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Impact of family history of alcoholism on glutamine/glutamate ratio in anterior cingulate cortex in substance-naïve adolescents

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ABSTRACT

Neuroimaging studies of individuals with family histories of alcoholism provide evidence suggesting neurobiological risk factors for alcoholism. Youth family history positive (FH+) for alcoholism exhibit increased impulsivity compared to family history negative (FH−) peers in conjunction with altered functional activation in prefrontal cortex, including anterior cingulate cortex (ACC). This study examined glutamate (Glu) and glutamine (Gln), amino acids vital to protein synthesis, cellular metabolism and neurotransmission, acquired from ACC and parieto-occipital cortex (POC) using magnetic resonance spectroscopy (MRS) at 4T. Participants were 28 adolescents (13 male, 12–14 yrs) and 31 emerging adults (16 male, 18–25 yrs), stratified into FH− and FH+ groups. Significantly higher ACC Gln/Glu was observed in emerging adults versus adolescents in FH− but not FH+ groups. In FH− adolescents, higher impulsivity was significantly associated with higher ACC Gln/Glu. In FH+ emerging adults, higher impulsivity was negatively associated with ACC Gln/Glu. No differences or associations were observed for POC. These findings provide preliminary evidence that family history of alcoholism is associated with a neurochemical profile that may influence normative age differences in glutamatergic metabolites and their association with impulse control, which together could confer greater genetic risk of addiction later in life.

1. Introduction

Alcohol use typically begins during adolescence, a time during which the still-maturing brain may be particularly vulnerable to its neurotoxic effects. However, while a number of differences in brain structure and function associated with early alcohol drinking have been identified (Squeglia et al., 2009), it remains unclear whether such neurological changes are antecedent or consequent to adolescent alcohol use. A family history of alcoholism (FH) constitutes a major risk factor for the development of alcohol use disorders (Conway et al., 2003). Thus, neuroimaging studies of adolescents with family histories of alcoholism can help identify neurobiological risk factors for alcohol use disorders and can help distinguish potential precursors of alcoholism from its sequelae. A number of neurobiological and behavioral differences have been identified between youth who are family history positive (FH+) for alcoholism and family history negative (FH−) peers, including increased impulsivity (Gierski et al., 2013) and differences in recruitment of regulatory brain regions during inhibitory demands, as revealed by functional magnetic resonance imaging (fMRI) (DeVito et al., 2013; Hardee et al., 2014; Silveri et al., 2011). While the role of neurochemistry in older adults with alcohol use disorders has been investigated (Meyerhoff et al., 2013, 2014; Sullivan and Pfefferbaum, 2014), neurochemical correlates of family history of alcoholism in youth has remained largely unstudied to date. To this end, the current study employed magnetic resonance spectroscopy (MRS) to investigate the glutamatergic system, including turnover of the general metabolic pool, as indexed by the ratio of glutamine (Gln) to glutamate (Glu) (Öngür et al., 2008; Yüksel and Öngür, 2010) in FH− and FH+ adolescents and emerging adults. Relationships between Gln/Glu and impulsivity were also examined in these populations.

Maturation of frontal brain regions, including the anterior cingulate cortex (ACC), supports normative reductions in impulsivity

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during adolescence, as regulatory brain circuitry follows a protracted developmental course that extends well into early adulthood (Casey et al., 2008; Gogtay et al., 2004; Luna and Sweeney, 2004; Rubia et al., 2006). Difficulty in regulation of impulsive actions during this age period may contribute to experimentation with alcohol, drinking binges, and alcohol abuse in youth. Furthermore, inhibitory control is prominent among the cognitive abilities most vulnerable to disruption by alcohol (Sher et al., 1997), leaving adolescents who drink alcohol at an enhanced risk for reckless decision-making and continued substance misuse. Moreover, age of initiation, magnitude of use, and prevalence of alcohol use disorders are influenced by genetic vulnerability, as early onset and greater use and abuse have been linked with having a positive family history of alcoholism among adolescents and young adults (Biederman et al., 2000; Conway et al., 2003; Hill et al., 2000). Although intellectual functioning in this at-risk population typically falls within the healthy range (Alterman et al., 1989), children of alcoholics demonstrate deficits in abstract reasoning and planning, lower IQ scores, and poorer spelling and math performance compared to children of non-alcoholics (Poon et al., 2000). Further, altered executive functioning has been reported in FH+ youth in conjunction with increased self-report ratings of impulsivity (Gierski et al., 2013) and fMRI studies have identified numerous brain areas that are differentially recruited by FH+ and FH− individuals during tasks requiring cognitive control. For instance, studies have reported increased ACC activation in FH+ versus FH− participants during inhibitory control on classic tasks such as the Stroop Color–Word Interference task (Silveri et al., 2011) and the Go–NoGo task (Hardee et al., 2014; Jamadar et al., 2012). Collectively, prior data suggest that differential ACC functioning may have an influential role in elevating risk for substance use and abuse in FH+ compared to FH− youth.

In recent years, high magnetic field strengths and advances in magnetic resonance spectroscopy (MRS) acquisition sequences have permitted investigation of important in vivo neurochemicals implicated in alcohol action, such as glutamate and gamma amino butyric acid (GABA) (Meyerhoff et al., 2014; Silveri, 2014). Notably, glutamate (Glu) and glutamine (Gln) can be resolved and quantified separately, particularly at high field (Hu et al., 2007; Jensen et al., 2009), allowing investigation of these amino acids that are vital to protein construction, cellular metabolism, and excitatory neurotransmission (Behar and Rothman, 2001; Patel et al., 2005; Sibson et al., 1998; Yüksel and Öngür, 2010). The ratio of Gln/Glu, thought to reflect Gln-Glu cycling, has been established as a potential index of neurotransmission (Yüksel and Öngür, 2010). Levels of Gln and Glu are of particular interest in alcohol research as alcohol use, dependence, and withdrawal have been shown to be associated with both acute and protracted alterations in glutamatergic systems (Hermann et al., 2012; Krystal et al., 2003; Tsai and Coyle, 1998). To date, however, only one study has used MRS to identify neurochemical correlates of risk for substance abuse in a FH+ population (Moss et al., 1997), in which phosphorous (^{31}P) MRS was applied to study peripubertal FH+ adolescents and a low-risk FH− comparison group, demonstrating lower parietal phosphodiester concentrations in the high-risk adolescents who also presented with behavior disorders.

Accordingly, the current study is the first to use proton (^{1}H) MRS to examine the association of age and FH status with markers of glutamatergic neurotransmission in ACC and a control region in parieto-occipital cortex (POC). It also evaluates relationships between ACC Glu/Gln ratios and cognitive and self-report measures of impulsivity in adolescents and emerging adults. It was hypothesized that the FH+ group would exhibit higher Gln/Glu ratios in ACC, but not in POC, compared to FH− counterparts, given increased vulnerability and relevance of the frontal lobe to addiction. Further, higher ACC Gln/Glu ratios were hypothesized to correlate positively with higher behavioral and self-report measures of impulsivity. Positive associations between Gln/Glu, FH+ status and impulsivity were predicted for both adolescent and emerging adult groups.

2. Materials and methods

2.1. Participants

Participants were 28 healthy adolescents (13 male), aged 12–14 years, and 31 healthy emerging adults (16 male), aged 18–25 years, stratified within each age group into low (FH−) or high (FH+) familial risk for alcoholism. Participants (all adolescents and a subset of emerging adults) were included in another published MRS study that investigated brain GABA levels using MEGAPRESS (Silveri et al., 2013). Participants were 96.7% non-Hispanic, 70.0% Caucasian. A summary of participant demographics is provided in Table 1. Participants reported no past or current psychological or neurological illnesses, history of head trauma, MRI contraindications, severe medical problems or psychoactive substance use. A urine screen was completed prior to scanning to rule out current psychoactive substance use and pregnancy. The Kiddie Schedule for Affective Disorder and Schizophrenia (KSADS) was used to rule out Axis I diagnoses in adolescents and the Structured Clinical Interview for DSM-IV Disorders (SCID) was used for emerging adults. Individuals were recruited from the community and were financially compensated for study participation. Adolescent subjects reported less than three episodes of lifetime alcohol use and no history of drug use. Emerging adults were non-smoking, light drinkers (alcohol use never exceeded three drinks per occasion, or five total occasions within a 30 day period for the duration of each individual's lifetime drinking history) who had minimal to no history of illicit substance use (less than 10 lifetime events). Parents/guardians of adolescent participants provided written informed consent and adolescent participants provided written assent prior to study participation. Emerging adults provided written informed consent prior to study participation. This study was approved by and conducted in accordance with the McLean Hospital/Partners Healthcare Internal Review Board.

2.2. Assessment of family history of alcoholism

Emerging adult participants and accompanying parents of adolescent participants underwent a Family History–Epidemiologic (FHE) structured interview and an unstructured family interview to obtain information about substance use disorders in second-degree relatives. This information was used to stratify subjects into FH− or FH+ groups. Individuals in the FH+ group each had at least one biological parent or grandparent with a diagnosed alcohol use disorder. Of note, no participants reported having an alcohol-dependent mother, alleviating concerns over possible confounding effects of in utero alcohol exposure. Family expression of alcoholism, or family history density (FHD) of alcoholism, was calculated for FH+ participants (Table 1), with a single parent with a history of alcoholism contributing 0.5 and a single grandparent 0.25, for a range of 0.0 (FH−) to 2.0 (0.25–2.0, FH+) (Stoltenberg et al., 1998).

2.3. Measures of impulsiveness

All participants completed the Barratt Impulsiveness Scale (BIS-11) (Fossati et al., 2002) to assess trait impulsivity, including total score and attention (rapid shifts in attention/impatience with complexity), motor (impetuous action), and non-planning (lack of future orientation) subscale impulsivity scores. Two cognitive tasks were used to assess response inhibition: a modified Stroop test (time to complete and number of errors on Color Naming, Word