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Effects of Family History of Alcohol Use Disorders on Spatial Working Memory BOLD Response in Adolescents

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Abstract

Background—A positive family history (FH) of alcohol use disorders (AUD) has been linked to increased risk for the development of AUD, and neurocognitive factors have been postulated as important underlying mechanisms of familial alcoholism transmission.

Methods—We used functional magnetic resonance imaging (fMRI) during a spatial working memory (SWM) and vigilance paradigm to investigate potential neurodevelopmental differences linked to familial density of AUD in 72 adolescents aged 12 to 14 years.

Results—Youth with denser family histories of AUD showed less activation during a simple vigilance condition relative to SWM in cingulate and medial frontal gyri ($\beta = 0.28, p = 0.03$), and a trend for more relative activity during rest ($\beta = -0.25, p = 0.07$) in this cluster.

Conclusions—Youth with greater familial densities of AUD may be less successful at modulating activity of the default network, potentially indicating a greater propensity for task-independent thought or reduced inhibition of task-irrelevant processing. Failure to moderate activation of the default network may have implications for cognitive efficiency and goal directed behavior in youth with dense FH. Further, aberrant activation in cingulate regions may be linked to genetic variation in GABA receptor units, suggesting a useful endophenotype for risk associated with alcohol dependence.

Keywords

Adolescence; fMRI; Spatial Working Memory; Family History of Alcoholism; Default Network; Cingulate

Youth with a positive family history (FHP) of alcohol use disorders (AUD) are 2 to 5 more times likely to develop drinking problems than those negative for this trait (FHN) (Cloninger et al., 1986; Schuckit, 1985). Underlying neurobiological mechanisms have been proposed as moderating this increased risk, as FHP youth often perform differently than FHN controls on tests of neurocognitive function. For example, nonabusing FHP adolescent males performed worse than FHN boys on tests of language functioning and academic achievement (Giancola et al., 1993; Hegedus et al., 1984; Najam et al., 1997; Poon et al., 2000; Sher et al., 2000; Tarter et al., 1984; Viken et al., 1999), organization of new information (Peterson et al., 1992), executive cognitive functioning (Giancola et al., 1996; Harden and Pihl, 1995), perseveration (Giancola et al., 1993), working memory (Corral et al., 1999; Harden and Pihl, 1995; Ozkaragoz et al., 1997), nonverbal memory (Sher et al., 1991), visuospatial skills (Berman and Noble, 1995; Corral et al., 1999; Garland et al., 1993;

Ozkaragoz and Noble, 1995; Ozkaragoz et al., 1997; Sher et al., 1991) and attention (Tarter et al., 1989). Multigenerational transmission (Conrod et al., 1995; LeMarquand et al., 1999; Peterson et al., 1996; Pihl and Bruce, 1995), high familial density (Hill et al., 2000a), early AUD onset in father (Tarter et al., 1989), active paternal alcoholism (Ozkaragoz et al., 1997), and genotypic features (Berman and Noble, 1995) increase the link between FHP and cognitive functioning. However, other studies have not observed relationships between FHP status and neurocognition (Finn and Justus, 1999; Schuckit et al., 1987), and the neural mechanisms predicting FHP individuals' risk for AUD remains unclear.

In an attempt to link neurobehavioral differences in FHP individuals to their increased risk for AUD, it has been proposed that a positive FH may involve familial transmission of a subtle neurodevelopmental delay. FHP youth have demonstrated smaller volumes of the right amygdala (Hill et al., 2001), which tends to increase in volume over childhood and adolescence. Slowed rate of change in P300 amplitude (Almasy et al., 1999; Begleiter et al., 1984; Polich et al., 1994; Porjesz et al., 1998) and delayed maturation of postural sway (Hill et al., 2000a,b) have also been found among FHP youth. Children of alcoholics demonstrate smaller intracranial volume, which may indicate reduced brain growth (Gilman et al., 2007). Differences in P300 amplitude and postural stability disappear over time, suggesting that these abnormalities may correspond to an inherited developmental lag (Bauer and Hesselbrock, 1999; Hill et al., 1999; Polich et al., 1994). During this period of prolonged neurodevelopment, FHP youth who initiate drinking could be at increased risk for problem behaviors (Hill et al., 2000a; Hingson et al., 2006; King and Chassin, 2007). Therefore, understanding the neural characteristics of FHP youth may help determine potential premorbid abnormalities in the brain functioning of individuals who develop AUD and how these factors contribute to increased risk.

The neural substrate of spatial working memory (SWM) may be especially relevant in identifying mechanisms of increased risk in FHP individuals. The neural mechanisms of spatial working memory (SWM) processing involve a frontoparietal network including the dorsolateral prefrontal cortex, posterior parietal cortices, cingulate regions, and medial frontal cortex (Casey et al., 1997; Courtney et al., 1998; Goldman-Rakic, 1987; McCarthy et al., 1996). While frontal regions are linked to executive control and parietal cortices to accurate and effortful performance (Nelson et al., 2000), the cingulate regions and medial frontal gyrus contribute to tasks effecting conflict and discrimination between responses (Casey et al., 1997), and are part of a "default network" activating in response to simple or rest conditions (Greicius et al., 2003), particularly after cognitively challenging tasks, as processing resources reallocate from areas engaged in task requirements (McKiernan et al., 2003). Studies of nondrinking FHP individuals have identified disorganization of P300 source density maps in the frontoparietal network (Hada et al., 2001), potentially indicating aberrant frontoparietal circuitry (Rangaswamy et al., 2004a) involved in SWM processing, and raising the possibility that reorganization of alcoholics' frontoparietal pathways used to complete SWM tasks (Pfefferbaum et al., 2001; Tapert et al., 2001, 2004) may be moderated by premorbid FH effects. Therefore, differences in the neural substrate of SWM may be linked to FH status, and aid identification of factors promoting alcohol drinking or related behaviors.

Because SWM substrates reorganize during adolescence (Nelson et al., 2000; Schweinsburg et al., 2005a; Thomas et al., 1999), its examination during this period may capture a subtle neurodevelopmental lag in FHP youth. For example, compared to adults, children show more widespread (Thomas et al., 1999) and bilateral (Courtney et al., 1997; Jonides et al., 1993; Smith et al., 1996) dorsolateral prefrontal cortex activation, while adults show more parietal activity (Thomas et al., 1999). Across adolescence (i.e. ages 12 to 18), increasing pre-frontal and inferior parietal activation and decreasing superior parietal response as well

as medial deactivation (i.e., activating more during baseline) is seen in response to SWM (Schweinsburg et al., 2005a). Thus, the underlying neural mechanisms of SWM develop over adolescence, shifting more inferior and posterior, and lateralizing to the right hemisphere, possibly reflecting shifts in strategic and cortical organization (Scherf et al., 2006; Schweinsburg et al., 2005a; Thomas et al., 1999). Considering these and other adolescent neurodevelopments (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2001), lags in neuromaturation may be detected, highlighting potential endophenotypes for the development of AUD.

Subtle delays in neurodevelopment might place FHP adolescents at increased risk for subsequent AUD due to lagged acquisition of cognitive and behavioral correlates. Typical neurodevelopments such as cortical thinning (Sowell et al., 2001), prefrontal myelination (Giedd et al., 1996; Gogtay et al., 2004), regional specialization (Durstun et al., 2006) accompany improved performances on cognitive abilities throughout adolescence. Progressed spatial working memory, verbal working memory, and executive functioning often parallel specific neurodevelopmental processes (Conklin et al., 2007; Durstun et al., 2006; Eigsti et al., 2006; Shaw et al., 2006). Changes in reward neurocircuitry are also theorized to develop across adolescence (Galvan et al., 2007). In sum, delayed neurodevelopment during adolescence may lead to increased vulnerability for problem behaviors. The aim of this study is to contrast blood oxygen level dependent (BOLD) response patterns to SWM and simple vigilance in youth with varied familial densities of AUD, utilizing a neurocognitive substrate that (1) changes in a predictable manner over adolescent development and (2) engages brain regions that appear sensitive to FH-related abnormalities. We hypothesize that youths with dense familial AUD will demonstrate BOLD activation patterns indicative of protracted neurodevelopment. Specifically, we predict that with increasing FH density, there will be greater BOLD activation to SWM in more superior and bilateral regions than among FH negative counterparts.

METHODS

Participants

Youth were selected from an ongoing longitudinal study that follows youth with and without risk factors for AUD (i.e., conduct disorder and positive family histories) from ages 12 to 14 through young-adulthood to identify neurocognitive risk factors for substance problems (Anderson et al., 2005; Nagel et al., 2005, 2006; Schweinsburg et al., 2005b). The focus of this analysis was to identify neural features of FHP youth vis-à-vis fMRI response to a SWM task. Recruitment fliers were mailed to households of San Diego area middle school students. Youth eligibility was preliminarily ascertained through a brief telephone interview. After a description of the study, written informed consent and assent, approved by the University of California San Diego Human Research Protections Program, were obtained from parents and adolescents, respectively. Eligible youth were administered a 90-minute detailed screening interview covering personal substance use histories using the Customary Drinking and Drug Use Record (Brown et al., 1998), psychiatric diagnoses using the Computerized Diagnostic Interview Schedule for Children (C-DISC-4.0; Shaffer et al., 2000), and FH using the Family History Assessment Module (FHAM; Rice et al., 1995). The FHAM and C-DISC were also administered to parents by different interviewers to corroborate adolescent reports. Diagnoses were considered present if either respondents' report or the combined report indicated the disorder. In cases of discrepancies, additional data were obtained, or data were coded to represent the lower level of functioning. Exclusionary criteria were: premature birth; reports of maternal drinking or drug use during pregnancy; parental history of psychosis, bipolar I, or antisocial personality disorder; history of neurological problems, head trauma, learning disabilities, Axis I psychiatric disorder other than conduct disorder or oppositional defiant disorder, or psychiatric medication use;

MRI contraindications (e.g., braces); noncorrectable sensory impairments; nonfluency in English; and left-handedness.

After excluding for excessive movement ($n = 5$), abnormal brain anatomy ($n = 4$), signal drop-out ($n = 4$), neuropsychological scores below the normal range ($n = 1$), or $\leq 50\%$ accuracy on the fMRI task ($n = 2$), remaining participants ($n = 72$, 43% female, 78% Caucasian) were ages 12 to 14, typically from upper middle to upper class families, and average to high average intellectually. History of alcohol and other drug use was minimal (see Table 1). Adolescents who met for conduct disorder ($n = 7$ “mild” and $n = 5$ “moderate” in severity) were included, as this was evenly distributed across FH density values.

Measures

Family History of Substance Use Disorders—Biological parents’ and grandparents’ lifetime history of AUD was obtained from both parents and participant using the FHAM. Most participants had 2 biological parents as informants, and all participants had at least one. For each participant, an index of FH density was computed: each parent with a history of AUD contributed 0.5 and each grandparent with AUD history added 0.25 to the score (range 0 to 2) (Zucker et al., 1994). Stoltenberg et al. (1998) found this density measure provided a valid characterization of familial AUD and may provide greater sensitivity than categorical approaches.

Family Background—Socioeconomic status scores for each participant were derived using the Hollingshead scale, which combines educational attainment and occupation of each parent (Hollingshead, 1965).

Psychiatric Functioning—Diagnoses were derived for participants using youth and parent reports from the C-DISC-4.0 (Shaffer et al., 1996). The Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001) provided levels of psychopathological syndromes based on parent report.

State Measures—Mood was assessed at the time of scanning with the Beck Depression Inventory (Beck, 1978) and state scale of the Spielberger State Trait Anxiety Inventory (Spielberger et al., 1970).

Self-Rating Scale for Pubertal Development—Physical development was assessed with a sex-specific 5-item self-report measure (Petersen et al., 1988). Youth selected 1 of 5 sex-specific statements ranging from “has not begun yet” to “seems complete” indicating current level of pubertal development. Multiple domains of secondary sex characteristic development (e.g., menstruation, facial hair growth, etc.) were sampled to most closely ascertain Tanner staging, characterized as pre-, early, mid-, late, or postpubertal. Pubertal staging is relevant here, as any FH-related differences could account for developmental discrepancies in brain activation.

Youth Substance Use—The Customary Drinking and Drug Use Record (Brown et al., 1998) provides a detailed assessment of past 3-month and lifetime use of alcohol, nicotine, and other drugs.

Neuropsychological Testing—The Vocabulary, Similarities, Block Design, and Matrices subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) were used to ensure participants’ scores fell within the normal range (Wechsler, 1999). Right-handedness was confirmed with the Edinburgh Handedness Inventory (Oldfield, 1971).

Procedures

Participants completed the protocol across 2 appointments, which included a 1-hour scan session. Images were acquired on a 1.5 Tesla General Electric Signa LX scanner. A high-resolution structural image was collected in the sagittal plane using an inversion recovery prepared T1-weighted 3-dimensional spiral fast-spin echo sequence (repetition time = 2,000 ms; echo time = 16 ms; field of view = 240 mm; resolution = 0.9375 mm × 0.9375 mm × 1.328 mm) (Wong et al., 2000). Functional imaging was collected in the axial plane using T2-weighted spiral gradient recall echo imaging (repetition time = 3,000 ms; echo time = 40 ms; flip angle = 90°; field of view = 240 mm; 20 continuous slices; slice thickness = 7 mm; in-plane resolution = 1.875 mm × 1.875 mm; 156 repetitions).

Task stimuli were presented from a laptop computer through a data projector to a screen in the MRI room near the foot of the scanner bed. The participant viewed stimuli through a mirror mounted on the head coil. The fMRI task (Kindermann et al., 2004; Tapert et al., 2001), adapted from McCarthy and colleagues (McCarthy et al., 1994), was chosen to explore the neural substrates of SWM functioning and probe the integrity of these brain regions in adolescents at risk for AUD. The task consists of 18 20-second blocks alternating between experimental (SWM) and baseline (vigilance) condition, with blocks of rest (fixation cross in the center of the screen) in the beginning, middle, and end. In the SWM condition, abstract line drawings appear 1 at a time in 1 of 8 locations. Participants are to press a button when a design appears in a location already occupied in that block. On average, 3 of the 10 trials in each block are repeat locations, and repeats are 2-back. In the vigilance condition, the same stimuli are presented in the same locations, but a dot appears above figures on 30% of trials, and participants are to press a button when a dot appears. The purpose of the vigilance condition is to control for simple motor and attention processes involved in the SWM condition. In both conditions, stimuli are presented for 1,000 ms, and each interstimulus interval is 1,000 ms (total time: 7 minutes, 48 seconds). Upon completion, participants and parents are financially compensated for their time.

Data Analysis

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI; afni.nimh.nih.gov; Cox, 1996). Motion in the time series data was corrected by registering each acquisition to a minimally deviant repetition with an iterated least squares algorithm (Cox and Jesmanowicz, 1999); 3 rotational and 3 displacement parameters were output for each repetition of each participant. Trained raters examined the corrected time series data and removed repetitions containing residual visually discernible head motions. If >22% of repetitions were removed, the participant was not included ($n = 5$ not described in this paper). On average, 6% of repetitions were removed due to movement. Time series data were deconvolved with a reference vector coding the alternating task conditions while covarying for linear trends and the motion correction applied to control for spin history effects (Bandettini et al., 1993), and modeling typical delays in the hemodynamic response (Bandettini et al., 1993; Boynton et al., 1996). Functional data were transformed into standardized space (Lancaster et al., 2000; Talairach and Tournoux, 1988) and resampled into 3.5 mm³ voxels, and a spatial smoothing Gaussian filter (full-width half maximum = 3.5 mm) was applied. These steps resulted in a fit coefficient for each voxel representing BOLD response to SWM relative to the vigilance task condition; separate coefficients modeled SWM relative to fixation, and vigilance relative to rest.

To determine whether bulk motion during the task differed as a function of FH, each participant's absolute mean for each of the 6 motion parameters across the time series data was evaluated with Spearman rank-order correlations. For estimating task-correlated motion,

the 6 parameters were correlated with the task reference vector for each participant. These values were also correlated with FH density scores with Spearman rank-order correlations.

A single sample *t*-test was conducted to indicate voxels responding to SWM relative to vigilance across all participants ($n = 72$). To control for Type I error, a combination of *t*-statistic magnitude and cluster volume thresholding was applied (Forman et al., 1995; Ward, 1997) by only interpreting clusters comprised of at least 22 contiguously activated voxels at $\alpha < 0.025$ ($\geq 943 \mu\text{l}$ in volume). Eleven clusters surpassed this threshold. The largest cluster (342,486 μl) was reduced into 9 smaller regions of interest defined using regional proximity, established correlates of brain structure to function (Heilman and Valenstein, 1972, 2003), and the direction of BOLD activation (i.e., areas activating preferentially to SWM were grouped separately from those activating to vigilance; see Fig. 1). For each of the resulting 19 clusters (see Table 3), average activation for each participant was converted into z-scores.

Z-scores representing SWM response relative to vigilance for each of the 19 clusters were screened for outliers using 3 regression-based diagnostic approaches: Studentized deleted residuals $> \pm 3$, leverage values > 0.17 , and Mahalanobis distance $>$ critical value > 16.27 ($p = 0.001$, $dfbetas > \pm 1$ or $dfits > \pm 1$). One case was determined as unduly influential in the right cerebellar tonsil.

To determine whether FH density predicted BOLD response in regions that reliably activated to SWM relative to vigilance, the average activations for 15 of these 19 clusters were entered as dependent variables for hierarchical regressions performed in SPSS 14.0 (Chicago, IL). The right cerebellar tonsil cluster was excluded as a statistical outlier (see above). Three other clusters (left cerebellar tonsil, and left and right precentral motor cortices) were not entered into the equation because FH effects were not expected in these regions. Bulk motion in the roll and pitch directions were included as covariates, and FH density was entered on the second step. The presence of conduct disorder was not related to independent or dependent variables, and mothers' education was related to FH but not activation, and therefore not included. Bonferroni correction was applied, and regressions were considered significant at $\alpha \leq 0.003$.

RESULTS

Participant Characteristics

FH density was not significantly related to gender, conduct disorder diagnosis, CBCL scores, or other indicators of mood or demography. FH density negatively correlated with maternal years of education ($r = -0.25$, $p = 0.03$, see Table 1). Performance on neuropsychological tests and the SWM task did not differ as a function of FH density (see Table 2). Increased age was related to faster reaction time in the vigilance condition ($r = -0.31$, $p = 0.01$) and to better accuracy in SWM ($r = 0.28$, $p = 0.02$) and vigilance conditions ($r = 0.28$, $p = 0.02$). Pubertal development scores indicated that, on average, males were nearly at mid-puberty, while females were between mid- to late puberty. Pubertal development was not related to SWM task performance or neuropsychological test scores ($ps > 0.05$).

Motion

The maximum values of rotation and displacement were modest (roll = 0.18° , pitch = 1.28° , yaw = 0.35° , superior = 0.80 mm, left = 0.24 mm, posterior = 0.39 mm). Spearman rank-order correlations demonstrated that FH density was not related to bulk motion in any direction ($ps > 0.20$), but FH density was related to task-correlated motion in the roll (i.e., ear-to-shoulder) and yaw (i.e., nodding) rotations ($\beta = 0.27$, $p = 0.03$; $\beta = 0.28$, $p = 0.02$, respectively).

SWM Activation and Family History

Across participants, the pattern of SWM relative to vigilance was consistent with existing literature (Barch et al., 1997; Courtney et al., 1998; D'Esposito et al., 1998; Jonides et al., 1993; Smith and Jonides, 1998), involving bilateral dorsolateral prefrontal and parietal cortices activating to SWM blocks, and medial frontal and cingulate regions activating to vigilance blocks (see Table 3). A hierarchical regression determined whether FH density would predict SWM relative to vigilance response in the 15 areas of interest that reliably activated to the task. Task-correlated motion (roll and yaw) parameters were entered on step 1, and centered FH density was entered on step 2. Considering a Bonferroni correction for the number of regressions evaluated ($\alpha = 0.05/15 = 0.003$), greater FH density was related to decreased SWM response relative to vigilance in a region encompassing bilateral cingulate, posterior cingulate, and extending into the medial frontal gyri at a trend level, above and beyond effects of motion [$F(3,66) = 4.26, p = 0.008; R^2\Delta = 7\%, \beta = 0.28, p = 0.03$] (see Fig. 2).

Follow-Up Analyses

To clarify this pattern of activation, 2 single-sample *t*-tests in AFNI compared SWM relative to fixation, and vigilance relative to fixation activations ($\alpha < 0.025, \geq 943 \mu\text{l}, n = 70$). In the SWM relative to fixation contrast, many regions activated preferentially to SWM, and the cingulate/medial frontal gyrus region activated more during fixation blocks than during SWM blocks. In the vigilance relative to fixation contrast, the cingulate/medial frontal gyrus cluster, superior cingulate, medial frontal gyrus, and paracentral lobule showed significantly greater BOLD response during fixation blocks, while more inferior areas of the cingulate activated preferentially to the vigilance condition (see Fig. 3). Two separate regressions examined the relationship between BOLD response and FH density for each subregion of activation within the larger cluster, for the vigilance relative to fixation contrast. The superior portion of the cluster, which activated preferentially to the fixation condition, showed a trend-level negative relationship between BOLD response to vigilance relative to fixation and increasing FH density [$F(3,62) = 2.49, p = 0.07, \beta = -0.25, p = 0.07$]. The inferior area, which activated preferentially to the demands of vigilance, did not relate to FH density. Taken together, these results suggest *less* BOLD response during vigilance and *more* activity during fixation (or rest-related response) with increasing FH density.

DISCUSSION

The goal of this study was to explore the relationship between FH of AUD and brain response to SWM and simple vigilance in adolescents ages 12 to 14 with very limited histories of alcohol or drug use. We predicted there would be greater BOLD activation to SWM in more superior and bilateral brain regions with increasing FH density, suggesting a neurodevelopmental lag in brain regions sensitive to FH-related abnormalities. Contrary to our hypothesis, FH status did not predict activation to the SWM task. Therefore, findings do not necessarily support a neurodevelopmental delay as a mechanism through which youth with familial AUD are at risk for AUD. However, adolescents with greater familial densities of AUD demonstrated less response than FHN youth during a simple vigilance baseline condition in medial brain regions including the posterior cingulate, cingulate gyrus, and medial frontal gyrus. In addition, participants with greater FH densities demonstrated more BOLD response than FHN youth during rest periods in the more superior aspects of this medial region. While unrelated to the a priori hypothesis, these findings may provide interesting insights to the cognitive style of youth with familial AUD.

Midline structures such as the posterior cingulate cortex, medial frontal gyri, and anterior cingulate have been consistently found to “deactivate,” or respond preferentially to the

baseline condition as compared to the more demanding condition of many fMRI paradigms (Binder et al., 1999; Greicius et al., 2003; Hampson et al., 2006; McKiernan et al., 2003). This increased midline activity during a passive state (e.g., fixation) or conditions requiring little cognitive processing (e.g., vigilance), relative to regions needed for cognitively demanding conditions, has been linked to a propensity for stimulus independent thought, or mind wandering (Gusnard et al., 2001; Mason et al., 2007; McGuire et al., 1996; McKiernan et al., 2006). This could in turn relate to compromised appraisal of emergent risk situations and reduced tendencies to carefully consider outcomes of behavioral selections. We observed that increased FH density was linked to more fixation-related BOLD response and less vigilance response in the cingulate. Potentially, this may indicate that adolescents with denser FH engage in less stimulus independent thought during easy task conditions (i.e., in response to a vigilance task), but more such thought when task demands cease (i.e., during fixation). A task with varied rest durations and task demands could help ascertain if this activation pattern is beneficial to performance by maintaining cognitive arousal (Mason et al., 2007), or counter-productive, by allocating resources away from the target task.

Previous work investigating the utility of the default network suggests that activation in midline structures decreases in response to greater task difficulty (Greicius and Menon, 2004; Greicius et al., 2003; McKiernan et al., 2003). McKiernan et al. (2003) contrasted BOLD activation during a parametrically-manipulated short-term memory condition to response obtained during a target discrimination condition. As task demands increased, processing reserves were reallocated from default areas to regions necessary for the active condition. The authors concluded that the magnitude by which midline activation changed represented the degree to which resting state activity was inhibited to maintain successful task-relevant processing. Functional connectivity studies also support the notion that opposing activation patterns between default and higher-order cortical regions may serve to enhance performance (Greicius et al., 2003). Hampson et al. (2006) reported that increasing working memory performance positively correlated with the strength of connectivity in the default network, and proposed that lateral prefrontal regions may actively suppress activation of midline structures to augment performance. Similarly, a greater inverse correlation between activity in the default network and task-related activation was positively associated with intra-individual consistency in behavioral performance (Clare Kelly et al., 2008). In other words, the strength of the correlation may represent an index of neural regulation between default and task-active “modes” (Clare Kelly et al., 2008). Together, current findings suggest that adolescents with dense FH may be less successful in moderating the default network in response to cognitive load. This difference could have potential consequences for downstream cognitive functioning, or serve as an additional endophenotype to help identify youth at greater risk of developing CNS disinhibitory related behaviors.

In FH dense adolescents, compromised neural regulation of midline regions may have direct behavioral sequelae. The functional consequences of these findings may be evident in the poorer neurocognitive and academic performance of some individuals (Corral et al., 1999; Giancola et al., 1996; Hegedus et al., 1984; Najam et al., 1997; Poon et al., 2000), or mark behavioral disinhibition. However, in this sample, youth with greater familial AUD did not score differently from FHN youth on neuropsychological tests, and measures of behavioral inhibition were not linked to this pattern of activation. Thus, an alternative explanation for smaller magnitudes of vigilance-related activation with increasing FH density is that FH-dense adolescents were less challenged by the SWM condition than FHN youth, thus requiring fewer cognitive resources to complete the task. Future studies that parametrically manipulate task difficulty will help characterize how the default network develops across adolescence, and elucidate whether this finding supports an FH-related developmental lag.

Additionally, studies that include participants with more behavioral problems might uncover a relationship.

Our findings have potentially interesting implications for the interpretation of anomalous electrophysiological characteristics theorized to be biological vulnerabilities for AUD and behavioral disinhibition, such as reduced P300 amplitude and increased resting beta frequency (Bauer and Hesselbrock, 1993; Hesselbrock et al., 2001; Polich et al., 1994; Porjesz et al., 2005; Rangaswamy et al., 2004a). The relationship between genetic features that determine characteristics of brain oscillations could participate in the mechanism for such predispositions. Specifically, EEG beta frequency has been linked to receptor genes for gamma-aminobutyric acid (GABA) that are involved in inhibitory neural networks (Rangaswamy et al., 2004b). The balance of inhibitory inter-neurons and excitatory pyramidal cells depends on the action of GABA subunits (Whittington et al., 2000). Because alcoholics and their children demonstrate increased beta activity, this may indicate an imbalance between excitation and inhibition (Porjesz and Rangaswamy, 2007). Variations in GABA receptor genes affect neural inhibition and thus the level of neural excitability, thereby influencing the predisposition to develop alcohol dependence and related disinhibitory disorders (Begleiter and Porjesz, 1999). Interestingly, GABA appears to specifically influence activity in the default network regions (Northoff et al., 2007) that here demonstrated decreased vigilance and increased fixation response in FHP youth. Northoff et al. (2007) reported that GABA concentration predicted the magnitude of negative BOLD response (relative to a resting state) in the anterior cingulate. Additionally, the anterior and posterior cingulate gyri and medial frontal gyri have been indicated as potential sources of the P300. For instance, Ardekani et al. (2002) found a correlation between event-related potentials and BOLD activation to a visual odd-ball task. However, studies mapping anatomical origins of electrophysiological data have yet to reach consensus. Nonetheless, an intriguing body of emerging evidence suggests that suboptimal modulation of default networks in response to cognitive demands may relate to atypical electrophysiological activity and behavioral disinhibition in nondrinking FHP individuals.

Additional data support the link between substance use risk and activation of structures involved in the default network. Paulus et al. (2005) reported that decreased BOLD activation in response to a decision making task in the posterior cingulate and medial frontal gyrus predicted relapse in stimulant dependent adults. They proposed that relapsing individuals may be impaired in gathering adequate controlled processing resources during decision making, resulting in poor assessment abilities (Paulus et al., 2005). Taken together with our results, difficulty engaging this region even for simple tasks may be connected to CNS disinhibition and risk for impulsive behaviors. While the neural underpinnings of relapse and risk for AUD are likely distinct, we suggest that subtle neural response differences may influence the risk FHP adolescents have for developing patterns of problem drinking.

This study has several limitations. First, participant motion, although relatively modest, was related to FH density, and thus needed to be controlled statistically. Second, characterizing the relationship between brain regions supporting higher-order cognitive demands and the default network will require functional connectivity analyses, which are beyond the scope of this report. Third, most participants had highly educated, affluent parents, and all were free from medical and psychiatric problems; while this minimizes a variety of potential confounds, results may not generalize to the broad population of youths at risk for AUD. Fourth, activation in the default network has not been characterized across adolescence, so we cannot yet determine if the response pattern observed here represents a developmental lag. Finally, FH results were relatively modest and did not survive strict Bonferroni correction.

The current investigation suggests that functional neuroimaging may be useful for identifying neurocognitive risk factors associated with familial density of AUD. Although we did not find evidence that BOLD response specifically during spatial working memory demands was related to FH, we observed that greater neural activity during rest and reduced activity during an active baseline condition were linked to denser FH. We theorize that this may indicate an imbalance between excitatory and inhibitory action during neural transmission determined by genetic variation in GABAergic mechanisms. Behaviorally, CNS disinhibition might translate into reduced ability to inhibit task irrelevant stimuli or an increased risk for impulsive behavior. Further understanding of the default network in relation to CNS disinhibition and behavioral inhibition may help inform prevention programming and identify youth at risk for substance problems. Longitudinal studies may establish a causal link between neurocognitive characteristics and the risk for developing AUD.

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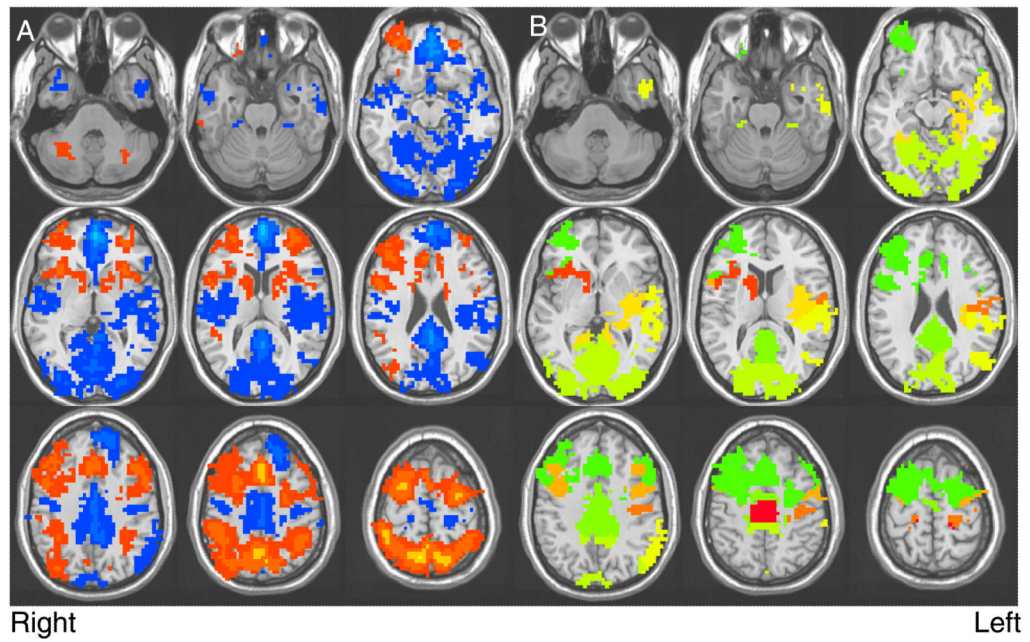


Fig. 1. (A) Results of the single sample *t*-test, showing regions with significant activation among adolescent participants ($n = 72$) during the SWM task; red indicates increased BOLD response contrast to the SWM blocks, and blue indicates increased BOLD response contrast to the vigilance blocks ($p < 0.025$, clusters $> 943 \mu\text{l}$). (B) Delineation of regions resulting from reduction of the largest cluster that significantly activated to the SWM task.

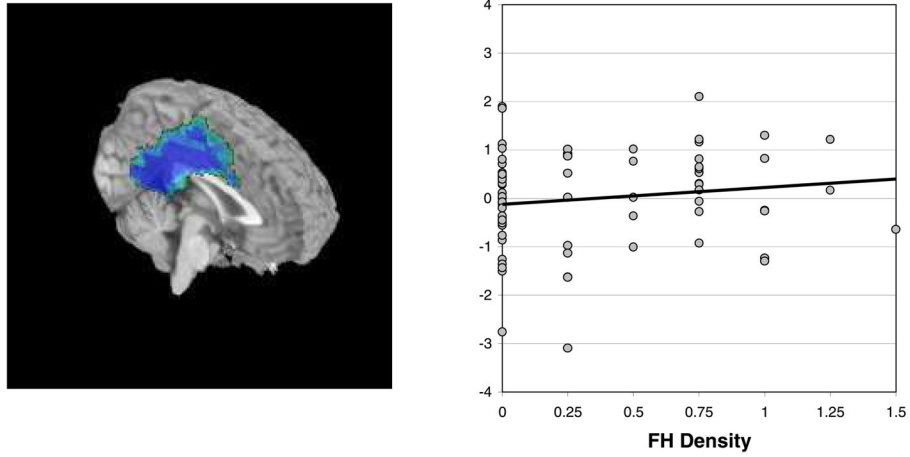


Fig. 2. Denser FH was linked to less vigilance response relative to SWM response ($\beta = 0.28$, $p = 0.03$) in the cingulate gyrus, posterior cingulate, and medial frontal gyrus (highlighted area). Most participants activated more to the vigilance condition than to the SWM condition in this region, but this was less true for those with greater FH density.

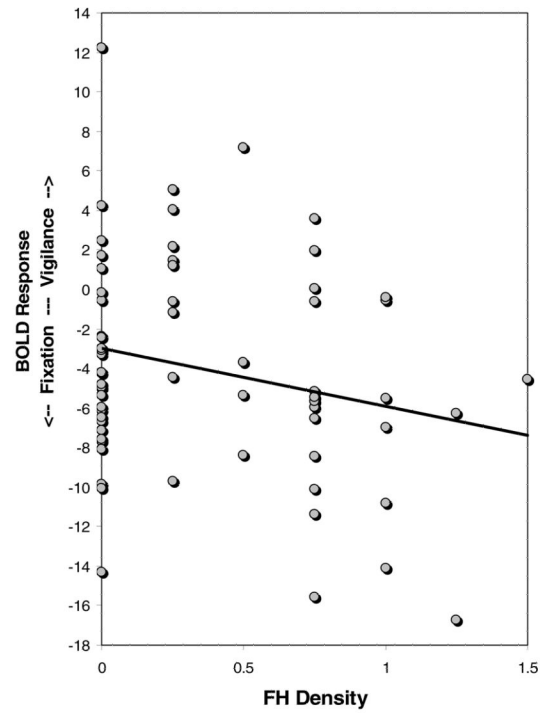
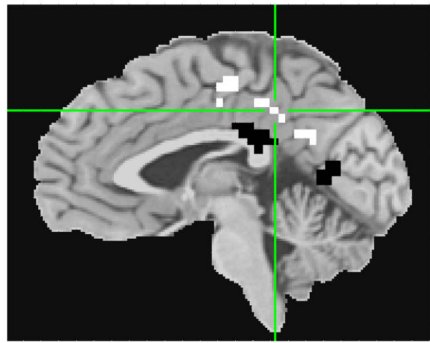


Fig. 3. Activation during vigilance relative to fixation was examined in the region in which SWM relative to vigilance related to FH density. The area in white (superior cingulate; denoted with crosshairs) preferentially activated to fixation, and was related to FH density at a trend level (see graph; $\beta = -0.25$, $p = 0.07$). The regions in black (posterior cingulate) preferentially activated to vigilance condition, but were not related to FH density scores.

Table 1Participant Characteristics and Correlations With Family History Density ($n = 72$)

	M (SD)	Pearson r	p -value
Age in years (range 12–14)	13.25 (0.81)	−0.11	0.34
Pubertal development			
Girls	3.65 (0.71)	−0.21	0.26
Boys	2.89 (0.70)	−0.03	0.88
Father education	16.35 (2.20)	−0.20	0.11
Mother education *	15.49 (2.32)	−0.25	0.03
Father annual salary (\$K)	87.88 (68.04)	0.34	0.77
Mother annual salary (\$K)	35.59 (42.49)	−0.12	0.31
CBCL Internalizing T -score	46.55 (6.41)	0.15	0.22
CBCL Externalizing T -score	45.85 (6.41)	0.08	0.55
Beck Depression Inventory total	2.60 (3.12)	0.05	0.71
Spielberger State Anxiety T -score	28.68 (7.03)	0.16	0.19
Lifetime uses of alcohol	0.85 (2.68)	−0.10	0.40
Alcoholic drinks per occasion	0.17 (0.53)	−0.08	0.50
Lifetime uses of cigarettes	0.10 (0.42)	−0.14	0.25
Lifetime uses of marijuana	0.23 (0.74)	−0.07	0.54
ANOVAs comparing FH density across categories:			
	%	F -value	
Sex (% female)	43	1.65	0.15
Ethnicity (% Caucasian)	78	1.12	0.36
Conduct disorder diagnosis	16	1.92	0.09
Parental marital status		1.34	0.25
Single	4		
Married to each other	81		
Divorced	14		
Other	1		
Living arrangement *		2.67	0.02
Both biological parents	81		
Single parent	10		
Parent and step-parent	8		

* $p < 0.05$.

Table 2Neurocognitive Scores and Correlations With Family History Density ($n = 72$)

	Mean	SD	Pearson r	p -value
Spatial working memory accuracy %	91.00	6.24	0.16	0.20
Spatial working memory reaction time (ms)	604.38	79.96	-0.18	0.16
Vigilance accuracy %	95.67	2.60	-0.09	0.47
Vigilance reaction time (ms)	654.32	58.26	0.02	0.89
WASI Vocabulary T -score	56.56	8.05	-0.10	0.41
WASI Similarities T -score	56.40	9.14	0.07	0.55
WASI Block Design T -score	56.26	7.72	0.14	0.24
WASI Matrix Reasoning T -score	54.50	6.07	-0.06	0.59

Table 3

Regions Activated to SWM Relative to Vigilance Conditions (Clusters > 943 μ l, $p < 0.025$, $n = 72$)

RL	AP	IS	BA	+/-SWM	Brain regions
-13	-18	37	6, 8, 47	+	Medial middle, superior & inferior frontal gyri; anterior to posterior cingulate ^d
-7	56	51	19, 7, 40, 39, 5	+	Precuneui, superior & inferior parietal lobules
1	74	5		-	Occipital, lingual & fusiform gyri ^d
6	-46	11	9,10	-	Medial & middle frontal gyri
0	34	29	18, 30	-	Cingulate regions and middle frontal gyrus, posterior cingulate, medial frontal gyri ^d
-42	10	6	13, 4, 41, 42, 22, 21, 40	-	Insula, striatum; inferior frontal gyrus; transverse, superior & middle temporal gyri; para/hippocampal gyri, amygdala; inferior parietal lobe
51	32	8	42, 21, 34	-	Temporal gyri, inferior parietal lobe, supramarginal, middle & superior temporal gyri ^d
25	21	3	35, 28	-	Parahippocampal gyri, hippocampus, insula, thalamus ^d
26	-12	8	44, 47	+	Caudate, insula, cingulate, middle frontal gyrus; thalamus, putamen; inferior frontal gyrus
-23	-11	10		+	Insula, caudate, striatum ^d
31	-47	9	10	+	Middle & superior frontal gyri
2	25	47		-	Paracentral lobules ^d
-32	-7	-34	38, 36, 21	-	Superior & middle temporal gyri, uncus
54	-21	10	45	-	Inferior frontal gyrus, precentral gyrus
-56	29	-15	20	+	Middle temporal gyrus into inferior temporal gyrus

+ , clusters activated preferentially to the SWM condition;

- , clusters activated preferentially to the vigilance condition.

^dDivided from the largest cluster.