neurocognitive measures of executive function (Gierski et al., 2013; Nigg et al., 2004) and attentional processing (Benegal et al., 1995; Hill et al., 1999). These premorbid deficits indicate that the familial susceptibility to alcoholism is likely to be linked to a neurodevelopmental process that may underlie heritable aspects of an AUD.

Externalizing temperaments and disorders (including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant (ODD) and conduct disorders (CD) in childhood and adult ADHD, antisocial personality disorder (ASPD) in young adults) strongly predict vulnerability for early-onset alcohol and other substance use disorders (SUDs) (Brook et al., 2010; Kuperman et al., 2005; McGue et al., 2001). The overlap is so high that SUDs are considered a part of the externalizing-spectrum of disorders (Krueger et al., 2005; Witkiewitz et al., 2013). While family environmental effects do moderate risk vulnerability in offspring outcomes (Jacob et al., 2003; Verhulst et al., 2015), both SUDS and externalizing disorders are estimated to be highly heritable

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(Bornovalova et al., 2010; Goodwin, 1979; Hicks et al., 2013; Verhulst et al., 2015), and exhibit extensive overlaps in endophenotype measures between them (Salvatore et al., 2015).

Previous studies examining endophenotypic risk for alcoholism and related externalizing disorders, have reported differences in focal brain morphology and activity. However, it is increasingly apparent that these foci represent nodes of aberrant functional brain-networks and a network paradigm is critical for understanding the functional aberrations that are associated with familial-risk for alcoholism (Cservenka et al., 2015a). The resting state functional connectivity has proved to be a useful measure for investigating functionally coupled intrinsic networks in the human brain (Biswal et al., 1995; Fox and Raichle, 2007). Popular methods for analyzing resting-state data include seed-based approaches, independent component analysis, and graph methods (Lee et al., 2013). Graph theory analysis of resting-state fMRI (rsfMRI) data offer powerful tools in characterizing and quantifying the subject specific alterations in the large-scale functional brain network architecture (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Sporns et al., 2004).

Graph theory-based approaches model the brain as a complex network represented graphically as a collection of *'N'* nodes denoting neural elements (neurons or brain regions) that are linked by *'E'* edges representing functional connections. Two basic measures that are used to characterize functional brain-networks in graph model are the clustering coefficient (C), which quantifies the local connectivity as an index of network segregation, and the characteristic path length (L), which quantifies the global connectivity as an index of network integration. A typical Erdos-Renyi type of random network is characterized by low local segregation and high global integration, whereas a non-random ordered network has high local segregation with low global integration. A small world network is said to possess best of both worlds, defined by high local segregation as well as high global integration (Watts and Strogatz, 1998), providing an efficient temporospatial system at remarkably low wiring and energy costs (Bullmore and Sporns, 2009). Moreover, such resting state functional brain graph properties exhibit substantial heritability (Fornito et al., 2011; Glahn et al., 2010; Smit et al., 2010, 2008) and have also found applications in characterizing adolescent brain development (Sato et al., 2014; Vogel et al., 2013). As such, these graph measures could be used to decipher distinct neural signatures underlying the developmental vulnerability to externalizing disorders and addictions.

The exact mechanisms underlying familial susceptibility to alcoholism in alcohol-naïve HR offspring are not fully understood, and we primarily hypothesized that the brain regions that are implicated in task-related studies that examine familial vulnerability to alcoholism (Herting et al., 2011; Rangaswamy et al., 2004; Wetherill et al., 2012) may also show disrupted graph-theoretical measures, of segregation and integration, during resting state. Given that the period from early adolescence to young adulthood is a time of heightened risk for the emergence of alcohol abuse, we additionally explored the age-related differences in network segregation measures between the risk-groups, using a cross-sectional approach. We also explored the relationship of externalizing symptom profile and the density of alcoholism family loading with measures of network segregation.

## 2. Methods

### 2.1. Participants

The study population consisted of 90 consenting male participants −50 HR alcohol-naïve subjects from high-density AUD families and 40 LR alcohol-naïve control subjects (without a family history of alcohol or other substance dependence, in first degree relatives), matched on age, education, sex, handedness and socioeconomic status. The HR subjects were ascertained by selecting alcohol-naïve male offspring of a treatment-seeking alcohol dependent father from high-density AUD family, recruited from the Centre for Addiction Medicine, National Institute of Mental Health and Neurosciences (NIMHANS), a tertiary care neuropsychiatry hospital in Bangalore, India. A high-density AUD family was identified when the affected father had an established diagnosis of alcohol dependence (DSM-IV criteria) before the age of 25 (early-onset) and had at least two further affected first-degree relatives (parents, siblings and/or other children) with alcohol dependence. All such male offspring (age $\leq$21 years) who fulfilled these criteria were enrolled. The LR subjects were recruited through community advertisement in local schools and hospitals. Subjects were excluded from the assessments if they had any of the following during a detailed clinical interview and physical examination: (1) recent substance use (i.e., positive breath-analyzer test and/or urine screen) or significant lifetime alcohol or substance use (> 1 lifetime alcoholic drinks, > 2 cigarettes/day and/or any other drug use); (2) presence of comorbid psychiatric (exception of sub-syndromal externalizing spectrum), medical, neurological disorder or a history of lifetime or recent use of psychoactive or neurological drugs; (3) presence of contraindications for MRI and (4) lifetime history of head injury, seizures or neurosurgery. Written informed consent and assent were obtained from all participants and their parents in accordance with the NIMHANS Institutional Ethics Review Board.

### 2.2. Clinical assessments

#### 2.2.1. Assessment of participants

All HR and LR subjects were assessed on the semi-structured assessment for genetics of alcoholism (SSAGA II), child, adolescent or adult versions (Bucholz et al., 1994) as indicated to assess externalizing symptoms specifically and to rule out any other syndromal psychiatric diagnoses. This instrument has previously been translated and used in relevant regional languages (Hindi and Kannada) (Benegal et al., 2007; Venkatasubramanian et al., 2007). The items pertaining to the externalizing spectrum [ADHD, ODD and CD diagnoses from child/adolescent versions (age < 18y); and adult ADHD, ASPD diagnoses from adult version (age 18y+)] were added and proportionally scaled to compute a cross-diagnoses dimensional externalizing symptom score (ESS) (Benegal et al., 2007; Dick et al., 2008; Venkatasubramanian et al., 2007). The symptom counts were square-root transformed to approximate normality and stabilize the variance as per a Box-Cox power transformation analysis (optimal $\lambda = 0.52$) (Snedecor and Cochran, 1989). The Annett's handedness questionnaire (Annett, 1967) was used to ascertain that all subjects were right-handed.

#### 2.2.2. Assessment of parents

The SSAGA II – Adult version was also used to assess alcohol and related disorders as well as in screening out other psychiatric disorders in parents. The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) was used with three or more adult informants in the family, to document family loading (FL) for alcoholism and to screen for other psychiatric disorders in first-degree relatives. FL was calculated as per family patterns of alcoholism analyses criteria (Turner et al., 1993). Parents and grandparents, with diagnosable AUDs, each contributed a score of 1. Scores for aunts, uncles and siblings were the proportion of AUDs in each of their sibships. The LR subjects had no relatives with a history of AUDs. HR offspring with the mother having diagnosable AUDs or use of alcohol during the index pregnancy were excluded, to rule out fetal alcohol effects. Further, Lewis Murray obstetric complications scale (Lewis and Murray, 1987) was used for recall of the pregnancy history from mother to rule out significant adverse obstetric and perinatal events at birth as a confounding etiology for brain developmental delays or deficits. Socioeconomic status (SES) was ascertained using the revised Kuppuswamy's Socioeconomic Status scale (Kumar et al., 2012). This scale provides a composite three-factor SES index based on education and occupation of the head of the family along with monthly income of the household.