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Atypical frontal lobe activity during verbal working memory in youth with a family history of alcoholism

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ABSTRACT

Background: Abnormal brain functioning during verbal working memory (VWM) tasks has been shown in individuals with alcohol use disorders (AUDs). Since adolescents with a familial history of alcoholism (FHP) are at high risk for developing an AUD, it is important to consider whether atypical brain activity during VWM may help to explain FHP vulnerability toward developing alcoholism.
Methods: To that end, using functional magnetic resonance imaging, we examined brain response during a VWM 2-back task in 19 FHP adolescents and 16 age and gender-matched family history negative (FHN) controls.
Results: Despite no group differences in task accuracy, FHP youth had significantly slower average reaction time when making correct responses during the 2-back condition than FHN youth. In contrast to a vigilance control condition, while covarying for reaction time, FHP adolescents showed less activation during VWM than FHN youth in multiple areas of the prefrontal cortex (PFC) – a brain region crucial to intact working memory skills.
Conclusions: These results suggest that even prior to heavy alcohol use, FHP adolescents show atypical executive brain functioning during VWM, and that these differences are independent of slower working memory reaction time in FHP youth. Given the importance of working memory in numerous areas of day-to-day functioning, such as adaptive decision-making, these abnormalities may contribute to FHP youth vulnerability toward developing AUDs.

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1. Introduction

Adolescents with a family history of alcoholism (FHP) are at greater risk for developing an alcohol use disorder (AUD) than their family history negative (FHN) peers (Dawson et al., 1992). Previous investigations have found that in the absence of heavy alcohol use, FHP adolescents have atypical brain structure (Hill et al., 2001, 2007), as well as aberrant brain functioning (Heitzeg et al., 2008, 2010; Herting et al., 2011; Schweinsburg et al., 2004; Silveri et al., 2011; Spadoni et al., 2008) and behavior (Corral et al., 2003, 1999; Harden and Pihl, 1995; Nigg et al., 2004; Tapert and Brown, 2000) compared to FHN youth. These neurobiological and behavioral phenotypes may help to explain an increased vulnerability for developing an AUD in FHP youth.

Interestingly, deficits in executive functioning have been reported in both adults with AUDs and FHP individuals on measures assessing decision-making (Bechara et al., 2001; Lovallo et al., 2006), working memory (Ambrose et al., 2001; Harden and Pihl, 1995; Lovallo et al., 2006; Noel et al., 2001), response inhibition (Lawrence et al., 2009; Nigg et al., 2004; Noel et al., 2007), and attention (Ahveninen et al., 2000; Corral et al., 1999; Tapert and Brown, 2000). Thus, atypical executive functioning may not only be a consequence of alcohol abuse, but could also be a pre-morbid marker for future alcohol dependence (Hesselbrock et al., 1991; Peterson et al., 1992). In order to develop effective prevention strategies for FHP youth, it is important to better characterize specific brain and behavior deficits related to executive functions in this population.

Working memory, or the temporary manipulation and maintenance of information (Baddeley and Hitch, 1974), is an important skill for adaptive decision-making and successful day-to-day functioning. Neuroimaging has been used to characterize the neural substrates of working memory, which broadly involve a network of brain activity including the premotor cortex, dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, frontal poles, inferior and posterior parietal cortex, and cerebellum (Owen et al., 2005). Prior investigations have shown performance deficits during working memory in both alcoholics and FHP adults (Ambrose et al., 2001; Lovallo et al., 2006; Noel et al., 2001), which may contribute to deficits in decision-making (Finn, 2002). Consequently, sub-optimal decision-making may lead to poor choices

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with regards to alcohol consumption. Furthermore, investigations using functional magnetic resonance imaging (fMRI) have found atypical brain activity in alcoholics during working memory tasks. Studies in adults with AUDs have shown largely weaker, but in some cases greater brain activity during both verbal (Desmond et al., 2003; Park et al., 2010) and spatial (Tapert et al., 2001) working memory tasks. These differences have been reported in the prefrontal cortex (PFC) (DLPFC, inferior frontal gyrus (IFG), anterior PFC (APFC), medial frontal gyrus (MEFG), premotor cortex) and parietal lobe (inferior parietal lobule (IPL), superior parietal lobule (SPL)), brain regions that undergo substantial maturation over the course of development (Crone et al., 2006). Interestingly, risk for alcoholism itself may also be associated with brain activity on tasks involving working memory. For example, non-alcohol abusing FHP young adults show weaker fronto-parietal brain response compared to their peers during a visual oddball task (Rangaswamy et al., 2004) in the IFG and IPL. Since behavioral and fMRI studies in both alcoholics and FHP individuals have reported atypical working memory performance and brain activity, this makes it difficult to disentangle the effects of alcohol abuse versus risk for alcoholism on poor working memory functioning.

It is possible that fronto-parietal dysfunction may be present in FHP individuals at much earlier stages of development, long before the initiation of heavy alcohol use and thus may be a neurobiological marker of risk for the development of future AUDs. To date, there has been only one neuroimaging study of working memory in largely alcohol and substance naïve FHP youth, which found atypical default mode network activity during the vigilance control condition in FHP versus FHN youth (Spadoni et al., 2008). While no group differences in spatial working memory brain activity were present in this study, other types of working memory functioning, that may rely on different brain regions (D'Esposito et al., 1998), have not been investigated in FHP youth. While information on VWM performance and brain activity in FHP youth has been absent from the adolescent literature, a recent study in adults with AUDs (Park et al., 2010) found weaker brain activity when comparing alcoholics and control subjects in both frontal (DLPFC, IFG, MEFG) and parietal lobes (SPL, paracentral lobule) during a 2-back VWM task. Notably, regions of the PFC may be specifically important for the maintenance of verbal information (Wager and Smith, 2003), which relies on phonological processing and rehearsal (Baddeley and Hitch, 1974). Aberrant brain activity during working memory in prefrontal cortical areas may also affect decision-making skills (Suhr and Hammers, 2010). Thus, it is important to examine if VWM brain response is altered in FHP youth, in the absence of heavy alcohol use, to understand whether these pathways may be atypical and thus contribute to the higher rates of AUDs seen in this population.

The goal of the current study was to investigate VWM brain activity and behavior in FHP and FHN adolescents to better understand neural and behavioral phenotypes that may predict AUD risk in FHP youth. To this end, we used fMRI to examine brain response during a VWM 2-back task. Based on previous findings of weaker prefrontal and parietal brain response in adults with AUD (Park et al., 2010; Tapert et al., 2001), we hypothesized that even in the absence of heavy alcohol use, FHP youth would show weaker prefrontal activity in the DLPFC and IFG, as well as weaker BOLD response in the parietal lobes in both the SPL and IPL during VWM than their FHN peers.

2. Materials and methods

2.1. Participants

Participants included 19 FHP (6 females, 13 males) and 16 FHN (8 females, 8 males) youth, ages 12–15 years. All youth had an absence of heavy alcohol and substance use, as defined by our criteria (see below and Table 1). Participants were recruited through advertisements and mailings distributed throughout the community as part of an ongoing study focused on adolescent neurodevelopment in at-risk youth. Briefly, following written consent and assent, separate structured telephone interviews were conducted with both the youth and one of their parents. Interviews consisted of the Diagnostic Interview Schedule for Children Predictive Scales (DISC-PS-4.32b; Hoven et al., 2005; Lucas et al., 2001), the Family History Assessment Module (FHAM; Rice et al., 1995), the Brief Lifetime version of the Customary Drinking and Drug Use Record (Brown et al., 1998), and the Structured Clinical Interview (SCI; Brown et al., 1994). Exclusionary criteria for adolescents included left-handedness (Edinburgh Handedness Inventory (Oldfield, 1971)), lifetime history of a diagnosed DSM-IV psychiatric disorder, absence of family history information, significant alcohol and/or substance use (>10 lifetime alcoholic drinks or >2 drinks/occasion, >5 uses of marijuana, any other drug use, or >4 cigarettes per day), neurological illness, significant head trauma (loss of consciousness >2 min), serious medical problems, learning disability, prenatal exposure to drugs or alcohol, reported history of psychotic disorders in biological parents, irremovable metal, and pregnancy. All procedures were in accordance with the ethical standards of the Oregon Health and Science University (OHSU) Institutional Review Board.

2.1.1. Family history of alcohol and substance use disorders. Dichotomizing individuals based on first, or first and second degree relatives with a AUD, has been shown to be a valid predictor of alcohol use vulnerability and future dependence (Stoltenberg et al., 1998). Thus, the FHAM was administered during the structured telephone interview with both the youth and their biological parent to assess DSM-IV criteria for substance abuse and dependence of first and second degree relatives. Both youth and parent were administered the FHAM in order to examine any instances in which youth reported parental use that met criteria for an AUD, but the biological parent did not. No discrepancies in reporting existed for the current sample. Based on the information provided on the FHAM, youth were considered FHP if a history of alcohol abuse and/or dependence was reported for at least one biological parent or two or more second degree relatives on either the maternal or paternal side of the family; youth with a complete absence of substance abuse/dependence among relatives were considered FHN. In the FHP group, a family history density (FHD) score was calculated for each participant based on the youth's familial relatedness to the relative(s) with an AUD. Biological parents received a score of 0.5, grandparents a score of 0.25, while aunts and uncles with an AUD received a weighted ratio of 0.25 divided by the total number of aunts and uncles on the maternal or paternal side of the family in which the AUD was reported. FHD scores in the FHP youth ranged from 0.06 to 1.00 with mean = 0.49 and standard deviation (SD) = 0.26.

2.2. Imaging procedures

Images were acquired on a 3.0 Tesla Siemens Magnetom Tim Trio System at OHSU's Advanced Imaging Research Center. Whole-brain, high-resolution structural anatomical images were acquired in the sagittal plane using a T_1 weighted MPRAGE scanning sequence (TI = 900 ms, Flip Angle = 10 degrees, TE = 3.58 ms, TR = 2300 ms, acquisition matrix = 256 × 240, resolution = 1 mm × 1 mm × 1.1 mm). Whole-brain functional images were collected in the axial plane oblique to the AC-PC, using a T_2^* – weighted echo planar blood oxygen level dependent (BOLD) sequence (TR = 2000 ms, TE = 30 ms, FOV = 240 mm, flip-angle = 90°, 33 slices no gap, resolution = 3.75 mm × 3.75 mm × 3.8 mm).

A modified block design fMRI task was used to assess VWM (Nagel et al., 2007). The task included 8 blocks of an alternating experimental VWM 2-back condition and a control, vigilance condition, with brief presentations of fixation between block conditions. In the VWM condition, white alphabetical letters were presented in various locations on a black screen, and participants were told to "Press for the same letter as 2 screens prior" (see Fig. 1). For each block, 5 out of the 16 trials was a 2-back verbal letter repeat. In the vigilance condition, gray and white dots appeared in random locations on the screen, and subjects were told to "Press the button when a gray dot appears" (see Fig. 1). Each block of the vigilance condition had 8 trials, with 3 out of 8 trials requiring a button press. The purpose of the vigilance condition was to control for attentional and simple motor processes involved during the VWM condition. In each condition, stimuli were presented on the screen for 500 ms, with an inter-trial stimulus interval and stimulus response window of 1500 ms.

2.3. Image processing

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Preprocessing included slice timing correction, motion correction, co-registration of functional to anatomical images, and spatial smoothing using a Gaussian filter (full-width half maximum = 6 mm kernel). Time repetitions that showed >2.5 mm or 2.5° in any of six displacement or rotational parameters were removed from the subsequent analyses. In addition, analysis of root mean square indicated no differences in movement between FHP and FHN youth ($U_{33} = 120$, $Z = -1.06$, $p = 0.29$). Next, functional masks were created to mask out non-brain areas, and time series data were normalized to its mean, resulting in images scaled by percent signal change. Time series data were then correlated with a vector representing the task design, in light of the delay of the hemodynamic response, while covarying for motion and linear trends (Cohen, 1997). The fit coefficients derived from fitting the time series data to the model represented the blood oxygen level-dependent (BOLD) response, which was contrasted between the VWM and vigilance, VWM